**CHRONIC GASTRITIS**

Chronic gastritis, by definition, is a histopathological entity characterized by chronic inflammation of the stomach mucosa.

**Frequency**

In the US: Approximately 35% of adults are infected with H pylori, but the prevalence of infection in minority groups and immigrants from developing countries is much higher. Children aged 2-8 years in developing nations acquire the infection at a rate of about 10% per year; whereas, in the United States, children become infected at a rate of less than 1% per year. This major difference in the rate of acquisition in childhood is responsible for the differences in epidemiology between developed countries and developing countries. Socioeconomic differences are the most important predictor of the prevalence of the infection in any group. Higher standards of living are associated with higher levels of education and better sanitation, so the prevalence of infection is lower.

Internationally: An estimated 50% of the world population is infected with H pylori; therefore, chronic gastritis is extremely frequent. H pylori infection is highly prevalent in Asia and in developing countries, and multifocal atrophic gastritis and gastric adenocarcinomas are more prevalent in these areas. Autoimmune gastritis is a relatively rare disease, most frequently observed in individuals of northern European descent and African Americans. The prevalence of pernicious anemia, resulting from autoimmune gastritis, has been estimated at 127 cases per 100,000 members of the population in the United Kingdom, Denmark, and Sweden. The incidence of pernicious anemia is increased in patients with other immunological diseases, including Graves disease, myxedema, thyroiditis, and hypoparathyroidism.

Morbidity of chronic gastritis is strongly related to the underlying cause. Chronic gastritis as a primary disease, such as H pylori–associated chronic gastritis, may progress as an asymptomatic disease in some patients, while other patients may report dyspeptic symptoms.

The clinical course may be worsened when patients develop any of the possible complications of H pylori infection such as peptic ulcer or gastric malignancy.

H pylori–associated chronic gastritis appears to be more common among Asian and Hispanic people than in people of other races.

In the United States, H pylori infection is more common among black, Native American, and Hispanic people than among white people, a difference that has been attributed to socioeconomic factors.

Autoimmune gastritis is more frequent in individuals of northern European descent and in African American people, and it is less frequent in southern European and Asian people.

Chronic H pylori–associated gastritis affects both sexes with similar frequency.

The female-to-male ratio for autoimmune gastritis has been reported to be 3:1.

H pylori gastritis is usually acquired during childhood, and complications typically develop later.

Patients with autoimmune gastritis usually present with pernicious anemia, which is typically diagnosed in individuals aged approximately 60 years. However, pernicious anemia can be detected in children (juvenile pernicious anemia).

**Causes**

Types of chronic gastritis include the following:

**Infectious gastritis**

* Chronic gastritis caused by H pylori infection - This is the most common cause of chronic gastritis.
* Infection by Helicobacter heilmanii
* Granulomatous gastritis associated with gastric infections in mycobacteriosis, syphilis, histoplasmosis, mucormycosis, South American blastomycosis, anisakiasis, or anisakidosis
* Chronic gastritis associated with parasitic infections - Strongyloides species, schistosomiasis, Diphyllobothrium latum

**Noninfectious gastritis**

* Autoimmune gastritis
* Chemical gastropathy, usually related to chronic bile reflux or NSAID and aspirin intake
* Uremic gastropathy

**Gastritises can be classified based on the underlying**

* etiologic agent (eg, Helicobacter pylori, bile reflux, nonsteroidal anti-inflammatory drugs [NSAIDs], autoimmunity, allergic response)
* the histopathological pattern, which may suggest the etiologic agent and clinical course (eg, H pylori–associated multifocal atrophic gastritis).

Other classifications are based on the endoscopic appearance of the gastric mucosa (eg, varioliform gastritis). Although minimal inflammation is observed in some gastropathies, such as those associated with NSAID intake, these entities are discussed in this article because they are frequently included in the differential diagnosis of chronic gastritis.

Sydney classification of gastritis by ethiology:

* Helicobacter gastritis
* Autoimmune gastritis
* Chemical or reactive gastritis
* Idiopatic gastritis
* Special variant of gastritis (Infectious granulomatous gastritis, Chronic noninfectious granulomatous gastritis, Lymphocytic gastritis, Eosinophilic gastritis)

Helicobacter gastritis is a primary infection of the stomach and is the most frequent cause of chronic gastritis. Cases of histologically documented chronic gastritis are diagnosed as chronic gastritis of undetermined etiology or gastritis of undetermined type when none of the findings reflects any of the described patterns of gastritis and a specific cause cannot be identified.

Chemical or reactive gastritis is caused by injury of the gastric mucosa by reflux of bile and pancreatic secretions into the stomach, but it can also be caused by exogenous substances, including NSAIDs, acetylsalicylic acid, chemotherapeutic agents, and alcohol. These chemicals cause epithelial damage, erosions, and ulcers that are followed by regenerative hyperplasia, histologically detectable as foveolar hyperplasia and damage to capillaries, with mucosal edema, hemorrhage, and proliferation of smooth muscle in the lamina propria. Inflammation in these lesions caused by chemicals is minimal or lacking; therefore, the term gastropathy or chemical gastropathy is more appropriate to describe these lesions than is the term chemical or reactive gastritis as proposed by the updated Sydney classification of gastritis. Importantly, mixed forms of gastropathy and other types of gastritis, especially H pylori gastritis, may coexist.

**Pathophysiology**

The pathophysiology of chronic gastritis complicating a systemic disease, such as hepatic cirrhosis, uremia, or another infection, is described in the relevant disease articles. The pathogenesis of the most common forms of gastritis is described as follows.

**1. H pylori–associated chronic gastritis**

H pylori are gram-negative rods that have the ability to colonize and infect the stomach. The bacteria survive within the mucous layer that covers the gastric surface epithelium and the upper portions of the gastric foveolae. The infection usually is acquired during childhood. Once the organism has been acquired, has passed through the mucous layer, and has become established at the luminal surface of the stomach, an intense inflammatory response of the underlying tissue develops.

The presence of H pylori always is associated with tissue damage and the histological finding of both an active and chronic gastritis. The host response to H pylori and bacterial products is composed of T- and B-cell lymphocytes, denoting chronic gastritis, followed by infiltration of the lamina propria and gastric epithelium by polymorphonuclear leukocytes that eventually phagocytize the bacteria. The presence of polymorphonuclear leukocytes in the gastric mucosa is diagnostic of active gastritis.

The interaction of H pylori with the surface mucosa results in the release of proinflammatory cytokine interleukin (IL)-8, which leads to recruitment of polymorphonuclear cells and may begin the entire inflammatory process. Gastric epithelial cells express class II molecules, which may increase the inflammatory response by presenting H pylori antigens, leading to further cytokine release and more inflammation. High levels of cytokines, particularly tumor necrosis factor-a (TNF-a) and numerous ILs (eg, IL-6, IL-8, IL-10), are detected in the gastric mucosa of patients with H pylori gastritis.

Leukotriene levels are also quite elevated, especially leukotriene B4, which is synthesized by host neutrophils and is cytotoxic to gastric epithelium. This inflammatory response leads to functional changes in the stomach, depending on the areas of the stomach involved. When inflammation affects the gastric corpus, parietal cells are inhibited, leading to reduced acid secretion. Continued inflammation results in loss of parietal cells, and the reduction in acid secretion becomes permanent.

Antral inflammation alters the interplay between gastrin and somatostatin secretion, affecting G cells (gastrin-secreting cells) and D cells (somatostatin-secreting cells), respectively. Specifically, gastrin secretion is abnormal in individuals who are infected with H pylori, with an exaggerated meal-stimulated release of gastrin being the most prominent abnormality. When the infection is cured, neutrophil infiltration of the tissue quickly resolves, with slower resolution of the chronic inflammatory cells. Paralleling the slow resolution of the monocytic infiltrates, meal-stimulated gastrin secretion returns to normal.

Differences in virulence factors that characterize different strains of H pylori influence the clinical outcome of H pylori infection. People infected with H pylori strains that secrete the vacuolating toxin A (vacA) are more likely to develop peptic ulcers than people infected with strains that do not secrete this toxin. Another set of virulence factors is encoded by the H pylori pathogenicity island (PAI). The PAI contains the sequence for several genes and encodes the CAGA gene. Strains that produce CagA protein (CagA+) are associated with a greater risk of development of gastric carcinoma and peptic ulcer. However, infection with CagA- strains also predisposes the person to these diseases.

2. H pylori–associated chronic gastritis progresses with the following 2 main topographic patterns that have different clinical consequences:

* Antral predominant gastritis is characterized by inflammation and is mostly limited to the antrum. Individuals with peptic ulcers usually demonstrate this pattern of gastritis.
* Multifocal atrophic gastritis is characterized by involvement of the corpus and gastric antrum with progressive development of gastric atrophy (loss of the gastric glands) and partial replacement of gastric glands by an intestinal-type epithelium (intestinal metaplasia). Individuals who develop gastric carcinoma and gastric ulcers usually demonstrate this pattern of gastritis.

Most of the people who are infected with H pylori do not develop significant clinical complications, and they remain carriers with asymptomatic chronic gastritis. Some individuals who carry additional risk factors may develop peptic ulcer, gastric mucosa–associated lymphoid tissue (MALT) lymphomas, or gastric adenocarcinomas.

**2. Autoimmune gastritis**

This type of gastritis is associated with serum antiparietal and anti-intrinsic factor (IF) antibodies. The gastric corpus undergoes progressive atrophy, IF deficiency occurs, and patients may develop pernicious anemia.

The development of chronic atrophic gastritis limited to corpus-fundus mucosa and marked diffuse atrophy of parietal and chief cells characterize autoimmune atrophic gastritis. Autoimmune gastritis is associated with serum antiparietal and anti-IF antibodies that cause IF deficiency, which, in turn, causes decreased availability of cobalamin and, eventually, pernicious anemia in some patients.

Autoantibodies are directed against at least 3 antigens, including IF, cytoplasmic (microsomal-canalicular), and plasma membrane antigens. Two types of IF antibodies are detected, ie, types I and II. Type I IF antibodies block the IF-cobalamin binding site, thus preventing the uptake of vitamin B-12. Cell-mediated immunity also contributes to the disease. T-cell lymphocytes infiltrate the gastric mucosa and contribute to epithelial cell destruction and resulting gastric atrophy.

**Histologic Findings**

H pylori–associated gastritis can display different levels of severity. H pylori organisms are found within the gastric mucous layer and frequently accumulate in groups of bacteria at the apical side of gastric surface cells, occasionally in the lower portions of the gastric foveolae, and rarely within the deeper areas of the mucosa in association with glandular cells.

Patients with typical cases of infection initially develop chronic active gastritis in which H pylori are observed in both the antrum and corpus, but the organisms usually are more numerous in the antrum. Polymorphonuclear leukocytes infiltrate the lamina propria, glands, surface epithelium, and foveolar epithelium, occasionally spilling into the lumen and forming small microabscesses. Lymphoid aggregates and occasional well-developed lymphoid follicles are observed expanding the lamina propria of the mucosa, and occasional lymphocytes permeate the epithelium.

In disease of longer duration, significant loss of gastric glands is observed, in a condition known as gastric atrophy. Gastric atrophy may result from the loss of gastric epithelial cells that were not replaced by appropriate cell proliferation, or atrophy may result because the epithelium was replaced by intestinal-type epithelium (intestinal metaplasia). In advanced stages of atrophy associated with chronic H pylori infection, both the corpus and antrum display an extensive replacement by intestinal metaplasia that is associated with the development of hypochlorhydria. With expansion of intestinal metaplasia, the number of H pylori organisms that are detectable in the stomach decreases because H pylori is excluded from areas of metaplastic epithelium.

The histological changes of autoimmune atrophic gastritis vary in different phases of the disease. During an early phase, multifocal diffuse infiltration of the lamina propria by mononuclear cells and eosinophils and focal T-cell infiltration of oxyntic glands with glandular destruction occurs. Focal mucous neck cell hyperplasia (pseudopyloric metaplasia) and hypertrophic changes of parietal cells are also observed.

During the florid phase of the disease, increased lymphocytic inflammation, oxyntic gland atrophy, and focal intestinal metaplasia occur. The end stage is characterized by diffuse involvement of the gastric corpus and fundus by chronic atrophic gastritis associated with little intestinal metaplasia. The antrum is spared.

**CLINICAL**

**History**

H pylori infection: Acute H pylori infection usually is not clinically detected, but experimental infection results in a clinical syndrome characterized by epigastric pain, fullness, nausea, vomiting, flatulence, malaise, and (sometimes) fever. The symptoms resolve in about a week whether or not the organism is eliminated. Persistence of the organism causes H pylori chronic gastritis, which usually is asymptomatic but may manifest as gastric pain or, rarely, with nausea, vomiting, anorexia, or significant weight loss. Symptoms may occur with the development of complications of chronic H pylori gastritis, which include peptic ulcers, gastric adenocarcinoma.

Autoimmune gastritis: The clinical manifestations are primarily related to the deficiency in cobalamin, which is not adequately absorbed because of IF deficiency as a result of severe gastric parietal cell atrophy. The disease has an insidious onset and progresses slowly. Cobalamin deficiency affects the hematologic, gastrointestinal, and neurologic systems.

* Hematologic manifestations

The most significant manifestation is megaloblastic anemia, but, rarely, purpura due to thrombocytopenia may develop. Symptoms of anemia include weakness, light-headedness, vertigo and tinnitus, palpitations, angina, and symptoms of congestive failure.

* Gastrointestinal manifestations

The lack of cobalamin is associated with megaloblastosis of the gastrointestinal tract epithelium. Patients sometimes report having a sore tongue. Anorexia with moderate weight loss that is occasionally associated with diarrhea may result from malabsorption associated with megaloblastic changes of the small intestinal epithelial cells.

* Neurologic manifestations

These result from demyelination, followed by axonal degeneration and neuronal death. The affected sites include peripheral nerves, posterior and lateral columns of the spinal cord, and cerebrum. Signs and symptoms include numbness and paresthesias in the extremities, weakness, and ataxia. Sphincter disturbances may occur. Mental function disturbances vary from mild irritability to severe dementia or psychosis. The neurologic disease may occur in a patient with hematocrit and red cell parameters within the reference range.

**Physical**

The physical examination is of little contributory value in chronic gastritis.

However, some findings are specifically associated with the particular complications of H pylori–associated gastritis and autoimmune gastritis.

In uncomplicated H pylori–associated atrophic gastritis, clinical findings are few and nonspecific.

Epigastric tenderness may exist.

If gastric ulcers coexist, guaiac-positive stool may result from occult blood loss.

Bad breath (ie, halitosis) and abdominal pain or discomfort may occur, with bloating associated with bacterial overgrowth syndrome.

Physical findings may result from the development of pernicious anemia and neurologic complications in patients with autoimmune atrophic gastritis.

With severe cobalamin deficiency, the patient is pale and has slightly icteric skin and eyes. The pulse is rapid, and the heart may be enlarged. Auscultation usually reveals a systolic flow murmur.

**Lab Studies**

The diagnosis of chronic gastritis can only be ascertained histologically. Therefore, histological assessment of endoscopic biopsies is essential. The identification of the underlying cause of chronic gastritis and the assessment of specific complications can require several laboratory tests.

Atrophic gastritis may be assessed by measuring serum levels of the pepsinogen I–to–pepsinogen II ratio. Pepsinogen I (PGA, PGI) and pepsinogen II (PGC, PGII) are synthesized and secreted by gastric chief cells. After secretion into the gastric lumen, they are converted into proteolytic active pepsins. The level of PGA in the serum decreases as loss of gastric chief cells during gastric atrophy occurs, resulting in a decreased PGI/PGII ratio. Gastric carcinoma occurs, especially the intestinal type, usually in association with severe atrophic gastritis. Measuring the levels of pepsinogen I and II and the pepsinogen I/II ratio in the serum is useful for screening atrophic gastritis and gastric cancer in regions with high incidence of these diseases. Pepsinogen determination is especially useful in epidemiological studies; however, the sensitivity and specificity of the assay is relatively low, with 84.6% and 73.5% values, respectively, reported in a recent study.

Rapid urease test from gastric biopsy tissue

Bacterial culture of gastric biopsy: This is usually performed in the research setting or to assess antibiotic susceptibility in patients for whom first-line eradication therapy fails.

* Procedures

Performing an upper GI endoscopy is essential to establish a diagnosis of gastritis.

Although some studies have suggested that H pylori infection can be determined on the basis of unique endoscopic features, particularly the presence of antral nodularity, a specific relationship between H pylori and macroscopic features remains controversial. The endoscopic findings in chronic H pylori infection may include areas of intestinal metaplasia. Sample multiple biopsies. Tissue sampling from both the gastric antrum and corpus is essential to establish the topography of gastritis and to identify atrophy and intestinal metaplasia, which usually is patchy.

**Diagnosis of autoimmune gastritis**

Antiparietal and anti-IF antibodies in the serum

Achlorhydria, both basal and stimulated, and hypergastrinemia

Low serum cobalamin (vitamin B-12) levels (<100 pg/mL)

Possible abnormal result on Schilling test (can be corrected by IF)

**Diagnosis of H pylori–associated gastritis:**

The criterion standard method to assess whether H pylori is the underlying cause of gastritis is histological identification of the organism. Histological examination is also used to evaluate the degree and distribution of gastritis. Obtain at least 2 biopsies from the gastric antrum, 2 from the corpus, and 1 from the incisura.

Special stains to identify H pylori, such as Warthin-Starry, Giemsa, or Genta stain, may be necessary when the organisms are not observed and chronic gastritis is obvious.

At late stages of infection with extensive atrophic gastritis, the numbers of H pylori organisms are markedly decreased because intestinal metaplasia creates an unfavorable environment for H pylori. In these cases, other tests, such as the urea breath test, and serological evidence of infection may provide evidence for H pylori infection.

**TREATMENT**

**Medical Care**

Treatment of chronic gastritis can be directed to a specific etiologic agent, when it is known. In other situations in which gastritis represents gastric involvement of a systemic disease, treatment is targeted to the primary disease.

The treatment approach for H pylori infection is described in detail in this article and elsewhere. Treatment for other diseases is detailed in specific disease articles.

Some entities manifested by chronic gastritis do not have well-established treatment protocols. For example, in lymphocytic gastritis, some cases of spontaneous healing have been reported. However, because the disease has a chronic course, treatment is recommended. Some studies have reported successful treatment of exudative lymphocytic gastritis with omeprazole. Until recently, specific recommendations for H pylori eradication were limited to peptic ulcer disease. However, at the Digestive Health Initiative (DHI) International Update Conference on H pylori held in the United States, the recommendations for H pylori testing and treatment were broadened. H pylori testing and eradication of the infection were also recommended after resection of early gastric cancer and for low-grade MALT lymphoma. Further, if H pylori infection is identified as the underlying cause of gastritis, the idea that eradication of the organism should follow is now almost generally accepted.

H pylori infection is not easily cured, and research has shown a need for multidrug therapy. H pylori are bacteria that infect the mucosal surface. As with other bacterial infections, the mainstay of therapy is antimicrobials to which the bacterium is sensitive. The antibiotics that have proven effective include clarithromycin, amoxicillin, metronidazole, tetracycline, and furazolidone. Cure rates with single antibiotic agents have been poor, ranging from 0-35%. Monotherapy is associated with the rapid development of antibiotic resistance, especially to metronidazole and clarithromycin.

Five regimens are approved by the FDA for the treatment of H pylori infection. A version of the traditional bismuth, metronidazole, tetracycline (BMT) triple therapy has been approved and is available commercially as Helidac. The regimen combines a histamine 2 (H2) receptor antagonist, bismuth subsalicylate, metronidazole, and tetracycline, which are administered for 14 days. The antibiotics and bismuth are provided in a convenient dose pack that is thought to enhance compliance. Three different combinations using clarithromycin have been approved, including 2 dual therapies consisting of 500 mg of clarithromycin 3 times daily plus either omeprazole or ranitidine bismuth citrate ([RBC] Tritec). The cure rates reported in the packaging literature suggest that the 3 combinations are similarly effective. Clinical experience has shown that the ranked order of effectiveness is the BMT triple therapy, RBC plus clarithromycin, followed by omeprazole plus clarithromycin.

Because higher success rates can be achieved when a third drug is added to the dual therapies, most authorities now recommend triple drug combinations. This recommendation has been confirmed by the recent approval of the combination of a proton pump inhibitor (PPI), lansoprazole (Prevacid), plus clarithromycin and amoxicillin. The cure rate with this combination is greater than 85%. Lansoprazole plus amoxicillin was also approved, but the tremendous variability with this dual therapy makes it a very poor choice.

Currently, the most widely used efficient therapies to eradicate H pylori are triple therapies, and they are recommended as first-line treatments; quadruple therapies are recommended as second-line treatment when triple therapies fail to eradicate H pylori. In both cases, the best results are achieved by administering therapy for 10-14 days, although some studies have limited the duration of treatment to 7 days. The accepted definition of a cure is that no evidence of H pylori exists for 4 or more weeks after ending the antimicrobial therapy.

Prognosis is related to the underlying cause of gastritis.

Chronic gastritis associated with H pylori may exist as an asymptomatic process for the entire life of the individual, or it may manifest by nonspecific dyspeptic symptoms or by specific complications.

Eradication results in rapid curing of the infection with disappearance of the neutrophilic infiltration of the gastric mucosa.

Disappearance of the lymphoid component of gastritis might take several months after treatment.

Results from studies evaluating the evolution of atrophic gastritis after eradication of H pylori have been conflicting.

Follow-up for as long as several years after H pylori eradication has not demonstrated regression of gastric atrophy in most studies, while others report improvement in the extent of atrophy and intestinal metaplasia.

Another important question is whether H pylori eradication in a patient with atrophic gastritis reduces the risk of gastric cancer development. Limited data are available, but a prospective study in a Japanese population reported that H pylori eradication in patients with endoscopically resected early gastric cancer resulted in the decreased appearance of new early cancers, while intestinal-type gastric cancers developed in the control group without H pylori eradication. These findings support an intervention approach with eradication of H pylori if the organisms are detected in patients with atrophic gastritis; the goal is to prevent the development of gastric cancer.

**GASTRIC ULCERS**

Peptic ulcer disease (PUD) is one of the most common diseases affecting the GI tract. It causes inflammatory injuries in either the gastric or duodenal mucosa, with extension beyond the submucosa into the muscularis mucosa. The etiologies of this condition are multifactorial and are rarely related simply to excessive acid secretion. Even though gastric ulcer is a common disease, diagnosis can be difficult because it has a wide spectrum of clinical presentations, ranging from asymptomatic to vague epigastric pain, nausea, and iron-deficiency anemia to acute life-threatening hemorrhage.

**Frequency**

In the US: The annual incidence of gastric ulcer is largely determined from the statistics of the pre–H pylori era (prior to 1979). It is estimated to affect 0.92% of the population, or, 1.6 million persons. Epidemiological studies show that from 1970-1985, a marked decrease in the rate of duodenal ulcer occurred, while the rate of gastric ulcer remained stable. People with low socioeconomic status are more likely to acquire H pylori infection. Infected individuals are 3 times more likely to develop gastric ulcer compared to those unexposed to the bacteria.

Internationally: In Denmark, lifetime prevalence of gastric cancer is 1.2% for men and 0.6% for women. The annual incidence of gastric ulcers varies from approximately 1 case per 1000 population in Japan to 1.5 cases per 1000 population in Norway to 2.7 cases per 1000 population in Scotland.

In the United States, the prevalence of gastric ulcer has shifted in the past 2 decades, from a disease predominantly affecting males to one that is equally present in both sexes. The male-to-female ratio is 1:1 in the United States and 18:1 in India.

The incidence of gastric ulcer increases with age because of a combination of increasing NSAID use and a high prevalence of H pylori infection in persons older than 50 years. The prevalence of H pylori in elderly individuals is the result of a cohort effect of the generally poorer socioeconomic condition in the United States in past decades compared to today.

**Causes**

The 2 major etiological factors for PUD are H pylori infection and the consumption of NSAIDs.

Currently, 70% of all gastric ulcers in the United States can be attributed to H pylori infection.

NSAID-induced ulcers account for approximately 25% of gastric ulcers, and PUD is believed to develop secondary to the decrease in prostaglandin production resulting from the inhibition of cyclooxygenase.

A rare cause of PUD is Zollinger-Ellison syndrome (ie, gastrinoma).

**Pathophysiology**

The normal stomach maintains a balance between the protective factors (ie, mucus and bicarbonate secretion, blood flow) and aggressive factors (ie, acid secretion, pepsin). Gastric ulcers develop when aggressive factors overcome the protective mechanism.

The 2 major etiological factors for PUD are Helicobacter pylori infection and the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs).

Currently, 70% of all gastric ulcers occurring in the United States can be attributed to H pylori infection. In addition to an increase in acid secretion, H pylori also predisposes patients to PUD by disrupting mucosal integrity. The bacterium's spiral shape and flagella facilitate its penetration into the mucous layer and its attachment to the epithelial layer. Subsequently, it releases phospholipase and proteases, which cause further mucosal damage. A cytotoxin-associated gene (cag A) has been isolated in approximately 65% of the bacteria. The products of this gene are associated with more severe gastritis, gastric ulcer, gastric cancer, and lymphoma.

Cigarette smoking can affect gastric mucosal defense adversely. Cigarette smoking is believed to play a facultative role in H pylori infection, ie, people who smoke tend to develop frequent and recurrent ulcers and their ulcers are more resistant to therapy. No evidence indicates that dietary habits or alcohol consumption predisposes individuals to gastric ulcer.

NSAID-induced ulcers account for approximately 25% of gastric ulcers, and they are believed to be secondary to a decrease in prostaglandin production resulting from the inhibition of cyclooxygenase. The greatest risk of developing an ulcer occurs during the first 3 months of NSAID use; thereafter, the risk decreases but continues to be present. Whether concurrent H pylori infection and NSAID use are synergistic in producing gastric ulcers remains unclear.

A rare cause of PUD is Zollinger-Ellison syndrome (ie, gastrinoma). The hallmark of Zollinger-Ellison syndrome is the profound hypersecretion of gastric acid. Significant disruption of the mucosal integrity often results in multiple duodenal and gastric ulcers.

* Histologic Findings

The histology of gastric ulcer depends on its chronicity. The surface is covered with slough and inflammatory debris. Beneath this neutrophilic infiltration, active granulation with mononuclear leukocytic infiltration and fibrinoid necrosis may be seen. In chronic superficial gastritis, lymphocytes, monocytes, and plasma cells often infiltrate the mucosa and submucosa.

**CLINICAL**

**History**

Patients may present with a wide variety of symptoms, or they may remain completely asymptomatic.

Gastric and duodenal ulcers usually cannot be differentiated based on history alone.

The pain from gastric ulcer is typically located in the epigastrium; however, it can also be perceived in the right upper quadrant.

Pain with radiation to the back is suggestive of a posterior penetrating gastric ulcer complicated by pancreatitis.

Classic gastric ulcer pain is described as pain occurring shortly after meals, for which antacids provide minimal relief.

Patients with bleeding gastric ulcers may give a history of hematemesis, melena, or episodes of presyncope.

**Physical**

Physical examination usually is not helpful.

Epigastric tenderness may or may not be present.

Right upper quadrant tenderness may suggest a biliary etiology or, less frequently, PUD.

In the presence of gastric outlet obstruction, abdominal distension and succussion splash may be found.

A palpable mass should raise the suggestion of a gastric malignancy.

Involuntary guarding is indicative of peritonitis secondary to gastric perforation.

**Lab Studies**

The diagnosis of gastric ulcer can be made based on a characteristic clinical history; however, a high index of suspicion for gastric ulcer is needed in patients without risk factors for PUD.

Routine laboratory tests, such as complete blood cell count and iron studies, can help detect anemia, which is an alarm signal and mandates early endoscopy to rule out PUD or other sources of chronic GI blood loss.

The diagnosis of gastric ulcer can be confirmed by performing high-quality video endoscopy and obtaining multiple mucosal biopsy specimens.

**Imaging Studies:**

* Upper GI radiography

A double-contrast barium study performed by an expert GI radiologist has equivalent accuracy in diagnosing a typical gastric ulcer. However, diagnostic biopsies cannot be performed with radiological studies, and radiographic evidence of a healing ulcer is not adequate to rule out gastric cancer.

Benign gastric ulcers are normally found on the lesser curvature, although they can occur anywhere in the stomach. These ulcers tend to project beyond the contour of the stomach, with radiating folds extending to the ulcer margin.

In contrast, malignant ulcers usually have irregular heaped-up margins that protrude into the lumen of the stomach.

**Other Tests**:

H pylori testing: A strong relationship exists between PUD and H pylori infection. Therefore, to prevent recurrence of ulcer disease, diagnosing and eradicating H pylori infection is important. H pylori infection can be diagnosed using various invasive or noninvasive methods.

**Invasive tests**

* Biopsy

Identification of the organism in an endoscopically obtained biopsy specimen remains the criterion standard for diagnosis of H pylori infection. Routinely, 2 biopsy samples are obtained from the antrum and the body of the stomach. Gastritis is apparent on routine histological slides stained with hematoxylin and eosin; however, special staining with Giemsa or Warthin-Starry silver stain provides almost 100% accuracy.

* Culture

This is the most specific method; however, it is not routinely performed in clinical practice because of the fastidious nature of the organism.

* Rapid urease test

This test contains urea-impregnated agar and a pH indicator that changes color if urease is present in the biopsy sample. This test is quick and accurate, with a sensitivity and specificity of higher than 90%.

**Noninvasive tests**

* Antibody testing

 Serological testing is simple and widely available, although it is of limited value because findings cannot be used to differentiate between past exposure and active infection.

* Urea breath testing

This test is useful for documenting the eradication of H pylori after treatment. H pylori produces a large amount of urease. Patients ingest carbon-labeled urea (ie, carbon 13 or carbon 14) that is broken down by urease with release of the labeled carbon. A failure to detect exhaled labeled carbon dioxide confirms the eradication of the bacteria.

* Stool antigen

This test helps identify bacterial antigens in stool and has recently been approved by the US Food and Drug Administration. It has been shown to be extremely accurate for helping diagnose infection or document eradication.

**Procedures:**

* Esophagogastroduodenoscopy

The ability to directly visualize the mucosa makes endoscopy the preferred modality for the diagnosis of gastric ulcer and gastric cancer.

A repeat endoscopy after 6 weeks of therapy is recommended to confirm healing of a gastric ulcer and to help definitively rule out gastric malignancy.

Upper endoscopy with biopsy is the most sensitive and specific method for diagnosing esophageal and gastric cancer.

A single biopsy offers 70% accuracy in diagnosing gastric cancer, but 7 biopsy samples obtained from the base and ulcer margins increase the sensitivity to 99%.

Brush cytology has been shown to increase the biopsy yield, and this method may be useful particularly when bleeding is a concern in a patient with coagulopathy.

**Gross appearance**

Gastric ulcer is a discrete mucosal lesion with a punched-out smooth ulcer base, which often is filled with whitish fibrinoid exudates. Ulcers tend to be solitary and well circumscribed and usually are 0.5-2.5 cm in diameter.

Most gastric ulcers tend to occur at the junction of the fundus and antrum, along the lesser curvature.

Benign ulcers tend to have a smooth, regular, rounded edge with a flat smooth base and surrounding mucosa that shows radiating folds.

Malignant ulcers usually have irregular heaped-up or overhanging margins. The ulcerated mass often protrudes into the lumen, and the folds surrounding the ulcer crater are often nodular and irregular.

**TREATMENT**

**Diet**

Insufficient data exist to support any special diet for the healing of gastric ulcers. In the event of acute upper GI bleeding, patients should be kept without food for the initial 24 hours so that endoscopic evaluation can be expedited without fear of aspiration.

**Activity**

Normal activity is encouraged.

**Medical Care**

The medical treatment of gastric ulcers is aimed at restoring the balance between the aggressive (acid secretion) and mucosal protective factors. In patients infected with H pylori, the most effective treatment is therapy to eradicate the organism and therapy for acid suppression.

* Histamine 2 blockers

Therapy can be directed toward histamine release, ie, H2 blockers, such as cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), and nizatidine (Axid). These agents selectively block the H2 receptors in the parietal cells.

All H2 blockers are comparable in efficacy and, when used in twice-daily doses for a period of 8 weeks, have a healing rate of higher than 70%.

* Hydrogen pump antagonists or proton pump inhibitors

Proton pump inhibitors (PPIs) are drugs that covalently bind and irreversibly inhibit the H+/K+ adenosine triphosphatase (ATPase) pump, effectively inhibiting acid release. Omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), and pantoprazole (Protonix) given in daily or twice-daily doses for 4 weeks heal 80-100% of gastric ulcers if H pylori infection is not present or has been eradicated.

All PPIs seem to have equal efficacy. The PPI should be taken on an empty stomach to allow maximum inhibition of H+/K+ pumps. Prilosec binds irreversibly with the H+/K+ pumps and suppresses acid secretion. This inhibition is at its maximum in 24-48 hours, and when Prilosec is stopped, the secretory activity gradually returns to normal in the next 2-3 days.

* Mucosal protectants

Mucosal protectants, such as bismuth and sucralfate, can also be effective in healing gastric ulcers; however, they are not as effective as H2 blockers.

Patients taking NSAIDs should discontinue them if possible. If discontinuing NSAIDs is not possible, omeprazole at 40 mg/d should be given concurrently. However, only misoprostol (Cytotec) has been shown to be cytoprotective when taken with NSAIDs. The use of misoprostol is limited by adverse effects, including diarrhea and abdominal pain observed in 14-40% of patients, and because it is administered in 4 doses/d.

**H pylori eradication**

Multiple regimens have been evaluated for the eradication of H pylori infection; however, triple therapy consistently has been shown to eradicate the organism more than 90% of the time.

The 5 different regimens approved by American College of Gastroenterology are as follows (all 5 regimens are given for a total of 2 wk):

1. Bismuth, metronidazole, and tetracycline qid with H2 blockers bid

2. Bismuth, metronidazole, and tetracycline bid with a PPI

3. Prilosec, amoxicillin, and clarithromycin bid

4. Prilosec, metronidazole, and clarithromycin bid

5. Ranitidine, bismuth, and clarithromycin with amoxicillin, metronidazole, or tetracycline bid

* Endoscopic therapy

Upper GI bleeding secondary to a bleeding peptic ulcer is a common medical condition. Endoscopic evaluation of the bleeding ulcer can decrease the duration of the hospital stay by identifying patients at low risk for rebleeding. Moreover, endoscopic therapy can reduce mortality, reduce the likelihood of recurrent bleeding, and decrease the need for surgery.

**Surgical Care**

With the advent of aggressive PPI use, effective therapy for H pylori infection, and advanced endotherapy, most ulcers can be managed effectively with medical treatment. However, surgery still has a role in life-threatening hemorrhage that cannot be controlled with medical management alone.

Other indications for surgical therapy are ulcer perforation, gastric outlet obstruction, giant gastric ulcer, and a transfusion requirement of more than 6 units in 24 hours.

 **MEDICATION**

PPIs given daily or twice daily have an ulcer-healing rate of 80-100% and are the most effective drugs used to treat gastric ulcers. H2 blockers and mucosal protectants (ie, sucralfate, bismuth) are also effective.

Proton pump inhibitors -- These agents act by irreversibly binding the H+/K+-ATPase pump and effectively suppressing acid secretion.

Omeprazole (Prilosec) -- Decreases gastric acid secretion by inhibiting the parietal cell H+/K+-ATPase pump. Indicated for gastric ulcers, duodenal ulcers, GERD, erosive esophagitis, and for eradication of H pylori when combined with other medications.

Adult Dose 40 mg PO qd for 4-8 wk

Lansoprazole (Prevacid) -- Inhibits gastric acid secretion. Indicated for gastric ulcers, duodenal ulcers, GERD, erosive esophagitis, and for eradication of H pylori when combined with other medications.

Adult Dose 15-30 mg PO qd for 4-8 wk

Rabeprazole (Aciphex) -- For short-term (4-8 wk) treatment and relief of symptomatic erosive or ulcerative GERD. If not healed after 8 wk, consider additional 8-wk course.

Adult Dose 20 mg DR tab PO qd for 4-8 wk

Pantoprazole (Protonix) -- Indicated for short-term treatment of GERD associated with erosive esophagitis. Also effective in treating gastric ulcers, including those caused by H pylori. Adult Dose 40 mg PO qd

Esomeprazole magnesium (Nexium) -- S-isomer of omeprazole. Inhibits gastric acid secretion by inhibiting H+/K+-ATPase pump at secretory surface of gastric parietal cells.

Adult Dose 40 mg PO qd for 10 d

Histamine 2 blockers -- These drugs inhibit histamine stimulation of H2 receptor in gastric parietal cells.

Nizatidine (Axid) -- Effectively reduces gastric acid secretion, gastric volume, and hydrogen concentrations.

Adult Dose 75 mg PO bid 30-60 min ac or with beverages

Ranitidine hydrochloride (Zantac) -- Effectively reduces gastric acid secretion, gastric volume, and hydrogen concentrations.

Adult Dose 150 mg PO bid; not to exceed 600 mg/dAlternatively, 50 mg/dose IV/IM q6-8h

**Helicobacter pylori eradication agents**

Antibiotics and other agents are used as adjuvants to treat duodenal ulcer disease associated with H pylori.

Clarithromycin (Biaxin) -- Component of drug combination therapy that effectively treats duodenal ulcer or gastric ulcer associated with H pylori infection. Inhibits bacterial growth, possibly by blocking dissociation of peptidyl t-RNA from ribosomes, causing RNA-dependent protein synthesis to arrest.

Adult Dose 250-500 mg PO q12h for 7-14 d

Metronidazole (Flagyl) -- Component of drug combination therapy that effectively treats duodenal ulcer or gastric ulcer associated with H pylori infection. Active against various anaerobic bacteria and protozoa. Appears to be absorbed into cells. Intermediate-metabolized compounds formed bind DNA and inhibit protein synthesis, causing cell death.

Adult Dose 250 mg PO qid

Tetracycline (Sumycin) -- Component of drug combination therapy that effectively treats duodenal ulcer or gastric ulcer associated with H pylori infection. Treats gram-positive and gram-negative organisms and mycoplasmal, chlamydial, and rickettsial infections.

Adult Dose 250 mg PO qid for 14 d

Amoxicillin (Trimox) -- Component of drug combination therapy that effectively treats duodenal ulcer or gastric ulcer associated with H pylori infection. Interferes with synthesis of cell wall mucopeptides during active multiplication, resulting in bactericidal activity against susceptible bacteria.

Adult Dose 500 mg PO qid for 14 d

Bismuth subsalicylate (Pepto-Bismol) -- Component of drug combination therapy that effectively treats duodenal ulcer or gastric ulcer associated with H pylori infection. Antimicrobial and cytoprotective effects produced by bismuth and subsalicylate.

Adult Dose 2 tab or 30 mL PO qid

Gastrointestinal agents -- These agents protect GI lining. Shown to be effective in treating peptic ulcers and preventing relapse. Mechanism of action not clear. Multiple doses are required, and agents are not as effective as other options.

Sucralfate (Carafate) -- Forms viscous adhesive substance that protects GI lining against pepsin, peptic acid, and bile salts. Use for short-term management of ulcers.

Adult Dose 1 g PO qid

**Further Inpatient Care:**

Patients who have a rebleeding episode while in the hospital should have a second endoscopy prior to surgical management. Patients should continue taking H2 blockers or PPIs for at least 8 weeks.

**Further Outpatient Care:**

Patients should be reevaluated in 6-8 weeks with a repeat endoscopy to document complete healing of the gastric ulcer. If the ulcer is not healed, multiple biopsies of the ulcer are indicated to conclusively rule out gastric malignancy.

**Prevention:**

In patients with gastric ulcers, documenting the eradication of H pylori with a urea breath test, rapid urease test, or histology studies on a biopsy sample is imperative. If H pylori is not eradicated, treatment should be repeated with another regimen.

**Complications:**

Complications of gastric ulcers include hemorrhage, perforation, and gastric outlet obstruction.

Patients with gastric ulcers are also at risk of developing gastric malignancy.

The risk is approximately 2% in the initial 3 years.

One of the important risk factors is related to H pylori infection. H pylori is associated with atrophic gastritis, which, in turn, predisposes to gastric cancer.

H pylori infection is associated with gastric lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma. The normal gastric mucosa is devoid of organized lymphoid tissue. H pylori infection promotes acquisition of lymphocytic infiltration and often forms lymphocytic aggregates and follicles from which MALT lymphoma develops. Eradication of H pylori is very important in this group of patients because eradication of H pylori has been shown to cause a remission of MALT lymphoma.

**Prognosis:**

The prognosis of patients with benign gastric ulcers is excellent, especially if H pylori is completely eradicated and NSAIDs are avoided.

Patients with recurrent gastric ulcers should be questioned in detail about NSAID use (particularly over-the-counter varieties), and endoscopy with biopsies should be repeated to help rule out malignancy and to check for the persistence of H pylori. If H pylori is still present, it should be re-treated.

Malignancy should be strongly considered in the case of a persistent nonhealing gastric ulcer. Endoscopic ultrasound examination may be helpful for assessing mucosal invasion or detecting associated adenopathy in such patients. Surgical resection should be considered if evidence of cancerous transformation is present.

**DUODENAL ULCERS**

Duodenal ulcer (DU) is a common condition characterized by the presence of a well-demarcated break in the mucosa that may extend into the muscularis propria of the duodenum. More than 95% of DUs are found in the first part of the duodenum; most are less than 1 cm in diameter.

Proper diagnosis of DU is important because prompt initiation of treatment can effectively prevent potentially serious complications.

**Frequency**

In the: Currently, the prevalence of DU is estimated at 6-15% in the general population of US. Most of these cases do not have clinically significant ulcer disease. Prevalence is linked to the presence of H pylori. In younger men, approximately 10% of individuals are colonized with H pylori, and the proportion of people with the infection increases steadily with age.

As in the United States, disease prevalence is linked to H pylori infection. Wide variability in the prevalence of H pylori infection exists among countries and even in regions within countries.

Over the last several years, a trend toward increasing incidence of DU in females and decreasing incidence in males has been observed, especially younger males, in whom the prevalence of H pylori infection is decreasing.

Historically, DU was believed to be more common in men. Today, the prevalence is probably equal in men and women.

The prevalence of DU increases with age. This is probably related to the increased prevalence of H pylori infection in older age groups, coupled with increased use of NSAIDs.

**Causes**

The understanding of the etiology of DU has changed dramatically in the latter part of the 20th century. Historically, DU was thought to be a disease related to diet and environmental stress alone. Subsequent studies revealed the importance of pepsin and acid secretion in the pathogenesis of DU. The most revolutionary change in the knowledge of DU was the discovery in 1982 that the bacterium H pylori was present in most patients with DU.

* **H pylori**

H pylori are small, microaerophilic, spiral-shaped, gram-negative rods. The presence of H pylori in the stomach and duodenum probably is the most common bacterial infection in the world. H pylori infection is generally regarded as the most important etiologic factor in the development of DU. Most authors regard H pylori as the cause of 85-95% of DUs.

H pylori can be cultured from up to 95% of DUs. Moreover, areas with a higher prevalence of H pylori infection have a higher incidence of DU. Several mechanisms exist by which the bacterium can induce duodenal mucosal damage. All evidence supports the assertion that H pylori is the major cause of DU. However, the risk of developing a DU in an individual infected with H pylori is only about 1% per year, and only 10-15% of individuals with H pylori infection develop a DU at any point in life. Therefore, other pathogenic factors must function either independently or in concert with H pylori to produce DUs.

* **Other pathogenic factors**

In up to one third of patients with DU, basal acid output (BAO) and maximal acid output (MAO) are increased. In one study, increased BAO and MAO were associated with odds ratios of up to 3.5 and 7, respectively, for the development of DU. People at especially high risk are those with BAO greater than 15 mEq/h. The increased BAO may reflect the fact that, in a significant proportion of patients with DU, the parietal cell mass is increased to nearly twice the reference range.

In addition to increased gastric and duodenal acidity observed in some patients with DU, accelerated gastric emptying is often present in these patients. This leads to a higher acid load delivered to the first part of the duodenum, where 95% of DUs are located. Acidification of the duodenum leads to gastric metaplasia, which indicates replacement of duodenal villous cells with cells that share morphologic and secretory characteristics of gastric epithelium. Gastric metaplasia may create an environment that is well suited to colonization by H pylori.

Evidence that H pylori preferentially colonize gastric-type mucosa exists. Therefore, host characteristics, such as increased MAO and BAO and more rapid gastric emptying, may lead to duodenal epithelial damage followed by histologic change. This histologic change may be the mechanism that allows colonization with H pylori and subsequent development of DU. Because of these findings, some physicians regard gastric and duodenal acidity as the major etiologic factors and H pylori–induced damage simply is a consequence of increased acidity.

* Nonsteroidal anti-inflammatory drugs

Long before the discovery of H pylori, NSAIDs were known to be associated with GI toxicity, including the formation of GU and DU.

As many as 4-10% of patients on daily therapeutic-dose NSAIDs develop a DU within 3 months of initiation of therapy, and up to 1% of these DUs are clinically significant.

A clear dose-response relationship exists, with higher doses associated with increased risk of duodenal mucosal damage. Clinically, NSAID-induced DUs are more likely to bleed. In one study, NSAID use was associated with a relative risk for bleeding of 8.4, as opposed to only 1.5 for H pylori–associated DUs. Patients taking NSAIDs, especially elderly individuals, are more likely to present with a previously asymptomatic bleeding DU.

Factors associated with increased risk of DU in the setting of NSAID use are older age, female sex, high NSAID dose, long-term NSAID use, and severe comorbid illnesses. Corticosteroids do not increase the risk of DU by themselves, but risk of DU is increased when corticosteroids are used in combination with NSAIDs compared to NSAID use alone.

* H pylori–negative DU

Virtually all non–H pylori-related DUs were assumed to be secondary to NSAID use. However, H pylori–negative DUs have received much attention recently, and some studies have shown that the proportion of H pylori–related DUs is significantly less than the commonly reported 85-95%. One study examined 2400 endoscopically proven, non–NSAID-related DUs and found that only 73% patients were positive for H pylori. However, other studies have produced conflicting results, and one study found that antibiotic use within 1 month of diagnosis may have resulted in falsely negative results.

Non–H pylori DUs that are not related to NSAID use may be more common than was appreciated previously. This would support the assertion that the acid hypersecretion and rapid gastric emptying observed in many patients with DU are the most important risk factors.

Lifestyle factors influencing development of DU

* Smoking

Evidence that tobacco use is a risk factor for DU is not conclusive. Evidence supporting a pathogenic role for smoking in the development of DU comes from the finding that smoking may accelerate gastric emptying and decrease pancreatic bicarbonate production. However, studies evaluating smoking as a risk factor for DU have produced contradictory findings. In one prospective study of more than 47,000 men with DU, smoking did not emerge as a risk factor.

* Alcohol

Ethanol is known to cause gastric mucosal irritation and nonspecific gastritis. Evidence that consumption of alcohol represents a risk factor for development of DU is inconclusive. A prospective study of more than 47,000 men with DU did not find an association between alcohol intake and DU.

* Caffeine

Little evidence supports caffeine intake as associated with increased risk of DU.

* Diet

Historically, diet was considered one of the primary causes of PUD. However, current knowledge indicates that diet probably has little influence on the pathogenesis of DU. Deficiency of certain essential fatty acids necessary for prostaglandin production has been examined as a possible risk factor. Moreover, some physicians hypothesize that regional variability of DU prevalence not directly related to H pylori prevalence may be related to diet. In general, evidence linking diet and DU is weak.

* Genetics

More than 20% of patients with DU have a family history of DU, compared with only 5-10% of control groups. In addition, weak associations have been observed between DU and blood type O. Furthermore, patients who do not secrete ABO antigens in their saliva and gastric juice are known to be at higher risk. The reason for these apparent genetic associations is unclear.

A rare genetic association exists between familial hyperpepsinogenemia type I (a genetic phenotype leading to enhanced secretion of pepsin) and DU. However, H pylori can increase pepsin secretion, and a retrospective analysis of the sera of one family studied prior to the discovery of H pylori revealed that their high pepsin levels were more likely related to H pylori infection.

**Other causes of DU**

* Acid hypersecretory syndromes

Gastrinoma (Zollinger-Ellison syndrome [ZES]): First described in 1955, ZES is caused by a tumor of pancreatic islet cells that produces gastrin. It is associated with gastric acid hypersecretion and development of PUD. From 0.1-1% of DUs are thought to be secondary to an underlying gastrin-secreting tumor.

* Systemic mastocytosis

Systemic mastocytosis is a disease associated with diffuse infiltration of the skin, GI tract, bone marrow, spleen, and liver with mastocytes. Gastric acid hypersecretion occurs in response to histamine production by mastocytes.

* Basophilia

In the setting of a myeloproliferative disorder, basophilia can be associated with DU secondary to histamine production, as is systemic mastocytosis. This tends to occur more frequently after chemotherapy-induced cell lysis causing increased release of histamine from cells.

* Infection

Some evidence suggests that herpes simplex virus-1 (HSV-1) and cytomegalovirus (CMV) may be associated with DU and GU in a minority of patients.

* Chemotherapy

Chemotherapeutic agents, such as 5-fluorouracil, methotrexate, and cyclophosphamide, have been associated with development of DU.

* Crack cocaine: Use of crack cocaine causes localized vasoconstriction, and the reduced blood flow may lead to mucosal damage.

**Pathophysiology**

The duodenal mucosa resists damage from the effect of aggressive factors, such as gastric acid and the proteolytic enzyme pepsin, with the help of several protective factors such as a mucous layer, bicarbonate secretion, and protective prostaglandins.

The epithelial cells of the stomach and duodenum secrete mucus in response to irritation of the epithelial lining and as a result of cholinergic stimulation. A portion of the gastric and duodenal mucus exists in the form of a gel layer, which is impermeable to acid and pepsin. Other gastric and duodenal cells secrete bicarbonate, which aids in buffering acid that lies near the mucosa. Prostaglandins of the E type (PGE) have an important protective role because PGE increases the production of both bicarbonate and the mucous layer.

A DU occurs when an alteration occurs in the aggressive and/or protective factors such that the balance is in favor of gastric acid and pepsin. Any process that increases gastric acidity (eg, individuals with increased maximal and basal acid output), decreases prostaglandin production (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]), or interferes with the mucous layer (eg, Helicobacter pylori infection) can cause such an imbalance and leads to peptic ulcer disease.

Full understanding of the pathophysiology and pathogenesis of DU requires a brief discussion of the 2 major etiologies: **NSAID use and H pylori infection.**

1. NSAIDs are pathogenic through their inhibition of the cyclooxygenase-1 (COX-1) pathway, which normally produces protective prostaglandins.

2. Infection with H pylori likely is pathogenic through a variety of mechanisms, including the following:

* H pylori are urease-producing organisms. Urease hydrolyzes urea to ammonia and carbon dioxide. Hydroxide ions produced by equilibration of ammonia with water may damage the gastric and duodenal mucosa.
* H pylori produce proteins that may serve as chemotactic factors for neutrophils and monocytes, which act as proinflammatory cells.
* H pylori also affect the gastric and duodenal mucous layer because these organisms produce proteases that degrade the protective mucous layer.

**CLINICAL**

**History**

Patients with DU have a variety of clinical presentations, ranging from individuals who are completely asymptomatic to those who develop severe complications such as GI hemorrhage. Some generalizations can be made with respect to common clinical presentations of DU.

Some of the common symptoms in patients with DU are described below.

* Epigastric pain can be sharp, dull, burning, or penetrating.
* Many patients experience a feeling of hunger.
* The pain may radiate into the back.
* Twenty to 40% of patients describe bloating, belching, or symptoms suggestive of gastroesophageal reflux.
* Ulcer-related pain generally occurs 2-3 hours after meals and often awakens the patient at night. This pattern is believed to be the result of increased gastric acid secretion, which occurs after meals and during the late night and early morning hours when circadian stimulation of gastric acid secretion is the highest.
* Fifty to 80% of patients with DU experience nightly pain, as opposed to only 30-40% of patients with GU and 20-40% of patients with nonulcer dyspepsia (NUD).

Pain is often relieved by food, a finding often cited as being specific for DU. However, this symptom is present in only 20-60% of patients with DU and is probably not specific for DU.

The pain of DU generally is episodic in nature; however, the pain can evolve into a chronic, daily occurrence in some patients. A change in the patient's usual pattern of ulcer pain should be considered seriously because it may herald an imminent complication. When pain fails to be relieved by food or antacids or when it begins to radiate to new anatomical locations, a high index of suspicion is warranted.

* Concern especially is warranted in the setting of new-onset nausea and vomiting, decreased appetite, and weight loss.
* GI bleeding is a common complication of DU and can have serious consequences. Patients may present with melena, coffee ground emesis, or hematemesis. Passage of frank blood in the stool or maroon-colored stool in the presence of a bleeding DU suggests precipitous GI bleeding.
* Patients who develop gastric outlet obstruction as a result of chronic, untreated DU usually report a history of fullness and bloating associated with nausea and emesis occurring several hours after food intake. A common misconception is that adults with gastric outlet obstruction present with nausea and emesis immediately after a meal.
* Note that a minority of individuals is completely asymptomatic. According to one study, typical epigastric pain was rare in patients older than 65 years with peptic ulcer disease (PUD), ie, GU and DU. Elderly patients are more likely to present in an asymptomatic fashion, which is especially common in the setting of NSAID use.

**Physical**

No characteristic physical findings are associated with DU. In general, most patients have tenderness over the epigastrium, and tenderness is present less often over the right upper quadrant (RUQ), left upper quadrant (LUQ), or supraumbilical region. Most patients with an uncomplicated DU do not have any other physical findings.

In the presence of a complication such as gastric outlet obstruction, the physician may note upper abdominal distention and hear a succussion splash on auscultation.

Perforation usually results in classic findings of diffuse peritonitis with abdominal rigidity, guarding, and rebound tenderness. Bowel sounds initially may be hyperactive but, with time, become absent.

The physical examination of a patient with a DU includes a digital rectal exam (DRE) to assess for evidence of GI bleeding. Melena is noted easily on such an examination.

**Lab Studies**

In general, laboratory studies are of little help in evaluating a patient with suspected DU, but tests such as CBC, amylase, lipase, and liver function tests (LFTs) may be useful in excluding other causes of upper abdominal pain.

Several noninvasive laboratory tests are available to aid in the diagnosis of H pylori infection.

* Urea breath test

The patient ingests radiolabeled urea, which, in the presence of urease produced by H pylori, is metabolized to carbon dioxide and ammonia. A laboratory assay then is used to detect the radiolabeled carbon dioxide. This test has a sensitivity of 90-95%. It can be used to diagnose infection but is employed more often to evaluate the success of treatment of H pylori infection.

* Serology

Enzyme-linked immunoassay (ELISA) can detect both immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies directed against H pylori. The sensitivity of most serologic tests is approximately 95%.

**Imaging Studies**

Several investigative techniques can be used to diagnose DU.

Single contrast barium radiography can detect 70-80% of DUs. The sensitivity increases to greater than 90% when double contrast radiography is performed and evaluated by an experienced radiologist.

The disadvantage of radiographic studies is that biopsy specimens of the lesion, either to test for H pylori infection or to evaluate for the presence of malignancy, cannot be obtained.

Other tests used to diagnose H pylori infection include the rapid urease tests, histology, and culture

The rapid urease test requires an endoscopically acquired biopsy specimen that is inserted into a receptacle containing a urea substrate and a pH indicator. In the presence of H pylori, the urea is metabolized and the color-sensitive pH indicator demonstrates a positive result.

Culture of tissue for the presence of H pylori is not a rapid or practical test and is available only in research settings.

As with culture, the presence of the organism can be detected histologically, but the expertise of a trained pathologist is required. Other more rapid tests clearly are faster and more cost effective.

**Procedures**

Endoscopy (esophagogastroduodenoscopy)

Although not as sensitive as autopsy or visual inspection during surgery, esophagogastroduodenoscopy (EGD) is the most sensitive test available to detect DU. It has a sensitivity greater than 95%.

With EGD, the ulcer can be visualized, a biopsy specimen can be obtained, and, if required, bleeding ulcers can be treated directly. EGD is a more invasive test and requires conscious sedation in many patients.

**TREATMENT**

**Medical Care**

Treatment of DU varies depending on the etiology and clinical presentation. The initial management of a stable patient with dyspepsia differs from management of an unstable patient with upper GI hemorrhage. In the latter scenario, failure of medical management not uncommonly leads to surgical intervention.

Although the therapeutic principles of these distinct clinical scenarios share some similarities, they differ sufficiently to warrant separate discussions. The principles of management of bleeding peptic ulcers outlined below are equally applicable to both GU and DU.

**Medical management of stable DU**

MEDICATION

Treatment of DU depends on the cause.

Because the 2 most common causes are H pylori infection and use of NSAIDs, the focus of this section is specific strategies aimed at treating DU in these settings.

The goals of pharmacotherapy are to eradicate H pylori infection, reduce morbidity, and prevent complications.

1. Proton pump inhibitors

2. H2-receptor antagonists

3. Antimicrobials

4. Antidiarrheal agents. May exhibit antisecretory and antimicrobial action.

5. Bismuth subsalicylate.

Used in combination with antibiotics and H2 receptor blockers or PPIs to treat active duodenal ulcers associated with H pylori.

In general, patients with documented DU who have H pylori infection should receive eradication therapy. Several studies have evaluated different regimens for H pylori eradication.

In 1998, the American College of Gastroenterology (ACG) published practice guidelines for the management of H pylori infection. The ACG guidelines recommend the following treatments:

1. Lansoprazole 30 mg PO bid or omeprazole 20 mg PO bid, plus amoxicillin 1000 mg PO bid and clarithromycin 500 mg PO bid for 14 days (other PPIs may also be substituted)

2. Lansoprazole 30 mg PO bid or omeprazole 20 mg PO bid, plus metronidazole 500 mg PO bid and clarithromycin 500 mg PO bid for 14 days

3. Ranitidine bismuth citrate 400 mg PO bid, plus clarithromycin 500 mg PO bid and amoxicillin 1000 mg PO bid or metronidazole 500 mg PO bid or tetracycline 500 mg PO bid for 14 days

4. Bismuth subsalicylate 525 mg PO qid, plus metronidazole 500 mg PO tid and tetracycline 500 mg PO qid and a PPI (eg, lansoprazole 30 mg PO [optimal dose] or omeprazole 20 mg PO [optimal dose]) for 14 days

5. Bismuth subsalicylate 525 mg PO qid, plus metronidazole 250 mg PO qid and tetracycline 500 mg PO qid and any H2RA for 14 days

**Medical management of NSAID ulcers**

Discontinuation of NSAIDs is paramount if it is clinically feasible. Treat H pylori infection if present.

If NSAIDs must be continued, changing to a COX-2 selective inhibitor is an option. Most NSAID ulcers heal with bid H2RA therapy, but large, complicated, or refractory ulcers may need a higher dose of PPI (bid) therapy. Generally, DUs require up to 8 weeks of therapy for complete healing.

**Surgical Care**

Endoscopic intervention is the primary mode of treating bleeding ulcers. Surgical management of DUs is generally reserved for refractory ulcers and bleeding ulcers that fail to respond to medical management.

* **Endoscopic therapy**

Endoscopic therapeutic intervention is indicated for bleeding DUs. Several tools are available to the endoscopist to achieve hemostasis, including bipolar cautery, heater probe, argon plasma coagulation, and local injection of epinephrine and other agents.

Bipolar cautery and heater probe both apply heat to the ulcer and cauterize the bleeding vessel. Injection with epinephrine achieves hemostasis through the vasoconstrictive effect of epinephrine. However, some physicians argue that it is effective mainly through the tamponade effect of local fluid injection. This is supported by the fact that injection of saline achieves comparable hemostasis. Argon plasma coagulation uses heat to achieve hemostasis. One study compared argon plasma coagulation with heater probe and found no difference in incidence of rebleeding or the need for surgical intervention.

* **Urgent surgical management**

The indications for urgent surgery include (1) failure to achieve hemostasis endoscopically, (2) recurrent bleeding despite endoscopic attempts at achieving hemostasis (many advocate surgery after 2 failed endoscopic attempts), and (3) perforation.

In general, 5% of bleeding ulcers eventually require operative management. Most emergent surgical procedures involve simple oversewing of the ulcer to achieve hemostasis.

* **Elective surgical management**

The indications for elective surgical management include (1) refractoriness to medical treatment, (2) intolerance to medications, and (3) noncompliance with medications.

With the advent of improved antisecretory therapy and with the discovery of H pylori, elective surgical management of DU has become much less common in areas where such treatment is readily available.

* Elective surgical approaches

Vagotomy involves resection of the vagus nerve, which eliminates the autonomic stimulation of the parietal cells. Historically, a truncal vagotomy was performed; however, this led to gastric atony and subsequent stasis in as many as 20% patients. Currently, selective vagotomies are the procedures of choice.

Selective vagotomy preserves the celiac and hepatic branches of the vagus nerve, thus decreasing the incidence of gastric atony. However, a gastric drainage procedure (eg, pyloroplasty) remains an essential component of this surgical approach. Highly selective vagotomy results in denervation of the parietal cells but preserves nerves supplying the pyloroantral region.

The Billroth I and Billroth II are the 2 types of truncal vagotomy and antrectomy. These surgical approaches carry a mortality rate of approximately 1% and are currently performed much less frequently.

**In/Out Patient Meds**

Patients with healing DU generally require maintenance H2RA or PPI therapy for as long as 8 weeks.

Patients with refractory ulcers may remain on once daily PPI therapy or half-standard H2RA doses at bedtime indefinitely.

* **Prevention**

The most important preventive measure is complete avoidance of NSAIDs. If NSAIDs are required, use of a COX-2 selective inhibitor may help prevent gastric and duodenal mucosal ulceration.

In certain high-risk patients, such as those taking NSAIDs and steroids or receiving chemotherapy, prophylactic use of PPIs may help prevent ulcer formation.

**Complications**

* Obstruction
* Perforation
* Penetration
* Hemorrhage