MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

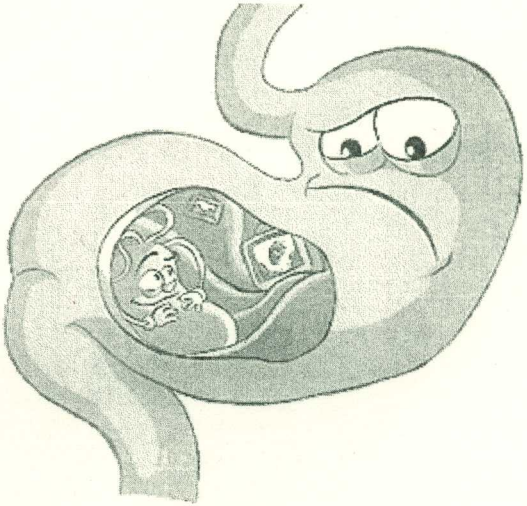
PUBLIC INSTITUTION
STATE UNIVERSITY OF MEDICINE AND PHARMACY
NICOLAE TESTEMITANU

Angela PELTEC Elina BERLIBA

GASTRITIS AND GASTROPATHY

BASIC FACTS

Guideline for students



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INTRODUCTION

Gastritis is an inflammatory condition of the gastric mucosa characterized by existence of elementary histological alternations. However these structural changes observed by the pioneer of gastric histology were noted more than a century ago, their etiology and proper interpretation for clinical practice required much longer time.

Ancient Egyptians wrote that the diseases of internal organs are difficult to detect even in well-preserved bodies, hence they were not able to comprehend outstanding discoveries on the stomach as they did on other organ diseases. The first major discovery in the field of gastric diseases was the description of gastric cancer by Persian *Avicenna* around 1000 (1). At the same time the discoveries of non-neoplastic gastric diseases, especially gastritis, was really elusive for quite a long time due to less macroscopic features and to post-mortem alternations. The inflammation of the inner lining of the stomach was first noted as "gastritis" by a German physician, *Georg Ernst Stahl* in 1728 (2). Italian pathologist *Giovanni Battista Morgagni* further described the signs of gastric inflammation. He gave the first classical description of an erosive or ulcerating gastritis. He stated that some of the erosions can become gangrenous, and described corrosive gastritis as it was the most well-known gastritis form of that time due to high number of lye intoxication. French physician, *François-Joseph-Victor Broussais* gathering information by autopsy of dead French soldiers between 1808 and 1831, described common chronic gastritis as he called "Gastritides", and sometimes got delusive conclusions as gastritis was the cause of ascites and other diseases, like typhoid fever and meningitis (2). *Jones Handfield and Wilson Fox* (1854) described microscopic changes of mucous membrane in gastric inflammation, which exists in diffuse and segmental forms. Not much later another British physician, *William Brinton* (1859) emphasized the symptomatic and microscopic differences of acut, subacute and chronic gastritis in his medical book entitled "Diseases of Stomach", and described haemorrhagic erosion and follicular ulceration. *Meanwhile Baron Carl von Rokitansky* besides his

major discoveries was the first to note hypertrophic gastritis in 1855. The next major footstep was done by *Samuel Fenwick* in 1870, who noted the presence of glandular atrophy due to gastric inflammation when classifying gastric lesions and anatomical alternations of the gastric mucosa (3). He also discovered that pernicious anaemia is associated with gastric mucosal atrophy. German surgeon, *Georg Ernst Konjetzny* using surgical specimens showed first that both gastric ulcer and gastric cancer are either secondary diseases or are associated in their pathogenesis to chronic gastric inflammation. *Shields Warren and Willam A. Meissner* described intestinal metaplasia of the stomach. They noted intestinal metaplasia as a feature of chronic gastritis, and found seldom extensive in duodenal ulcer patients, while it was extensive in stomachs removed due to carcinoma (4, 5).

DEFINITION

Gastritis describes a group of conditions with one thing in common: inflammation of the lining of the stomach. All or part of the gastric mucosa may be involved.Gastritis may be classified as acute or chronic.

Acute gastritis involves sudden, severe inflammation. The inflammation may involve the entire stomach (eg, pangastritis) or a region of the stomach (eg, antral gastritis). Acute gastritis can be broken down into 2 categories: erosive (eg, superficial erosions, deep erosions, hemorrhagic erosions) and nonerosive (generally caused by *Helicobacter pylori*).

Chronic gastritis is a histopathologic entity characterized by chronic inflammation of the stomach mucosa. **Chronic active gastritis** is the inflammation of the stomach characterized by the simultaneous presence of a mononuclear cell infiltrate and neutrophilic polymorphonuclear inflammation.

EPIDEMIOLOGY

Socioeconomic differences are the most important predictor of the prevalence of the infection. Higher standards of living are associated with higher levels of education and better sanitation, thus the prevalence of infection is lower. Epidemiologic studies of *H pylori* - associated chronic gastritis have shown that acquisition of the infection is associated with large, crowded households and lower socioeconomic status.

Well-defined preventive measures are not established. However, in the United States and in other countries with modern sanitation and clean water supplies, the rate of acquisition has been decreasing since 1950. The rate of infection in people with several generations of their families living at a high socioeconomic status is in the range of 10-15%. This is probably the lowest level to which prevalence can decline spontaneously until eradication or vaccination programs are instituted.

International statistics

An estimated 50% of the world population is infected with *H pylori;* consequently, 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.(6) In the United States, 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 (*Figure 1*).

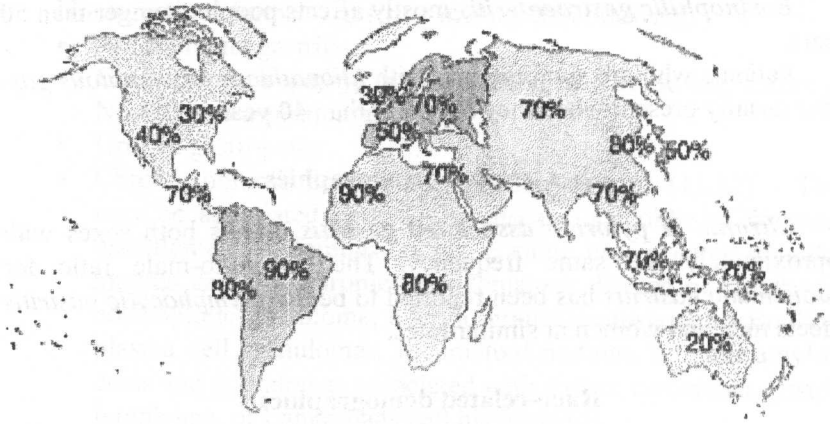

Figure 1. **Epidemiologic studies reflect the widespread incidence of Hp positive gastritis.**

Age-related demographics

Age is the most important variable relating to the prevalence of *H pylori* infection, with persons born before 1950 having a notably higher rate of infection than those born after 1950. For example, roughly 50% of people older than 60 years are infected compared with 20% of people younger than 40 years.

However, this increase in infection prevalence with age is largely apparent rather than real, reflecting a continuing overall decline in the prevalence of *H pylori* infection. Because the infection is typically acquired in childhood and is lifelong, the high proportion of older individuals who are infected is the long-term result of infection that occurred in childhood when standards of living were lower. The prevalence will decrease as people who are currently aged 40 years and have a lower rate of infection grow older (a birth cohort phenomenon).

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).

Lymphocytic gastritis can be observed in children but is usually detected in late adulthood. On average, patients are aged 50 years.

Eosinophilic gastroenteritis mostly affects people younger than 50 years.

Patients who are symptomatic with *idiopathic granulomatous gastritis* usually present when they are older than 40 years.

Sex-related demographics

Chronic H pylori – associated gastritis affects both sexes with approximately the same frequency. The female-to-male ratio for *autoimmune gastritis* has been reported to be 3:1. *Lymphocytic gastritis* affects men and women at similar rates.

Race-related demographics

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 black people, and it is less frequent in southern European and Asian people.

Sarcoidosis is more frequent in young black people, whereas *isolated granulomatous gastritis* is more common in older white people.

ETIOLOGY

Chronic gastritis may be caused by either infectious or noninfectious conditions. Infectious forms of gastritis include the following:

- Chronic gastritis caused by *H pylori* infection – This is the most common cause of chronic gastritis.
- Gastritis caused by *Helicobacter heilmannii* infection (9).
- 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, or *Diphyllobothrium latum*
- Gastritis caused by viral (eg, CMV or herpesvirus) infection (10).

Noninfectious forms of gastritis include the following:

- Autoimmune gastritis.
- Chemical gastropathy, usually related to chronic bile reflux or NSAID and aspirin intake.
- Uremic gastropathy.
- Chronic noninfectious granulomatous gastritis (11,12) – This may be associated with Crohn disease, sarcoidosis, Wegener granulomatosis, foreign bodies, cocaine use, isolated granulomatous gastritis, chronic granulomatous disease of childhood, eosinophilic granuloma, allergic granulomatosis and vasculitis, plasma cell granulomas, rheumatoid nodules, tumoral amyloidosis and granulomas associated with gastric carcinoma, gastric lymphoma, or Langerhans cell histiocytosis
- Lymphocytic gastritis, including gastritis associated with celiac disease (also called collagenous gastritis) (13).
- Eosinophilic gastritis.
- Radiation injury to the stomach.
- Graft-versus-host disease (GVHD).
- Ischemic gastritis (14).
- Gastritis secondary to drug therapy.

Some patients have chronic gastritis of undetermined etiology or gastritis of undetermined type (eg, autistic gastritis (15)).

PATHOPHYSIOLOGY

H pylori – associated chronic gastritis

H pylori is a gram-negative rod that has 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 is usually 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. (16)

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

Interaction of *H pylori* with the surface mucosa results in the release of interleukin (IL)-8, which leads to recruitment of PMNs 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-α (TNF-α) (17) and multiple interleukins (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 the level of 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 (*Figure 2*).

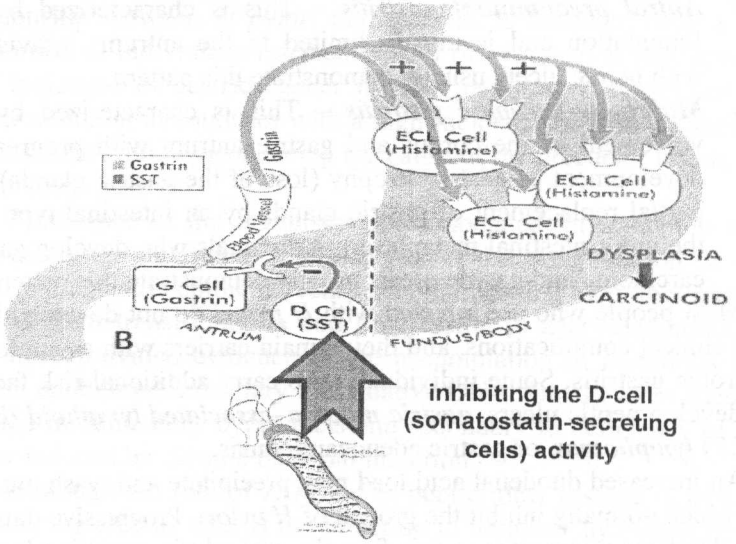

***Figure 2. H pylori* – associated Chronic Gastritis pathophysiology.**

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.

Various strains of *H pylori* exhibit differences in virulence factors and these differences 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 ulcers. However, infection with $CagA^-$ strains also predisposes the person to these diseases (8, 18, 19).

H pylori – associated chronic gastritis progresses according to the following 2 main topographic patterns, which have different clinical consequences:

- ***Antral predominant gastritis*** – This is characterized by inflammation and is mostly limited to the antrum; individuals with peptic ulcers usually demonstrate this pattern.
- ***Multifocal atrophic gastritis*** – This 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.

Most 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 ulcers, ***gastric mucosa–associated lymphoid tissue (MALT) lymphomas,*** or gastric adenocarcinomas.

An increased duodenal acid load may precipitate and wash out bile salts, which normally inhibit the growth of *H pylori.* Progressive damage to the duodenum promotes gastric foveolar metaplasia, resulting in sites for *H pylori* growth and more inflammation. This cycle renders the duodenal bulb increasingly unable to neutralize acid entering from the stomach until changes in bulb structure and function are sufficient for an ulcer to develop. *H pylori* can survive in areas of gastric metaplasia in the duodenum, contributing to the development of peptic ulcers.

MALT lymphomas may develop in association with chronic gastritis secondary to *H pylori* infection. The healthy stomach lacks organized lymphoid tissue, but after infection with *H pylori,* lymphoid tissue is universally present. Acquisition of gastric lymphoid tissue is thought to be due to persistent antigen stimulation from byproducts of chronic infection with *H pylori.*

The continuous presence of *H pylori*results in the persistence of MALT in the gastric mucosa, which eventually may progress to form low- and high-grade MALT lymphomas. MALT lymphomas are monoclonal proliferations of neoplastic B cells that have the ability to infiltrate gastric glands. Gastric MALT lymphomas typically are low-grade T-cell – dependent B-cell lymphomas, and the antigenic stimulus of gastric MALT lymphomas is thought to be *H pylori.*

Another complication of *H pylori* gastritis is the development of ***gastric carcinomas***, especially in individuals who develop extensive atrophy and intestinal metaplasia of the gastric mucosa. Although the relationship between *H pylori* and gastritis is constant, only a small proportion of individuals infected with *H pylori* develop gastric cancer. The incidence of gastric cancer usually parallels the incidence of *H pylori* infection in countries with a high incidence of gastric cancer and is consistent with *H pylori* being the cause of the precursor lesion, chronic atrophic gastritis.

Persistence of the organisms and associated inflammation during long-standing infection is likely to permit the accumulation of mutations in the gastric epithelial cells' genome, leading to an increased risk of malignant transformation and progression to adenocarcinoma. Studies have provided evidence of the accumulation of mutations in the gastric epithelium secondary to oxidative DNA damage associated with chronic inflammatory byproducts and secondary to deficiency of DNA repair induced by chronic bacterial infection.

Although the role of *H pylori* in peptic ulcer disease is well established, the clinical role of the infection in nonulcer dyspepsia remains highly controversial. *H pylori* eradication may be beneficial for symptom relief in a small proportion of patients, but routine *H pylori* testing and treatment in nonulcer dyspepsia are not currently widely accepted. Therefore, *H pylori* eradication strategies in patients with nonulcer dyspepsia must be considered on a patient-by-patient basis.

Infectious granulomatous gastritis

Granulomatous gastritis is a rare entity. Tuberculosis may affect the stomach and cause caseous granulomas. Fungi can also cause caseous granulomas and necrosis, a finding that is usually observed in patients who are immunosuppressed.

Gastritis in patients who are immunosuppressed

Cytomegalovirus (CMV) infection of the stomach is observed in patients with underlying immunosuppression. Histologically, typical intranuclear eosinophilic inclusions and, occasionally, smaller intracytoplasmic inclusions are found.

A patchy, mild inflammatory infiltrate is observed in the lamina propria. Viral inclusions are present in gastric epithelial cells and in endothelial or mesenchymal cells in the lamina propria. Severe necrosis may result in ulceration. Herpes simplex causes basophilic intranuclear inclusions in epithelial cells. Mycobacterial infections involving *Mycobacterium avium-intracellulare* are characterized by diffuse infiltration of the lamina propria by histiocytes, which rarely form granulomas.

Autoimmune gastritis

Autoimmune 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 (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 -lymphocytes infiltrate the gastric mucosa and contribute to epithelial cell destruction and resulting gastric atrophy.

One study reported that sex, age, vitamin B-12, folate, renal function, atrophic gastritis, and the methylenetetrahydrofolate (MTHF) 677TT genotype were significant determinants of homocysteine levels, which were positively related to incident cardiovascular diseases (20).

Chronic reactive chemical gastropathy

Chronic reactive chemical gastritis is associated with long-term intake of aspirin or NSAIDs. It also develops when bile-containing intestinal contents reflux into the stomach. Although bile reflux may occur in the intact stomach, most of the features associated with bile reflux are typically found in patients with partial gastrectomy, in whom the lesions develop near the surgical stoma.

The mechanisms through which bile alters the gastric epithelium involve the effects of several bile constituents. Both lysolecithin and bile acids can disrupt the gastric mucous barrier, allowing the back diffusion of positive hydrogen ions and resulting in cellular injury. Pancreatic juice enhances epithelial injury in addition to bile acids. In contrast to other chronic gastropathies, minimal inflammation of the gastric mucosa typically occurs in chemical gastropathy.

Chronic noninfectious granulomatous gastritis

Noninfectious diseases are the usual cause of gastric granulomas; they include Crohn disease, sarcoidosis, and isolated granulomatous gastritis. Crohn disease demonstrates gastric involvement in approximately 33% of the cases. Granulomas have also been described in association with gastric malignancies, including carcinoma and malignant lymphoma. Sarcoidlike granulomas may be observed in people who use cocaine, and foreign material is occasionally observed in the granuloma.

Lymphocytic gastritis

Lymphocytic gastritis is a type of chronic gastritis characterized by dense infiltration of the surface and foveolar epithelium by T lymphocytes and associated chronic infiltrates in the lamina propria. Because its histopathology is similar to that of celiac disease, lymphocytic gastritis has been proposed to result from intraluminal antigens.

High anti – *H pylori* antibody titers have been found in patients with lymphocytic gastritis, and in limited studies, the inflammation disappeared after *H pylori* was eradicated. However, many patients with lymphocytic gastritis are serologically negative for *H pylori.* A number of cases may develop secondary to intolerance to gluten and drugs such as ticlopidine.

Eosinophilic gastritis

Large numbers of eosinophils may be observed with parasitic infections such as those caused by *Eustoma rotundatum* and *Anisakis marina.* Eosinophilic gastritis can be part of the spectrum of eosinophilic gastroenteritis. Although the gastric antrum is commonly affected and can cause gastric outlet obstruction, this condition can affect any segment of the GI tract and can be segmental (21). Patients frequently have peripheral blood eosinophilia.

In some cases, especially in children, eosinophilic gastroenteritis can result from food allergy, usually to milk or soy protein. Eosinophilic gastroenteritis can also be found in some patients with connective tissue disorders, including scleroderma, polymyositis, and dermatomyositis.

Radiation gastritis

Small doses of radiation (up to 15 Gy) cause reversible mucosal damage, whereas higher doses cause irreversible damage with atrophy and ischemic-related ulceration. Reversible changes consist of degenerative changes in epithelial cells and nonspecific chronic inflammatory infiltrate in the lamina propria. Higher amounts of radiation cause permanent mucosal damage, with atrophy of fundic glands, mucosal erosions, and capillary hemorrhage. Associated submucosal endarteritis results in mucosal ischemia and secondary ulcer development.

Ischemic gastritis

Ischemic gastritis is believed to result from atherosclerotic thrombi arising from the celiac and superior mesenteric arteries.

HISTORY

H pylori infection

Acute *H pylori* infection usually is not detected clinically, 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 1 week, regardless of whether the organism is eliminated.

Persistence of the organism causes *H pylori* chronic gastritis, which is usually 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, and mucosa-associated lymphoid tissue (MALT) lymphoma.

Autoimmune gastritis

The clinical manifestations of autoimmune gastritis are primarily related to the deficiency in cobalamin, which is not adequately absorbed because of intrinsic factor (IF) deficiency resulting from severe gastric

parietal cell atrophy. The disease has an insidious onset and progresses slowly. Cobalamin deficiency affects the hematologic, gastrointestinal (GI), and neurologic systems.

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

The main GI manifestation is megaloblastosis of the GI tract epithelium, which is associated with the lack of cobalamin. 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 result from demyelination, followed by axonal degeneration and neuronal death. Affected sites include the 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 range from mild irritability to severe dementia or psychosis. Neurologic disease may occur in a patient with hematocrit and red cell parameters within the reference range.

Patients with pernicious anemia have an increased frequency of gastric polyps and gastric carcinoid and a 2.9-fold increase in the frequency of gastric cancer.

Granulomatous gastritis

In multisystemic diseases, specific symptoms related to gastric involvement may be minor. Caseous granulomas secondary to tuberculosis may be found in the absence of lung disease in patients who are malnourished, immunosuppressed, or alcoholic.

Patients with Crohn disease and gastric involvement may report gastric pain, nausea, and vomiting. Gastric involvement in Crohn disease is almost invariably associated with intestinal disease, and intestinal manifestations predominate.

Sarcoidosis of the stomach is usually associated with granulomatous inflammation in other locations, especially the lungs, hilar nodes, or salivary glands. About 10% of patients with sarcoid involvement in the stomach are asymptomatic. Patients who are symptomatic present with gastric ulcers, hemorrhage, pyloric stricture, and gastric outlet obstruction.

Idiopathic isolated granulomatous gastritis

The diagnosis of idiopathic isolated granulomatous gastritis is made only when known entities associated with granulomas are excluded. Patients who are symptomatic usually are older than 40 years at presentation and have epigastric pain, weight loss, and vomiting secondary to pyloric obstruction.

Lymphocytic gastritis

Lymphocytic gastritis mostly affects middle-aged or elderly patients. It may be associated with chronic *H pylori* infection, gluten-sensitive enteropathy, and Menetrier disease. It may represent a hypersensitivity reaction involving the gastric body. Lymphocytic gastritis has been described as complicating MALT lymphoma and gastric carcinoma.

Eosinophilic gastroenteritis

Some patients with eosinophilic gastroenteritis have underlying connective tissue disorders. Those with predominant mucosal involvement may report nausea, vomiting, and abdominal pain related to ingestion of specific foods. Those with involvement of the muscularis propria and resulting thickening and rigidity may present with outlet obstruction symptoms. Many patients have a history of allergy, peripheral eosinophilia, asthma, eczema, or food sensitivity. Some respond to removal of these items from the diet, and steroid treatment is often helpful.

Gastritis in graft versus host disease

Graft versus host disease (GVHD) follows allogeneic bone marrow transplantation or transfusions, especially in patients who are immunocompromised. Patients with isolated gastric GVHD have symptoms of nausea, vomiting, and upper abdominal pain without diarrhea (22).

PHYSICAL EXAMINATION

Physical examination contributes relatively little to the assessment and management of 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.

CHRONIC GASTRITIS WORKUP

Approach Considerations

The diagnosis of chronic gastritis can only be established on histologic grounds. Therefore, histologic assessment of endoscopic biopsies is essential. Identification of the underlying cause of chronic gastritis and assessment of specific complications can require several laboratory tests.

Failure to diagnose the underlying cause of chronic gastritis correctly may result in unnecessary morbidity. Failure to identify and treat *H pylori* infection in the presence of peptic ulcers may result in ulcer recurrence and complications.

Laboratory Studies

Atrophic gastritis may be assessed by measuring the ratio of pepsinogen I (PGI, PGA) to pepsinogen II (PGII, PGC) in the serum. PGI and PGII are synthesized and secreted by gastric chief cells. After being secreted into the gastric lumen, they are converted into proteolytic active pepsins. The level of PGI in the serum decreases as gastric chief cells are lost during gastric atrophy, 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 PGI and PGII and the PGI/PGII ratio in the serum is useful in screening for atrophic gastritis and gastric cancer in regions with a high incidence of these diseases. Pepsinogen determina-

tion is especially useful in epidemiologic studies; however, the reported sensitivity and specificity of the assay are relatively low (84.6% and 73.5%, respectively).

A rapid urease test should be done on gastric biopsy tissue. Bacterial culture of gastric biopsy tissue is usually performed in the research setting or to assess antibiotic susceptibility in patients for whom first-line eradication therapy fails.

The following test results suggest the diagnosis of autoimmune gastritis:

- Antiparietal and anti–intrinsic factor (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 (this can be corrected by IF).

Endoscopy

Magnifying endoscopy is helpful for analyzing the subepithelial microvascular architecture, as well as the mucosal surface microstructure, without tissue biopsy (23). Using this technique, investigators from the United Kingdom were able to describe the normal gastric microvasculature pattern and identify characteristic patterns in 2 cases of autoimmune atrophic gastritis (24).

Upper gastrointestinal (GI) endoscopy is essential for makinga diagnosis of gastritis (*Figure 3*). 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, whether there is a specific relation between *H pylori* and macroscopic features remains controversial. The endoscopic findings in chronic *H pylori* infection may include areas of intestinal metaplasia.

Multiple biopsy specimens should be obtained. Tissue sampling from the gastric antrum, incisura, and corpus is essential to establish the topography of gastritis and to identify atrophy and intestinal metaplasia, which usually is patchy. It is recommended that biopsy samples of the gastric body and those from the antrum and incisura be submitted in separate containers for pathologic evaluation.

Endoscopic findings in granulomatous gastritis include mucosal nodularity with cobblestoning, multiple aphthous ulcers, linear or serpiginous ulcerations, thickened antral folds, antral narrowing, hypoperistalsis, and duodenal strictures. Extensive gastric involvement may resemble linitis plastica.

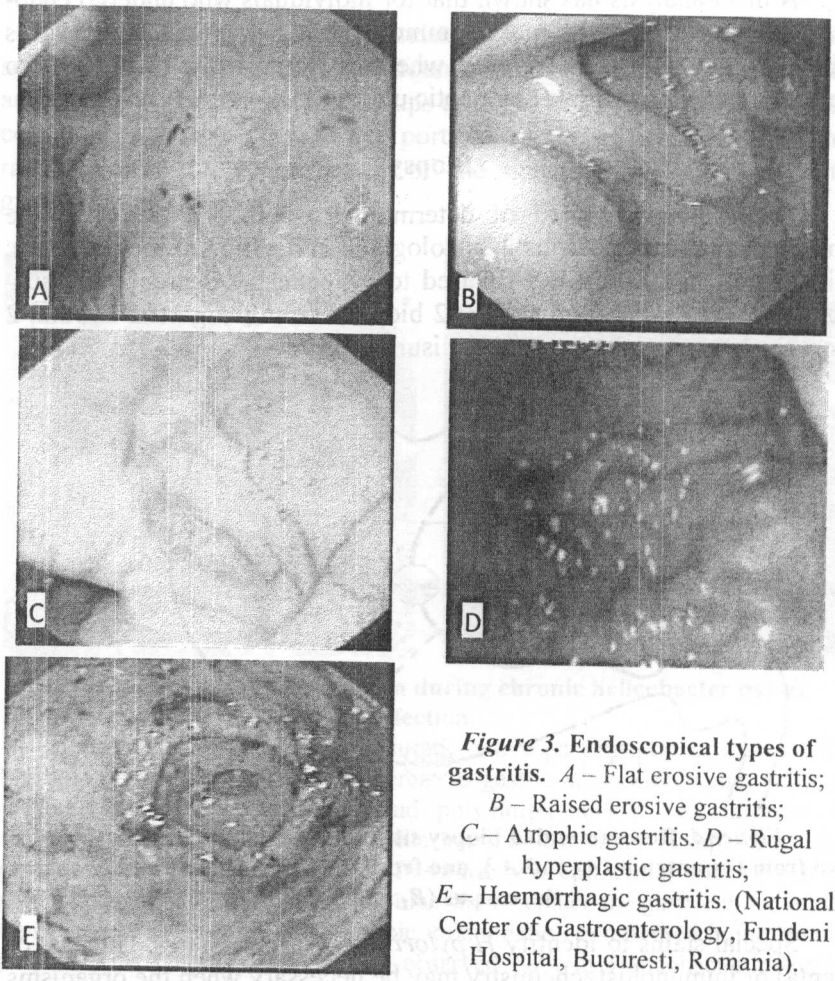

Figure 3. **Endoscopical types of gastritis.** *A* – Flat erosive gastritis; *B* – Raised erosive gastritis; *C* – Atrophic gastritis. *D* – Rugal hyperplastic gastritis; *E* – Haemorrhagic gastritis. (National Center of Gastroenterology, Fundeni Hospital, Bucuresti, Romania).

Endoscopic findings in lymphocytic gastritis include enlarged folds and aphthoid erosions, with the appearance of small, heaped-up, volcano

like mounds pocked with a central crater. This endoscopic pattern has also been described as varioliform gastritis.

The endoscopic findings of reflux and chemical gastropathy are those of a gastric mucosa that is red or has red streaks with areas of apparent hemorrhage.

A meta-analysis has shown that for individuals who undergo endoscopy for dyspepsia, the most common finding is erosive esophagitis (though the prevalence was lower when the Rome criteria were used to define dyspepsia), followed by peptic ulcers (25).

Biopsy

The standard method of determining whether *H pylori* is the underlying cause of gastritis is histologic identification of the organism. Histologic 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 (*Figure 4*).

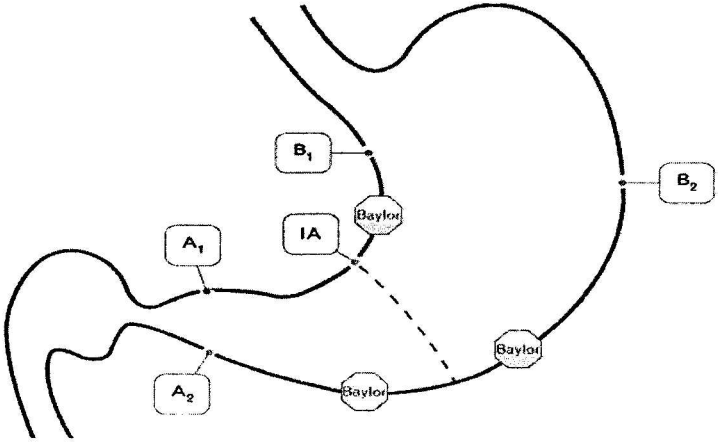

Figure 4. **Recommended biopsy sites for the Sydney System include two from the antrum (A_1 and A_2), one from the incisura (1A) and two from the corpus (B_1 and B_2).**

Special stains to identify *H pylori* (eg, Warthin-Starry, Giemsa, or Genta) or immunohistochemistry 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 (eg, the urea breath test) and serologic indicators of infection may provide evidence for *H pylori* infection.

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 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 (*Figure 5*).

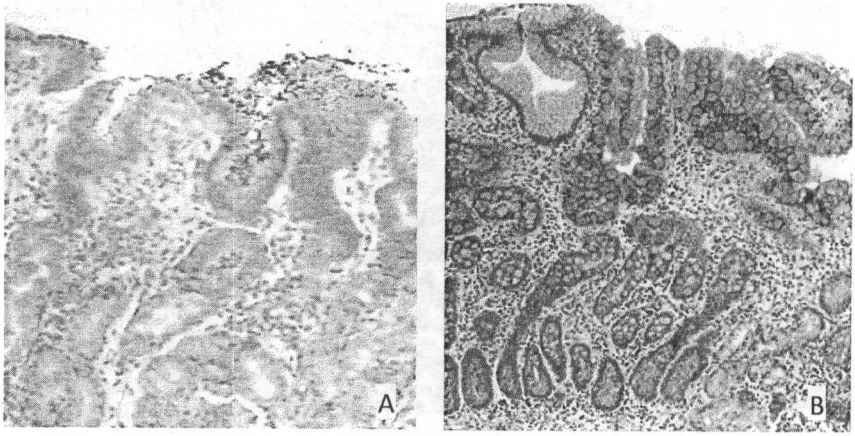

Figure 5. **Gastric mucosal lesion during chronic helicobacter pylori infection.**

A – Helicobacter pylori – caused chronic active gastritis. Genta stain (×20). Multiple organisms are visibly adherent to gastric surface epithelial cells. A mononuclear lymphoplasmacytic and polymorphonuclear cell infiltrate is observed in the mucosa. *B* – Atrophic gastritis. Intestinal metaplasia of the gastric mucosa (Genta stain, 20X). Intestinal-type epithelium with numerous goblet cells (stained with the Alcian blue stain) replace the gastric mucosa and represent gastric atrophy. Mild chronic inflammation is observed in the lamina propria. This pattern of atrophy is observed both in Helicobacter pylori – associated atrophic gastritis and autoimmune gastritis.

Patients with typical infections initially develop chronic active gastritis in which *H pylori* is observed in both the antrum and the corpus (usually in greater numbers in the antrum). Polymorphonuclear leukocytes (PMNs) 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 expandingthe lamina propria of the mucosa, and occasional lymphocytes permeate the epithelium (*Figure 6*).

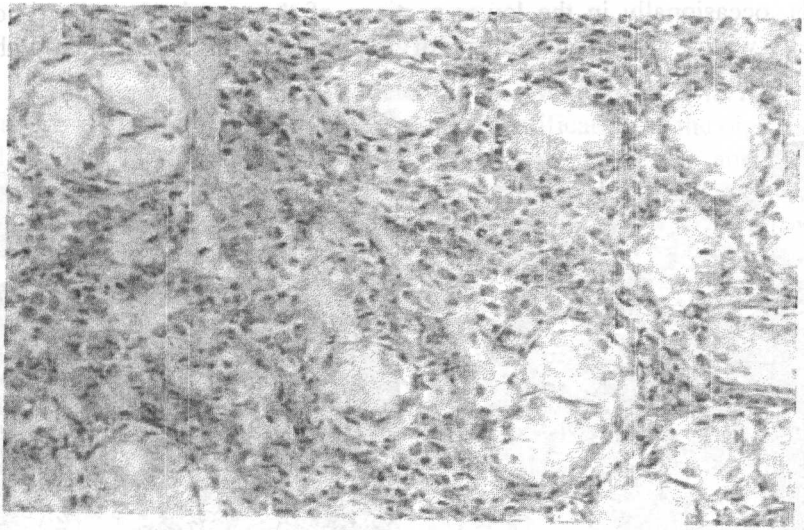

Figure 6. **Chronic gastritis associated with Helicobacter pylori infection. Numerous plasma cells in lamina propria.**

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 it may result from replacement of the epithelium with 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 histologic 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 are seen. 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.

Granulomatous gastritis predominantly affects the gastric antrum. In early stages, the only findings may be isolated granulomas in the mucosa and submucosa. In later stages of the disease, inflammation extends to the muscularis propria, and fibrosis may be prominent. Granulomas associated with tuberculosis are typically caseousPoorly formed granulomas can also be observed in syphilitic involvement of the stomach in the tertiary stage of the disease.

Noninfectious causes of gastric granulomas typically result in noncaseous granulomas; such causes include the following:

- Crohn disease
- Sarcoidosis
- Isolated granulomas

Crohn disease affecting the stomach consists of patchy inflammation with pit or gland abscesses. Lymphoid aggregates are common. Severe cases may show fissures, ulcers, transmural inflammation, and serosal and submucosal fibrosis. Noncaseating epithelioid granulomas may be observed. Diffuse inflammatory infiltration in the lamina propria and glandular atrophy occur. Gastric involvement is almost invariably synchronous with Crohn disease in the ileum or colon.

Sarcoidosis and ***isolated granulomas*** are characterized by bland granulomas with mild associated inflammation. Although sarcoidosis affecting the stomach typically coexists with sarcoidosis involving other organs, isolated granulomatous gastritis only affects the stomach and is a diagnosis of exclusion.

Cytomegalovirus (CMV) infection of the stomach is observed in patients with underlying immunosuppression. Histologically, typical intranuclear eosinophilic inclusions and, occasionally, smaller intracytoplasmic inclusions are found (*Figure 7*). Patchy, mild, inflammatory infiltrate is observed in the lamina propria. Viral inclusions are present in gastric epithelial cells and in endothelial or mesenchymal cells in the lamina propria. Severe mucosal necrosis may result in severe ulceration.

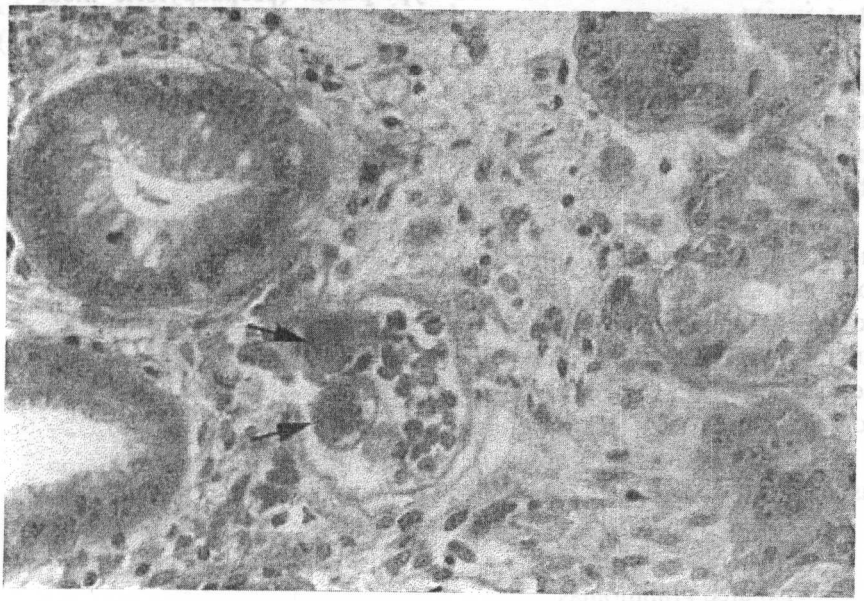

Figure 7. **Chronic Gastritis. Typical cytomegalovirus inclusions in lamina propria capillary endothelial cells. Image courtesy of Sydney Finkelstein, MD, PhD, University of Pittsburgh.**

Herpes simplex causes basophilic intranuclear inclusions in epithelial cells. *M avium-intracellulare* infections are characterized by diffuse infiltration of the lamina propria by histiocytes, which rarely form granulomas (*Figure 8*).

In cases of gastritis associated with ***graft versus host disease*** (GVHD), the stomach is rarely affected. Typical epithelial cell apoptosis and pit or gland dilatation occur. Pit and gland abscesses and nonspecific inflammation of the lamina propria may be observed. In severe

disease, glandular atrophy, focal intestinal metaplasia, and severe mucosal denudation may occur.

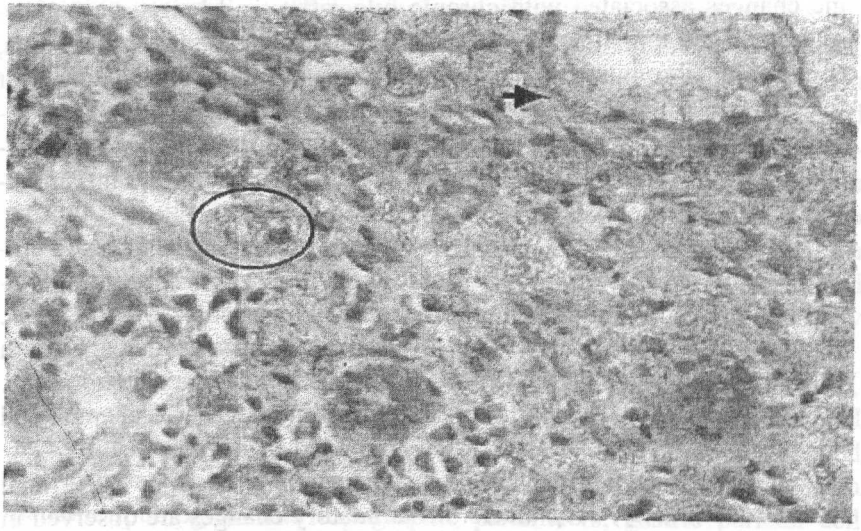

Figure 8. **Chronic gastritis. Mycobacterium avium-intracellulare in gastric lamina propria macrophages.**
(Sydney Finkelstein, MD, PhD, University of Pittsburgh).

In ***eosinophilic gastritis***, the mucosa shows intense patchy infiltration by numerous eosinophils, with occasional pit abscesses. The infiltrate typically contains 10-50 eosinophils per high-power field, as well as plasma cells. Mucosal edema, congestion, and necrosis of the surface epithelium with small erosions may be present. Mucosal infiltration by a bandlike eosinophil infiltrate in the lower lamina propria above the muscularis mucosa characterizes eosinophilic gastroenteritis associated with connective tissue disorders.

In ***lymphocytic gastritis***, the lamina propria and pit epithelium are infiltrated by large numbers of small mature T-lymphocytes. Abundant T-lymphocytes typically permeate the surface epithelium. A diagnosis can be rendered when 30 or more lymphocytes are observed per 100 consecutive epithelial cells, and performing the counts in biopsies from the gastric corpus is recommended.

In ***chemical gastropathy***, changes are more prominent in the prepyloric region but may extend to involve the oxyntic mucosa. Histologic changes associated with chronic bile reflux and long-term nonsteroidal anti-inflammatory drug (NSAID) intake include mucosal edema, congestion, fibromuscular hyperplasia in the lamina propria, and pit or foveolar hyperplasia that may create a corkscrew pattern. Cellular proliferation is associated with reactive nuclear features and epithelial reduction of mucin. Epithelial changes occur with a paucity of inflammatory cells.

In ***radiation gastritis***, radiation causes degenerative changes in epithelial cells and a nonspecific chronic inflammatory infiltrate in the lamina propria. These changes are reversible in a period of a few months. Higher amounts of radiation cause permanent mucosal damage, with atrophy of fundic glands, mucosal erosions, and capillary hemorrhage. Associated submucosal endarteritis results in mucosal ischemia and secondary ulcer development.

In ***ischemic gastritis***, chronic ischemia may produce superficial erosions and, rarely, deep ulcers. Inflammatory changes are observed in the context of ulcer repair. Ischemic ulcers are more frequently antral and are often surrounded by multiple erosions.

Idiopathic granulomatous gastritis demonstrates histopathology similar to sarcoid involvement of the stomach. Antral narrowing caused by transmural, noncaseating, granulomatous inflammation occurs. Inflammation and fibrosis are usually limited to the mucosa. Idiopathic granulomatous gastritis may represent isolated or limited forms of gastric sarcoid or Crohn disease.

CLASSIFICATION OF GASTRITIS

Historical aspect

In vivo diagnosis of gastritis got a huge drive with the development of routine gastroscopy. By the 1950's, *Rudolf Schindler's* part-flexible endoscopes became very common making rigid endoscopes to disappear. Since 1960's, the commercial introduction of flexible endoscopes gave easy access for gastric biopsy and diagnosis of gastritis (26). By the use of biopsy based histology *Schindler* gave overview of gastritis in his monograph entitled 'Gastritis' in 1947, he divided inflammation into

'superficial', 'atrophic' and 'hypertrophic' gastritis chronica (27). *Cheli and Dobero* in 1958 differentiated 'superficial', 'interstitial' and 'atrophic gastritis' in the terminology of gastric inflammatory lesions (28). Up to his time classifications lack topography, but in 1972, *Whitehead* distinguished antral, fundal, corporal and pyloric region inflammation based on classical pathomorphology. *Whitehead* divided chronic gastritis into 'superficial' and 'atrophic', both 'active' or 'inactive' based on the presence of granulocyte infiltration in epithelium and interstitium beside the inflammatory infiltration of lamina propria from lymphocytes and plasmatic cells (29). He suggested the use of a mild-moderate-severe scale to evaluate the atrophy. He also introduced the evaluation of intestinal and pseudopyloric metaplasia into everyday pathological assessment.

Based on recent research data, *Robert G. Strickland and Ian R. MacKay* proposed the classification of gastritis based on additional factors just beside just histology and topography (30). They suggested that immunological and etiological data should be included along with pathomorphological and topographic parameters; gastric parietal cell antibody and serum level of gastrin have to be seen to get better classification of chronic gastritis. They used the term ***'Type A gastritis'*** for gastric corporal inflammation mostly corresponding to pernicious anaemia, and ***'Type B'*** for antral gastritis suspected to be induced by duodeno-gastric reflux according to some thoughts. In 1975 *George B Jerzy Glass* and *Capecomorin S. Pitchumoni* added the ***'Type AB'*** to the classification. This term was aimed to be used for extended gastritis observed in corpus to pre-pyloric region (31). Those cases were named ***'AB-plus'*** where antibody positivity was also founds against parietal cells. In 1980, the classification was further modified by *Correa* dividing chronic gastritis into autoimmune chronic gastritis with pernicious anaemia, 'hypersecretory' and 'environmental' forms. He described the gastritis accompanying ulcer to hypersecretory. All the rest of gastritis was called environmental, which are mostly due to diet and geographic localization (32). Later as more data were known from histological assessments, he changed his classification for 'diffuse antral', 'diffuse corporal' and 'multifocal' gastritis. By seeing his nomenclature, sometimes showing etiology, sometimes reflecting topography, we are able to see the controversy existed between pathologist and clinicians in the field of gastritis at that time. The extensiveness in topography along

with histological and etiologic features were not to be combined in an uniformed nomenclature, even *Correa* in 1988 returned to his previous version of classification (33). Later, he went to different direction by dividing gastritis into two major categories of 'atrophic' and 'non-atrophic' gastritis.

The next major step was added by *Judith I. Wyatt and Michael F. Dixon* by the introduction of ***'type C'*** gastritis for chemical (drug)-induced inflammation of gastric mucosa (34). Two years later, examining 316 patients *Sobala* confirmed that most of reflux gastritis in intact (non-operated) stomach is not due to bile reflux but rather NSAID use. According to their proposition the term 'type C' or 'chemical' gastritis might be used for condition caused by both etiology (35).

Modern aspect

Modern aspects of gastritis classification and knowledge of its biological course and consequences were relatively well-known at the time when *Helicobacter pylori* (*H. pylori*) was discovered by *Robin Warren and Barry Marshall* in 1982 (36). Their discovery showed that the commonest form of gastritis is simply an infectious disease caused by an otherwise known pathogen. At that time gastroenterologist and pathologist had limited knowledge on even simple aspects of this chronic bacterial inflammation of gastric mucosa and the classification system used was confusing and differing from county to another. Very soon considerable amount of data became known about *H pylori*, its disease associations and their natural courses by many physicians, microbiologist and basic researchers entering the field. As a consequence in the late 1980's several pre-meeting of Working Party (*Anthony Axon, Wladimir Bogomoletz, Michael F. Dixon, Steart Goodwin, Jules Haot, Konrad L. Heilmann, Adrian Lee, Barry Marshall, George Misiewicz, Ashley Price, Penti Sipponen, Enrico Solcia, Manfred Stolte, Robert Strickland, Guido Tytgat*) was set up to review the biology and natural course of chronic gastritis and to propose a new classification for gastritis by the leadership of *George Misiewicz and Guido Tytgat*. The working party actually consisted of two groups mainly working parallel to another: as a pathological group and a clinical group (37). Based on new etiological facts and data collected, a new system of classification was presented at the World Congress of Gastroenterology held in

Sydney, Australia in 1990, and subsequently published as six papers in the *Journal Gastroenterology and Hepatology*. The existence of the two Working Parties reflects on the histological and endoscopic division of Sydney System. The histological division of Sydney System intended to be a practical guideline showing which of the morphological features of gastritis in endoscopic biopsy specimens should be documented (38, 39). Type, severity and extent of gastric inflammation linked to possible etiology should be detailed according to a chart designed (*Figure 9*). The Sydney System declared the routine biopsy sampling protocol, the number of biopsies should be taken, the biopsies' proper localization (two from antrum and two from corpus, both from anterior and posterior walls) and sample fixation in adequately labelled separate containers (38, 39, 40). Many pathologists think of these last as the most important conclusions of the system. The system also established a four-level scale for defining severity (extent) of pathomorphological elements.

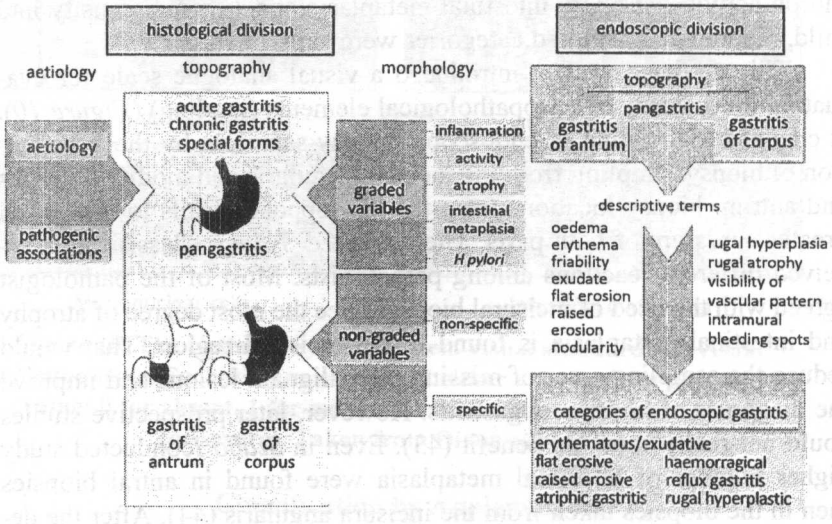

Figure 9. **The Sydney System of Classification of Gastritisd.** Describes the nomenclature should be used in histological reporting of gastritis. The etiological suffix phrases to topography and morphological features with grading suffixes to be documented in endoscopic biopsy reporting.

The Sydney System which actually allowed statements to be made on etiology, topography and morphology of gastritis for the first time, was not accepted everywhere immediately, especially in the United States. The main criticism was that the some of the commonly used descriptive names were not enabled into the system, like the 'multifocal atrophic gastritis' or 'diffuse antral gastritis'. Although, by that time it was already accepted that the Sydney System was not designed to be the textbook of gastric pathology, but to be a guide for standard methodology of reporting. *Correa and Yardley* criticized the system for missing out certain types of the gastritis and well as it is not a 'classification' (41). Consequently, a new system needed to gain wider acceptance.

In 1994, a two-day consensus meeting was held in Houston. After this another consensus report, "Up-dated Sydney System" was published in 1996 (42). Original classification of gastritis dividing into acute, chronic and special forms, and grading of chronic inflammation, polymorph activity, atrophy, intestinal metaplasia and *H pylori* density into mild, moderate andmarked categories were kept.

This up-dated system introduced a visual analogue scale for evaluating the severity of histopathological elements (grading) (*Figure 10*). It changed the routine of endoscopic biopsy sampling by the introduction of biopsy sampling from the incisura angularis and modified corpus and antrum biopsy locations from the two opposite walls to lesser and greater curvature of both parts. The Up-dated Sydney Classification received different reactions among pathologists. Most of the pathologist agreed with the need of incisural biopsy, since the most degree of atrophy and intestinal metaplasia is found in the incisural region. That would reduce the sampling error of missing premalignant lesions and improve the diagnosis of multifocal gastritis. However, later prospective studies could not really show its benefit (43). Even in *Szabo I*conducted study higher number of intestinal metaplasia were found in antral biopsies then in the biopsies taken from the incisura angularis (44). After the development of the visual analogue scale according to the Up-dated Sydney System, the grading of atrophy still continued to show a considerable inter-observer variability (45). The updated system categorised chronic gastritis into 'non-atrophic' and 'atrophic' forms with the latter divided into autoimmune (diffuse corpus atrophy) and multifocal. Histological reporting of gastritis should take into account the topographical pattern (antral or corpus predominant), and the final diagnostic term should

ideally combine morphology and etiology to maximize the clinical value of gastric biopsy diagnosis (46). The up-dated system beside its major benefits in further standardizing endoscopic sampling, histological assessment and formality of reporting, still showed weaknesses specially in grading atrophy as pointed out by *Johan A. Offerhaus* in 1999 (47). His proposition was to simplify the grading system to two grades (low and high).

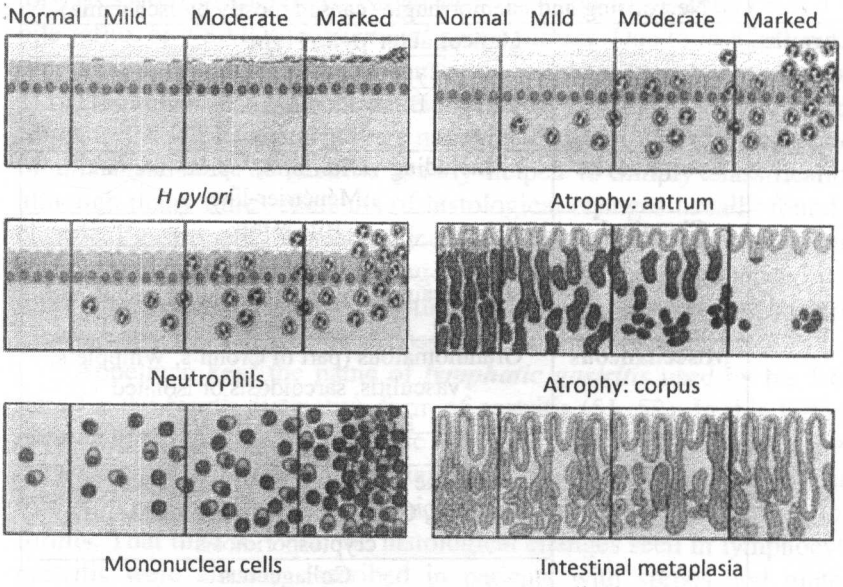

Figure 10. **The Updated Sydney System visual standardized visual analogue scale. Each feature is assigned either a numeric or descriptive value: 0 for absent, 1 for mild, 2 for moderate, and 3 for marked (or severe). Taken from Dixon et al (42).**

Classification by Appleman

The clearest division of gastritis for clinicians was published by Appleman in 1994. He divided gastric inflammatory diseases to *acute* and *chronic* (*Table 1*). The most common form of gastritis that was called earlier as chronic diffuse antral gastritis, chronic gastritis type B, chronic active antralis gastritis, non-specific gastritis or hypersecretions types of gastritis was named as ***Helicobacter pylori related gastritis***. At this time a lot of work proved that *H pylori* infection causes chronic

gastritis in the prepyloric region later leading to atrophy of glands and development of gastric adenocarcinoma and less frequently of lymphoma (48, 49).

Table 1

Appleman's classification of gastritis (1994)

Acute	Acute infectious gastritis (including Hp)	
	Erosive (caused mostly by NSAID or alcohol)	
	Necrotising and haemorrhagic (caused mostly by ischaemia)	
Chronic	**Helicobacter pylori type**	
	Atrophic	Type A: autoimmune, diffuse
		Type B: non-autoimmune, multifocal, enviromental
	Lymphocytic	Including varioliform, 'sprue-like' and Ménétrier-like
	Chemical*	Bile reflux
		NSAIDs
		others (caused by other damaging agents and physical trauma)
	Miscellaneous	Granulomatous (part of Crohn's, Whipple's, vasculitis, sarcoidosis or isolated granulomatous gastritis)
		Allergic
		Specific infectious (HIV, mycobacterial, syphilis, Cytomegalovirus, histoplasmosis, cryptosporidiosis
		Collagenous

*Gastropathies

According to Appelman's classification the autoimmune gastritis used to be called as gastritis autoimmunogenes, gastritis chronic atrophica typus A, gastritis chronic typus A and gastritis chronic diffusa corporis, was called to ***autoimmune chronic atrophic gastritis***. Appelman pointed out the presence of autoantibodies against parietal cells and intrinsic factor being important in diagnosis, enterochromaffinlike (ECL) cell hyperplasia and risk of carcinoma.

Appelman's classification of gastritis continues with the ***multifocal atrophic gastritis*** earlier called as environmental gastritis or type B chronic atrophic gastritis. At that time the cause of this form of gastritis was not clearly known. Beside known environmental factors responsible

for geographic differences in its epidemiology, raising circumstantial evidences from an Italian study examining gastric distribution of *H. pylori*, pointed out the role of *H. pylori* in its generation (50). Evidences suggested that *H. pylori* first infect the antrum, and later it involves the body leading to atrophic gastritis.

Appelman seeing similarity of the histological changes of patients with gastroenteric anastomosis and taking nonsteroidal anti-inflammatory (NSAID) medications, called third division of gastritis caused by bile reflux or NSAIDs to ***chemical gastropathies***. Due to less inflammation these histological changes consisting foveolar hyperplasia, decrease of mucin in foveolar cells, superficial oedema, increase of smooth muscle fibres in the lamina propria were named as 'gastropathies'. Recognition of this distinction of gastritis greatly helped to simply classification, although many times elements of histological changes usually found in chemical gastropathy can be noticed in other forms of gastritis as well as in other gastric disease. Finding them singular and unassociated with other changes like atrophy, intestinal metaplasia, presence of bacteria, ulcers, polyps, should raise the possibility of chemical gastritis.

Appelman kept the name of ***lymphatic gastritis*** used by his frontiers for the fourth distinctive form of gastritis (51, 52). In this form of chronic gastritis huge lymphocytic infiltration of the surface epithelium, superficial pits and lamina propria can be observed. Others used to call this as superficial gastritis, chronic erosive gastritis or gastritis varioliformis. That time in 1990, the histological changes seen in lymphocytic gastritis were already described in patients with sprues and gluten-sensitivity. Lymphocytic gastritis tends to form "varioliform gastritis" endoscopically. This includes thick folds and small bumps with central depression seen during endoscopy. But lymphocytic gastritis also can form giant folds leading clinical symptoms (Ménétrier's disease).

Appelman's division of gastritis contained a miscellaneous group of gastritis. There are many gastritis forms that do not differ significantly from similar inflammations found in other organs, including those that occur in syphilis, mycobacterial and cytomegalovirus, human immunodeficiency virus infections, histoplasmosis, candidiasis, cryptosporidiosis and other opportunistic fungi. There is a family of granulomatous reactions or ***granulomatous gastritis***. Some of these are part of a systemic or focal gut granulomatous disease, such as sarcoidosis or Crohn's disease, and some have been described as part of a systemic vasculitis

syndrome or Whipple's disease. There are still others which are not associated with any other diseases and designated as 'isolated granulomatous gastritis'. ***Allergic gastritis*** is usually part of a gastrointestinal allergic disease. Appelman also categorized the recently described ***collagenous gastritis*** into this miscellaneous group.

Precancerous lesions

Warren and Meissner describing intestinal metaplasia and recognizing the clinical-pathological pattern of gastritis described the bases of etiopathogenic relationship between gastric cancer and chronic gastritis (53, 54). In 1980, *Morson et al.* (55) defined gastric precancerous conditions as atrophic gastritis, gastric ulcer, pernicious anaemia, gastric stumps, gastric polyps, and Ménétrier's disease. They emphasized that epithelial dysplasia being a precancerous lesion is common in these conditions; dysplasia should be graded as mild, moderate and severe; and underlined the problems of differentiating inflammatory or regenerative changes from mild dysplasia, and intramucosal carcinoma from severe dysplasia (55). Japanese pathologists by studying serial sections of gastric mucosa obtained from gastric cancer patients described several border line lesions with histological and cytological changes. The premalignant significance of these was questioned for quite a long time; finally, the long-term follow-up studies closed this debate (56, 57). The high inter-observer inconsistency in histological assessment of premalignant lesions and new result supporting their neoplastic intraglandular nature obtained from genotyping studies highlighted the need of a broad consensus to re-define precancerous lesions uniformly. International group of pathologists met in ***Padova, Italy in April, 1998*** on an international consensus conference. The conference reached an agreement on the definitions of the spectrum of gastric premalignant lesions and on common glossary for pathologists and clinicians, and applied strict diagnostic criteria (58) (*Table 2*).

Table 2

Padova Classification of gastric dysplasia and related lesions (2000)

Negative for dysplasia	1.0 Normal	
	1.1 Reactive foveolar hyperplasia	
	1.2 Intestinal metaplasia	1.2.1 Complete type
		1.2.2 Incomplete type
Indefinite for dysplasia	2.1 Foveolar hyperproliferation	
	2.2 Hyperproliferative intestinal metaplasia	
Noninvasive neoplasma (flat or elevated)	3.1 Low-grade	
	3.2 High-grade	3.2.1 Including suspicious for carcinoma without invasion (intraglandular)
		3.2.2 Including carcinoma without invasion (intraglandular)
Suspicious for invasive carcinoma		
Invasive carcinoma		

Evaluation of atrophy

The Sydney System and Up-dated Sydney System attempted to incorporate etiologic, topographic, and morphologic criteria into a clinically relevant scheme to reach a broad consensus in classification of gastritis. One of the most controversial issues at the Houston Workshop was the concept of atrophy. It was pointed out that "normal" was not precisely defined; the loss of appropriate glands occurs with distinct patterns and has different functional significance in antrum and corpus; the relationship between atrophy and intestinal metaplasia remained incompletely understood; and the topographic patterns of distribution and its evolution made the atrophic gastritis to the most controversial topic of gastritis (59). Later long-term follow-up studies have confirmed that the extent of gastric mucosal atrophy parallels gastric cancer risk (60, 61, 62, 63, 64). At the same time Sydney System did not present a reporting terminology for chronic gastritis understandable and providing prognostic and therapeutic information for clinicians. Whereas, hepatitis staging had already improved useful, simple terminology for interdisciplinary communication representing disease progression and cancer risk.

Inspired by these facts, international group of gastroenterologists and pathologists named as ***Operative Link on Gastritis Assessment (OLGA)*** developed an improved histological staging system for gastric

atrophy (65, 66). OLGA system uses the gastric biopsy sampling protocol defined by Sydney System and the visual analogue system recommended by the Up-dated Sydney System. The gastritis staging is defined from combined extent of atrophy scored histologically with the topography of atrophy identified through biopsy mapping (*Figure 11*).

		Corpus			
	Atrophy score	No atrophy (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum	No atrophy (score 0) (including incisura angularis)	Stage 0	Stage I	Stage II	Stage II
	Mild atrophy (score1) (including incisura angularis)	Stage I	Stage I	Stage II	Stage III
	Moderate atrophy (score 2) (including incisura angularis)	Stage II	Stage II	Stage III	Stage IV
	Severe atrophy (score 3) (including incisura angularis)	Stage III	Stage III	Stage IV	Stage IV

Figure 11. **The Gastritis Staging by OLGA system.**
Atrophy is score in a four-tiered scale (0-3) in each compartment. The atrophy stage defined from the combination of atrophic changes assessed in gastric antral and corporal biopsies.

Long-term follow-up studies proved that gastritis OLGA staging conveys relevant information on clinic-pathological outcome of gastritis and therefore *H pylori* negative patients with low OLGA stages could be confidently excluded from secondary preventive surveillance invasive procedures (67). Whereas patients with high OLGA stages (Stages III and IV) should be considered definitely candidates for endoscopic surveillance. Significant correlation was shown between OLGA stages and pepsinogen serology (marker of gastric atrophy). The ratio of pepsinogen I and II gives adequate information on the severity of atrophy, but its measurement fails to differentiate between neoplastic and non-neoplastic disease among patients with high stages of gastric mucosal atrophy (67).

Similar to the OLGA system another system, called the ***Baylor system*** was also introduced. The Baylor system follows the Baylor biopsy protocol (which uses Sydney System biopsy sites with two additional distal corporal biopsies, see *Figure 4*) and scores the atrophy of antrum and corpus independently (68). Antral atrophy stage is an average score, but corpus atrophy stage is independent of antral atrophy, independent

of individual reading in each biopsy but dependent on location. As corpus atrophy starts at the incisura and extends in continuity proximally and towards the greater curve, atrophy in a distal biopsy is early and atrophy in the most proximal location is advanced. The comparison of the two atrophy grading systems is still controversial. Although there were studies performed showing the superiority of Baylor system over OLGA in identifying cancer risk (69), the evaluation of gastric atrophy by OLGA is more widely used, further developed and more studied.

Rugge et al. developed the ***OLGIM system*** for more precise evaluation of cancer risk. This system basically incorporates the OLGA frame, but replaces the atrophy score with an assessment of intestinal metaplasia (IM) alone. Examining a series of more than 4500 biopsies (2007-2009) showed that OLGIM staging is less sensitive than OLGA staging in the identification of patients at high risk of gastric cancer (70). However, replacement of atrophic gastritis by intestinal metaplasia in the staging of gastritis considerably increases inter-observer agreement. The correlation with the severity of gastritis remains at least as strong. Therefore, the OLGIM may be preferred over the OLGA for the prediction of gastric cancer risk in patients with premalignant lesions (71).

Even though above precursor lesions were commonly known and found in everyday practice, there were no international recommendations to guide the clinicians in management of patients with such lesions. This resulted wide heterogeneity of surveillance practice and failure in diagnosing patients with early, curable stage cancer. The European Society of Gastrointestinal Endoscopy (ESGE), the European Helicobacter Study Group (EHSG), the European Society of Pathology (ESP) and the Sociedade Portuguesa de Endoscopia Digestiva (SPED) have therefore combined efforts to develop evidence-based guideline on the *Management of Patients with Precancerous Conditions and Lesions in Stomach* (termed *MAPS*). ***Panel of European gastroenterologist pathologist and other researchers met in Barcelona, Spain in 2010,*** agreed on methodology, set up key questions for literature search and drafted preliminary statements. The panel divided into several subgroups searched for evidence on a certain question. Finally representatives of European national societies reviewed the evidence gathered and formed statements. Later, online sessions were held for voting and further comments; finally thesecond meeting held in Porto, Portugal finalized the guideline. The guideline details diagnostic assessment,

treatment and follow-up of individuals with atrophic gastritis or intestinal metaplasia or dysplasia of gastric mucosa (72) (*Figure 12*).

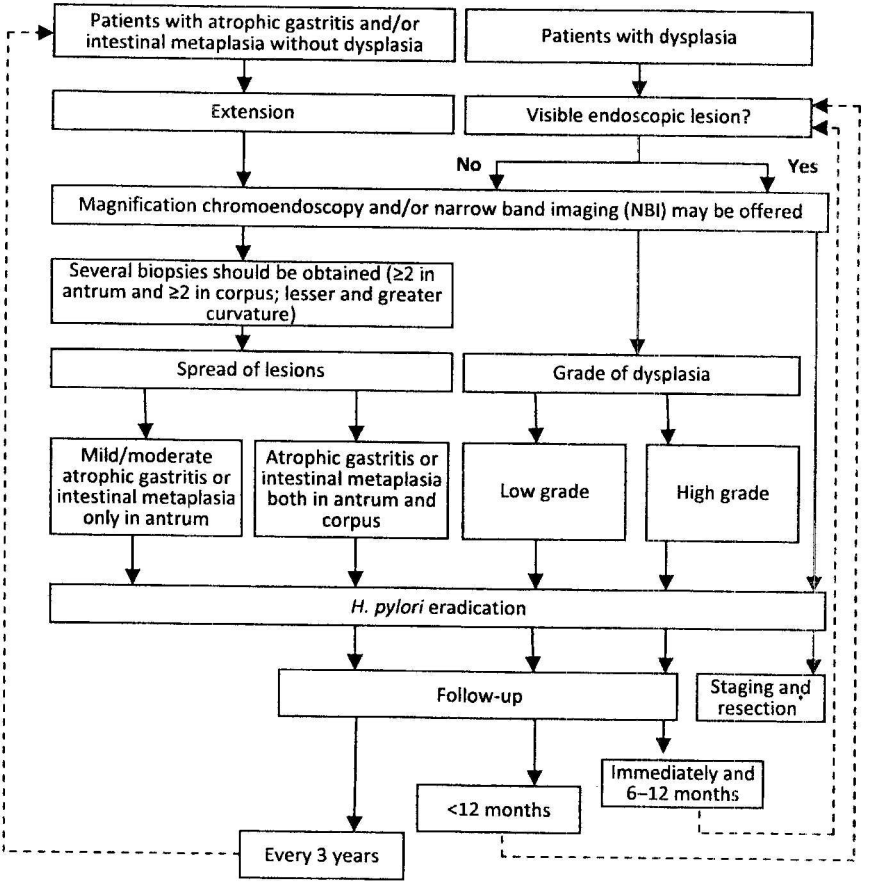

Figure 12. **Summary of management for patients with atrophic gastritis, gastric intestinal metaplasia and gastric epithelial dysplasia (72).**

The recommendations contain that conventional white light endoscopy cannot accurately differentiate between and diagnose preneoplastic gastric conditions/lesions. Thus, magnification chromoendoscopy or narrow-band imaging (NBI) endoscopy with or without magnification may be offered in these cases as it improves diagnosis of such lesions. In addition, at least four biopsies of the proximal and distal stomach, on

the lesser and greater curvature, are needed for adequate assessment of premalignant gastric conditions. Systems for histopathological staging (e.g. OLGA or OLGIM assessment) may be useful for identifying subgroups of patients with different risks of progression to gastric cancer namely those with extensive lesions (i. e., atrophy and/or intestinal metaplasia in both antrum and corpus). Although only low potential applicability was reported by participants for this indicator, low serum pepsinogen levels can also predict this phenotype and, in such patients, *H. pylori* serology may also be useful for further detection of high risk individuals. Beyond a family history of gastric cancer, either age, gender, *H. pylori* virulence factors, or host genetic variations change these clinical recommendations. Patients with extensive atrophy and/or extensive intestinal metaplasia should be offered endoscopic surveillance every 3 years. Patients with mild to moderate atrophy/intestinal metaplasia only in antrum do not need follow-up. If *H. pylori* infection is present, eradication should be offered to prevent high grade dysplasia or carcinoma. Patients with dysplasia without a visible endoscopic lesion should be closely followed up, either immediately and 6 to 12 months thereafter, or within 12 months, respectively, for those with high grade or low grade dysplasia. Those with dysplasia or cancer within an endoscopically visible lesion should undergo staging and resection (72) (*Figure 12*).

This review emphasizes the necessity of an international consensus meeting, which will establish a more uniform classification of gastritis respecting the wider multidisciplinary aspects (morphology, clinical picture, endoscopic view, immunology, bacteriology, molecular pharmacology, general medicine, oncology and causative factors as well as social/environmental circumstances of the people) in this field. (See the history of evolution of Classification of gastritis in *Table 3*).

Table 3

History of Classification of Gastritis

Year	Author/Classification	Comment
1728	**Stahl**	'Gastritis' defined (Bock, 1974)
1771	**Morgagni**	'Erosive' and 'ulcerating gastritis' described (Crawford et al, 1932)
1859	**William Brinton**	Acute, subacute and chronic gastritis differentiated
1855	**Rokitansky**	Hypertrophic gastritis described (Vaugham, 1945).
1870	**Fenwik**	Gastric atrophy described
1944	**Warren & Meissner**	Intestinal metaplasia described

Table 3 continues

1947	**Wood**	First gastric biopsy, 'Gastritis' defined (Wood et al, 1949)
1956	**Cheli & Dobero**	Superficial, Interstitial and Atrophic gastritis
1956	**Eder-Palmer**	Introduction of flexible fibre optic endoscope (Palmer, 1956)
1972	**Whitehead**	Superficial, Atrophic, both 'Active' or 'In-active'. Type and Stage of activity. Presence and type of metaplasia
1973	**Strickland & MacKay**	A (autoimmune) PCA+ in 95% and IFA+ in 75%, B (nonautoimmune = environmental)
1975	**Pitchumoni**	A (autoimmune-corpus), B (antrum), AB (both antrum and corpus) PCA+ or - (Glass & Pitchumoni, 1975)
1980	**Correa**	Autoimmune, Hypersecretory, Environmental
1988	**Correa**	Diffuse corporal (autoimmune), Chr. diffuse antral, Multifocal environmental, Chr. Superficial, Lymphocytic, Postgastrectomy
1989	**Owen**	Chr. non-specific type A, Chr. non-specific type B
1990	**Yardley**	H. pylori gastritis, Metaplastic atrophic (type A, autoimmune), Metaplastic atrophic (type B), Lymphocytic, Chemical
1990	**Dixon**	'Type C' proposed to reactive gastric lesions
1990	**Sobala**	Reflux gastritis defined as type C gastritis
1990	**Sydney**	Nonatrophic, Atrophic (Autoimmune, Multifocal), Special forms. Four-level scale, proper biopsy sampling & handling, standard reporting aiming etiology (Misiewicz et al, 1990)
1994	**Appelman**	Acute or Chronic; Helicobacter type, Atrophic (type A, type B), Lymphocytic, Focal & miscellaneous, Chemical gastropathies
1996	**Up-dated Sydney**	Biopsy location changed from anterior and posterior wall to greater and lesser curvature (Dixon et al, 1996)
2000	**Padova**	Classification of dysplasia and related lesions (Rugge et al, 2000)
2005	**OLGA**	Classification of grading mucosal atrophy (Rugge et al, 2005)

CHRONIC GASTRITIS TREATMENT & MANAGEMENT

Approach Considerations

Treatment of chronic gastritis can be aimed at a specific etiologic agent, if such an agent is known. Some cases of gastritis may resolve by themselves over time, or be relieved when the patient stops drinking alcohol, smoking cigarettes, or taking NSAIDs.When gastritis represents gastric involvement of a systemic disease, treatment is directed toward the primary disease.

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.

Once atrophic gastritis is diagnosed, treatment can be directed (1) to eliminate the causal agent, which is a possibility in cases of *H pylori* – associated atrophic gastritis; (2) to correct complications of the disease, especially in patients with autoimmune atrophic gastritis who develop pernicious anemia (in whom vitamin B-12 replacement therapy is indicated); or (3) to attempt to revert the atrophic process.

No consensus from different studies exists regarding the reversibility of atrophic gastritis; however, removal of *H pylori* from the already atrophic stomach may block further progression of the disease. Until recently, specific recommendations for *H pylori* eradication were limited to peptic ulcer disease. At the Digestive Health Initiative 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 also were recommended after resection of early gastric cancer and for low-grade mucosa-associated lymphoid tissue lymphoma. Furthermore, it is now widely accepted that if *H pylori* is identified as the underlying cause of gastritis, it should be eradicated.

Lifestyle

The treatment for gastritis that is caused by irritants is to stop using them. These include:

- Alcohol.
- Tobacco.
- Acidic beverages such as coffee (both caffeinated and decaffeinated), carbonated beverages, and fruit juices with citric acid.
- NSAIDS, such as aspirin and ibuprofen, acetaminophen.

These steps may also help.

Nutrition and Dietary Supplements

- Fiber rich diet.
- Foods containing flavonoids, like apples, celery, cranberries (including cranberry juice), onions, garlic, and tea may stop the growth of *H. pylori.*
- Antioxidant foods, including fruits (such as blueberries, cherries, and tomatoes), and vegetables (such as squash and bell peppers).
- Foods high in B vitamins and calcium, such as almonds, beans, whole grains (if no allergy), dark leafy greens (such as spinach and kale), and sea vegetables.
- Lean meats, cold water fish, tofu (soy, if no allergy) or beans for protein.
- Olive oil.
- Drink 6-8 glasses of filtered water daily.
- Identify and eliminate food allergies.
- Avoid beverages that may irritate the stomach lining or increase acid production including coffee (with or without caffeine), alcohol, and carbonated beverages.
- Avoid refined foods, such as white breads, pastas, and sugar.
- Reduce or eliminate trans - fatty acids, found in commercially baked goods such as cookies, crackers, cakes, French fries, onion rings, donuts, processed foods, and margarine.
- Avoid high fat foods. In animal studies, high fat foods increase inflammation in the stomach lining.

Pharmacotherapy for H pylori

At first, specific recommendations for *H pylori* eradication were limited to peptic ulcer disease. The European Helicobacter Study Group firsttook the initiative in 1996 in Maastricht to gatherdedicated experts in the field and to review anddiscuss all relevant clinical data to arrive atrecommendations for the clinical managementof H pylori infection (73). However, the 1997 Digestive Health Initiative (DHI) International Update Conference on *H pylori* broadened the recommendations for *H pylori* testing and treatment.

The Maastrichtconference has since been repeated at intervals of 4-5 years (*Figure 13*). (74, 75) Aspects related to the clinical role of H pyloriwere re-examined in Florence 2010 with theMaastricht methodology. The meeting focused onindications, diagnostics and treatments of H pyloriinfection with additional emphasis on diseaseprevention in particular, prevention of gastriccancer.In the 4th Maastricht/Florence ConsensusConference 44 experts from 24 countries tookactive part. Experts invited were chosen for theirexpertise and contribution to H pylori research and/or guideline methodology.

European Helicobacter Study Group
Founded in 1987

• **1996**	**Maastricht I consensus report**
	Eur J Gastroenterol Hepatol 1997; 9: 1–2.
• **2000**	**Maastricht II consensus report**
	Aliment Pharmacol Ther 2002; 16: 167–80.
• **2005**	**Maastricht III consensus report**
	Malfertheiner P et al. Gut 2007; 56: 772–81.
• **2010**	**Maastricht IV / Florence consensus report**
	44 experts from 24 countries
	Malfertheiner P et al. Gut 2012; 61: 646–664.

Figure 13. **The Maastricht conferences.**

H pylori infection is not easily cured, and research has shown that multidrug therapy is required. As with any bacterial infection, therapy must include antimicrobial agents to which the bacterium is sensitive. Antibiotics that have proven effective against *H pylori* include clarithromycin, amoxicillin, metronidazole, tetracycline, and furazolidone. Cure rates with single antibiotics have been poor (0-35%). Monotherapy is

associated with the rapid development of antibiotic resistance, especially to metronidazole and clarithromycin.

If *H pylori* is identified as the underlying cause of gastritis, subsequent eradication now is almost generally accepted practice. Protocols for *H pylori* eradication require a combination of antimicrobial agents and antisecretory agents, such as a proton pump inhibitors (PPIs), ranitidine bismuth citrate (RBC), or bismuth subsalicylate. Despite the combinatorial effect of drugs in regimens used to treat *H pylori* infection, cure rates remain, at best, 80-95%.

Lack of patient compliance and antimicrobial resistance are the most important factors influencing poor outcome. Currently, the most widely used and efficient therapies to eradicate *H pylori* are triple therapies (recommend as first-line treatments) and quadruple therapies (recommended as second-line treatment when triple therapies fail to eradicate *H pylori).* In both cases, 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 cure is no evidence of *H pylori* 4 or more weeks after ending the antimicrobial therapy.

Regimens available

- ***The triple treatment*** including PPI-clarithromycin andamoxicillin or metronidazole proposed at the first Maastrichtconference (73) to treat H pylori infection has become universalsince it was recommended by all the consensus conferencesheld around the world. However, the most recent data showthat this combination has lost some efficacy and often allowsthe cure of only a maximum of 70% of the patients, which isless than the 80% rate aimed for at the beginning and farbelow what should be expected for an infectious disease (76).
- While no new drug has been developed for this indication,a number of studies have been carried out in recent yearsusing different combinations of known antibiotics. Most datawere obtained with the so-called **'sequential treatment'**which includes a 5-day period with PPI amoxicillin, followedby a 5-day period with PPI-clarithromycin-metronidazole (ortinidazole) (77, 78).

- It was also proposed that the three antibiotics should betaken simultaneously together with a PPI (***non-bismuthquadruple therapy***) (79, 80).
- There was also a renewal of the old recipethat is, thebismuth-containing quadruple therapy following the developmentof a gallenic formulation including bismuth salts,tetracycline and metronidazole in the same pill (81-83).

There are several explanations for the decrease in efficacy of the standard triple therapy: compliance, high gastric acidity, highbacterial load, type of strains, but by far the most important isthe increase in H pylori resistance to clarithromycin (*Figure 14*). The globalclarithromycin resistance rate in Europe increased from 9% in 1998 (84) to 17.6% in 2008-9 (85). Resistance increased in mostparts of Europe, but it has now reached a prevalence >20% inmost countries in Central, Western and Southern Europe,which is considered a high resistance rate. In Northern Europeancountries it is <10%, which is considered a low resistancerate (86). Following the European Medicines Agency recommendationon evaluation of medicinal products indicated for treatment ofbacterial infection, three categories of bacterial species can bedefined according to their susceptibility to a given antibiotic:

- usually susceptible (0-10% resistant);
- inconstantly susceptible (10-50% resistant);
- usually resistant (>50% resistant).

Host factors	Bacterial factors
Compliance to therapy	***Primary resistance to antibiotics***
Gastric acid hypersecretion	Bacterial load in stomach
Genetic polymorphism of CYP 450	Bacterial coccoid forms
Gastroduodenal disease (NUD)	cagA status (negative)
Gastritis pattern (pangastritis)	vacA alleles status (s2m2 allele)
Obesity	dup A status*
Smoking	

*dup: duodenal ulcer promoting.

Figure 14. **Factors affecting H. pylori eradication** (Zullo A et al. J Clin Gastroenterol 2012; 46: 259–261).

H. pylorus now falls into the second category, except for Northern Europe (87).

Regions of low clarithromycin resistance

First-line treatment

In areas of low clarithromycin resistance, clarithromycin-containingtreatments are recommended for first-line empirical treatment. Bismuth-containingquadruple therapy is also an alternative. In these regions the standard PPI-clarithromycin-containingregimen is still recommended as the first-line treatment as wellas bismuth-containing regimens. (Figure Different ways of improving the PPI-clarithromycin-amoxicillin/metronidazole regimens have been proposed (*Figure 15*):

- The use of high-dose (twice a day) PPI increases the efficacy of tripletherapy. In addition,cure rates of standard triple therapy depend on the availability ofPPI, which itself depends on the CYP2C19 and multidrug resistance (MDR) polymorphisms.
- Extending the duration of PPI-clarithromycin-containing triple therapiesfrom 7 to 10-14 days improves the eradication success by about 5% and may beconsidered.
- PPI-clarithromycin-metronidazole (PCM) and PPI-clarithromycinamoxicillin(PCA) regimens are equivalent. When the PCM and PCA regimens were compared in patientswith clarithromycin-resistant strains, a statistically significant difference was seen ($p<0.001$), but this difference may be due to the heterogeneity of the studies.
- Adding an adjuvant treatment. Certain probiotics and prebiotics show promising results as an adjuvant treatment in reducing side effects. Lactoferrin has been used to improve H. pylori treatment. Probiotics are most likely to lead to a decrease ofadverse events, especially diarrhoea and indirectly may help toimprove the eradication rate.
- Other factors. PPI-clarithromycin-containing treatments do not need to be adapted to patient factors except for dosing. Besides the CYP2C19 and MDR1 polymorphisms, which affect the availability of the PPI administered, and the interleukin (IL)-1b polymorphisms, which affect the intragastric acidity present in the stomach in the case of H pylori infection, other factors have been considered: type of disease, BMI and smoking status. Treating patients with peptic ulcer disease shows a consistently better outcome than treating patients with functional dyspepsia.

In patients with high BMI, especially obese people, the distribution volume of the drugs being higher, it is most likely that the concentration at the gastric mucosal level will be lower and the risk of failure higher. Smoking is also a risk factor for failure. The reason may be a reduction of antibiotic delivery due to a decreased gastric blood flow, a decrease in intragastric pH in cases of smoking, and nicotine could potentiate the vacuolating toxin activity of H pylori in gastric cells. It may also be a marker of poor compliance.

Improving standard triple therapy (PAC)

• **Increase dose of PPI**	
Esomeprazole 40 mg bid increases eradication by 8–12%	
• **Increase length of treatment**	
10-day treatment	Increases eradication by 4%
14-day treatment	Increases eradication by 5–6%
• **Adjuvant treatment**	Lactoferrin – S. boulardii
	Promising results
	More studies needed

Figure 15. **Different ways of improving standard triple therapy** (Malfertheiner P et al. Management of HP infection: the Maastricht IV/Florence consensus report. Gut 2012; 61: 646–664).

Second-line treatment

(1) After failure of a PPI-clarithromycin-containing treatment, eithera bismuth-containing quadruple therapy or levofloxacin-containing triple therapy isrecommended.

(2) Rising rates of levofloxacin resistance should be taken into account.

The rationale is to abandon clarithromycin in an empiricalsecond-line-treatment because there is a likelihood that selectionof a clarithromycin-resistant strain occurred. Use of 10-day PPI-levofloxacin-amoxicillin is the other alternativesecond-line treatment based on the results obtained inrecent years. It is strongly advised thatlevofloxacin should not be used in a patient with chronicinfectious bronchopneumopathy who may have received fluoroquinolones.

Third-line treatment

After failure of second-line treatment, treatment should be guided byantimicrobial susceptibility testing whenever possible. After two treatment failures, it appears recommendable toempirically prescribe antibiotics not previously used but,whenever possible, to obtain gastric biopsy specimens to culture H pylori and perform susceptibility testing. It will enablethe best choice to be made among the various antibiotics thatcan be used and to which H pylori may develop resistance.

Besides clarithromycin and levofloxacin already mentioned, rifabutin is another candidate that may be used.

Regions or populastions of high clarithromycin resistance

First-line treatment

In areas of high clarithromycin resistance, bismuth-containing quadrupletherapies are recommended for first-line empirical treatment (*Figure 16*). If this regimen is notavailable, sequential treatment or a non-bismuth quadruple therapy is recommended (*Figure 17*).

Bismuth quadruple therapy (BMT)
Underutilized in clinical practice

• **PPI**	Standard dose, bid
• **Bismuth subcitrate**	420 mg, qid
• **Metronidazole/Tinidazole**	500 mg, tid
• **Tetracycline**	500 mg, qid
For 10–14 days	

Figure 16. **Bismuth quadruple therapy.**

Sequential therapy
"five plus five" day therapy

• **1st five days**	PPI (standard dose, bid)
	Amoxicillin (1 g, bid)
• **2nd five days**	PPI (standard dose, bid)
	Clarihromycin (500 mg, bid)
	Metronidazole/Tinidazole (500 mg, qid)
For 10 days	

Indicated in clarithromycin or nitroimidazole resistance strains.

Figure 17. **Sequential therapy.**

In regions of high clarithromycin resistance, bismuth-containing quadruple therapies are the first choice. It appears mandatory toavoid clarithromycin use in the standard regimen under suchcircumstances if this antibiotic cannot be tested. The treatmentrecommended contains bismuth salts for which no resistancehas been described, tetracycline for which resistance is seldomfound in Europe and metronidazole for which in vitro resistanceis common but can be overcome by increasing the length oftreatment. However, bismuth drugs may not be available in some areas. It is then necessary to prescribe sequential treatment. While notideal because it contains clarithromycin, it has been shown thatclarithromycin resistance could be overcome in a number ofcases. Non-bismuth quadruple therapy (the socalled 'concomitant' treatment) is also an option (*Figure 18*).

Concomitant therapy
"Non-bismuth quadruple therapy"

• **PPI**	Standard dose, bid
• **Amoxicillin**	1 g, bid
• **Clarithromycin**	500 mg, bid
• **Metronidazole/Tinidazole**	500 mg, bid
For 10–14 days	

Not indicated in high prevalence of Clari-R (>20–30%).

Figure 18. **Concomitant therapy.**

Second line therapy

(1) In areas of high clarithromycin resistance after failure of bismuth containingquadruple therapy, levofloxacin containing triple therapy is recommended.

(2) Rising rates of levofloxacin resistance should be taken into account.

After failure of the second-line treatment (with bismuth containing quadruple regimen), it is recommended to use thePPI-containing levofloxacin regimen. However, given therise in resistance to this antibiotic, the prevalence must be takeninto account.

Third-line therapy

After failure of second-line therapy, treatment should be guided byantimicrobial susceptibility testing, whenever possible. The recommendation is the same as in areas of low clarithromycinresistance.

Treatment options in patients with penicillin allergy

In patients with penicillin allergy, in areas of low clarithromycin resistance, for a first-line treatment, a PPI-clarithromycin-metronidazole combinationmay be prescribed and in areas of high clarithromycin resistance, the bismuthcontainingquadruple therapy should be preferred.

As a rescue regimen, in areas of low fluoroquinolone resistance, a levofloxacincontainingregimen (together with a PPI and clarithromycin) represents a second-linealternative in the presence of penicillin allergy.

Long-Term Monitoring

If a patient was treated for *H pylori* infection, confirm that the organism has been eradicated. Evaluate eradication at least 4 weeks after the beginning of treatment. Eradication may be assessed by means of noninvasive methods such as the urea breath test or the stool antigen test.

Follow-up may be individualized, depending on findings during endoscopy. For example, if dysplasia is found with endoscopy, increased surveillance is necessary. For patients with atrophic gastritis or dysplasia, follow-up endoscopy is recommended after 6 months.

The following supplements may help with digestive health:

- A multivitamin daily, containing the antioxidant vitamins A, C, E, the B vitamins, and trace minerals, such as magnesium, calcium, zinc, and selenium.
- Omega-3 fatty acids, such as fish oil, 1-2 capsules or 1 tablespoonful of oil 2-3 times daily – may help decrease inflammation. Fish oil may increase the risk of bleeding.
- Probiotic supplement (containing *Lactobacillus acidophilus*), may help maintain a balance in the digestive. Probiotics may help suppress *H. pylori* infection and may also help reduce side effects from taking antibiotics, the treatment for an *H. pylori* infection. Some probiotic supplements may need to be refrigerated for best results.

Herbs

Herbs are generally a safe way to strengthen and tone the body's systems. The herbs may be uses as dried extracts (capsules, powders, teas), glycerites (glycerine extracts), or tinctures (alcohol extracts).

- Cranberry *(Vaccinium macrocarpon)* 400 mg twice daily – Some preliminary research suggests cranberry may inhibit *H. pylori* growth in the stomach.
- Mastic *(Pistacia lentiscus)* standardized extract, 1,000-2,000 mg daily in divided dosages – Mastic is a traditional treatment which inhibits *H. pylori.*
- DGL-licorice (*Glycyrrhiza glabra*) standardized extract, 250-500 mg 3 times daily, chewed either 1 hour before or 2 hours after meals – may help protect against stomach damage from NSAIDs. Glycyrrhizin is a chemical found in licorice that causes side effects and drug interactions. DGL is deglycyrrhizinated licorice, or licorice with the glycyrrhizin removed.
- Peppermint *(Mentha piperita)* standardized, enteric coated tablet, 1 tablet 2-3 times daily – help relieve epigastric pain. Each tablet contains 0.2 ml of peppermint oil. Recommended to use the enteric coated form to avoid heartburn.

Homeopathy

Although few studies have examined the effectiveness of specific homeopathic therapies, professional homeopaths may consider the following remedies for the treatment of gastritis symptoms (such as nausea and vomiting) based on their knowledge and experience. Before prescribing a remedy, homeopaths take into account patient's constitution – physical, emotional, and psychological status. An experienced homeopath assesses all of these factors when determining the most appropriate individually treatment.

- *Pulsatilla* – for heartburn, queasiness, a bad taste in the mouth brought on by eating rich foods and fats (especially ice cream); symptoms may include vomiting partly digested food. This remedy is most appropriate for someone whose tongue is coated with a white or yellow substance.
- *Ipecacuahna* – for persistent and severe nausea, with or without vomiting and diarrhea, caused by an excess of rich or fatty foods.
- *Carbo vegetabilis* – for bloating and indigestion, especially with flatulence and fatigue.
- *Nux vomica* – for heartburn, nausea, retching without vomiting, and sour burps caused by overeating, alcohol use, or coffee drinking. This remedy is most appropriate for people who also feel irritable and sensitive to noise and light.

Acupuncture

Acupuncture may help reduce stress and improve overall digestive function.

Prognosis

The prognosis 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, whereas 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 gastritis is the most frequent cause of MALT lymphoma. Patients with chronic atrophic gastritis may have a 12- to 16-fold increased risk of developing gastric carcinoma, compared with the general population. Approximately 1 in 6 infected persons develop peptic ulcer, and, in the United States, approximately 25% develop hypochlorhydria or achlorhydria. The lifetime risk of gastric cancer is in the range of 1-3%.

Eradication of *H pylori* 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. Data on 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, whereas 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, whereas 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.

In patients with autoimmune gastritis, the major effects are consequent to the loss of parietal and chief cells and include achlorhydria, hypergastrinemia, loss of pepsin and pepsinogen, anemia, and an increased risk of gastric neoplasms. Autoimmune gastritis represents the most frequent cause of pernicious anemia in temperate climates. The risk of gastric adenocarcinoma appears to be at least 2.9 times higher in patients with pernicious anemia than in the general population.

Conclusion

During the last 150 years the knowledge on "gastritides" has enlarged enormously. The discovered new forms of gastritis, the new etiopathogenic evidences have continuously modified our views on gastritis classification. Recently, good agreement has been established among pathologists and clinicians to standardize the methodology of biopsy sampling, histological assessment and reporting leading to reproducible and clinically useful diagnosis. Recent recommendations for the management of bleeding, *H. pylori* infected or cancer risk patients help clinicians to endorse up-to-date therapy and follow-up. Presently there are still many unanswered questions regarding of lot of segments of various forms of gastritis. Pathologists still need to issue descriptive histological reports of 'chronic non-specific gastritis' to clinicians due to either lack of clinical information or knowledge of identification of gastric inflammations distinctive from known categories. To reduce the number of these cases further communication and consensus (as well as further consensus meetings) between pathologists and gastroenterologists are needed. The growing amount of information from research and clinical studies might show further new directions and require modification of classification. It is possible that one day the presently known different types of gastritis will be known as various stages of the same disease, or a partition of the present form could happen due to new discovered diverseetiology.

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Test

1. C.S. Classification system of Gastritis include all, except:
   A. Sydnei Classifictaion (1990)
   B. Baylor Classification
   C. OLGAClassification
   D. Los Angelas Classification
   E. Houston Update of Sydnei Classifictaion (1994)

2. C.S. The Lymphocytic gastritis has been reported in various parts of the world, but more commonly in:
   A. North America
   B. South America
   C. Africa
   D. Europe
   E. Asia

3. C.S. *H pylori* gastritis is the most frequent cause of:
   A. MALT lymphoma
   B. pernicious anemia
   C. sarcoidosis
   D. autoimmune gastritis
   E. eosinophilic gastroenteritis

4. C.M. Classification of acute gastritis include all, except:
   A. erosive
   B. nonerosive
   C. phlegmonous
   D. autoimmune
   E. lymphocytic

5. C.M. Gastritis can be classified based on the underlying etiologic agent as:
   A. Helicobacter pylori
   B. Bile reflux
   C. nonsteroidal anti-inflammatory drugs
   D. autoimmune
   E. lymphocytic

6. C.M. What kind of the Current Gastritis Staging Systems for Gastric Atrophyhave been introduced:
   A. Savary-Miller classification
   B. Baylor
   C. Los Angela
   D. OLGA
   E. Forrest classification

7. C.M. Infection granulomatous gastritis predominantly affects the gastric antrum and associated with:
   A. tuberculosis
   B. syphilitic involvement of the stomach
   C. histoplasmosis
   D. Helicobacter pylori
   E. fungi

8. C.M. Special forms of gastritis – chronic noninfectious granulomatous gastritis are associated with:
   A. Crohn disease
   B. tuberculosis
   C. sarcoidosis
   D. isolated granulomatous gastritis
   E. lymphocytic

9. C.M. Autoimmune gastritisis associated with following types of antibody:
   A. serum antiparietal
   B. antimitochondrial
   C. antinuclear
   D. anti-intrinsic factor
   E. anti-liver kidney microsomal

10. C.M. Chronic reactive chemical gastropathy is associated with:
   A. long-term intake of aspirin or NSAIDs
   B. Helicobacter pylori infection
   C. sarcoidosis
   D. bile-containing intestinal contents reflux into the stomach
   E. radiation

Answer

1. Correct answer: D
2. Correct answer: D
3. Correct answer: A
4. Correct answer: D, E
5. Correct answer: A, B, C, D
6. Correct answer: B, D
7. Correct answer: A, B, C, E
8. Correct answer: D, E
9. Correct answer: A, D
10. Correct answer: A, D

Case-based self-assessment questions

1. A 58-year-old man is evaluated for abdominal pain by his primary care physician. He reportssevere stress at his job for the last 3 months and has since noted that he has epigastric pain that isrelieved by eating and drinking milk. He has not had food regurgitation, dysphagia, or bloody emesis orbowel movements. He denies any symptoms in his chest. Peptic ulcer disease is suspected. Which ofthe following statements regarding noninvasive testing for Helicobacter pylori is true?

A. There is no reliable noninvasive method to detect H. pylori.
B. Stool antigen testing is appropriate for both diagnosis of and proof of cure after therapy for H. pylori.
C. Plasma antibodies to H. pylori offer the greatest sensitivity for diagnosis of infection.
D. Exposure to low-dose radiation is a limitation to the urea breath test.
E. False-negative testing using the urea breath test may occur with recent use of NSAIDs.

2. A 44-year-old woman complains of 6 months of epigastric pain that is worst between meals. Shealso reports symptoms of heartburn. The pain is typically relieved by over-the-counter antacidmedications. She comes to the clinic after noting her stools darkening. She has no significant pastmedical history and takes no medications. Her physical examination is normal except for diffusemidepigastric pain. Her stools are heme positive. She undergoes EGD, which demonstrates a wellcircumscribed2-cm duodenal ulcer that is positive for H. pylori. Which of the following isrecommended initial therapy given these findings?

A. Lansoprazole plus clarithromycin plus amoxicillin for 14 days.
B. Pantoprazole plus amoxicillin for 21 days.
C. Pantoprazole plus clarithromycin for 14 days.
D. Omeprazole plus bismuth plus tetracycline plus metronidazole for14 days.
E. Omeprazole plus metronidazole plus clarithromycin for 7 days.

3. A 57-year-old man with peptic ulcer disease experiences transient improvement withHelicobacter pylori eradication. However, 3 months later symptoms recur despite acid-suppressingtherapy. He does not take nonsteroidal anti-inflammatory agents. Stool analysis for H. pylori antigen isnegative. Upper GI endoscopy reveals prominent gastric folds together with the persistent ulceration inthe duodenal bulb previously detected and the beginning of a new ulceration 4 cm proximal to the initialulcer. Fasting gastrin levels are elevated and basal acid secretion is 15 meq/h. What is the best test toperform to make the diagnosis?

A. No additional testing is necessary.
B. Blood sampling for gastrin levels following a meal.
C. Blood sampling for gastrin levels following secretin administration.
D. Endoscopic ultrasonography of the pancreas.
E. Genetic testing for mutations in the MEN1 gene.

Answers

1. *The answer is D.* Noninvasive testing for H. pylori infection is recommended inpatients with suggestive symptoms and no other indication for endoscopy, e.g., GI bleeding, atypicalsymptoms. Several tests have good sensitivity and specificity, including plasma serology for H. pylori,14C or 13C-urea breath test, and the fecal H. pylori antigen test. Sensitivity and specificity are greaterthan 80% and greater than 90%, respectively, for serology, while the urea breath test and fecal antigentesting are greater than 90% for both. Serology is not useful for early follow-up after therapycompletion, as antibody titers will take several weeks to months to fall. The urea breath test, whichrelies on the presence of urease secreted by H. pylori to digest the swallowed radioactive urea andliberate 14C or 13C as part of ammonia, is simple and rapid. It is useful for early follow-up, as itrequires living bacteria to secrete urease and produce a positive test. The limitations to the test includethe requirement for ingestion of radioactive materials, albeit low dose, and false-negative results withrecent use of PPI, antibiotics, or bismuth compounds. Stool antigen testing is cheap and convenient, butis not established for proof of eradication.

2. *The answer is A.* H. pylori should be eradicated in patients with documented peptic ulcer disease no matter the number of episodes, severity, presence of confounding factors (e.g., NSAID ingestion), or symptomatic status. Documented eradication of H. pylori is associated withsubstantially lower recurrence rates and symptom improvement. Treating patients with GERD whorequire long-term acid reduction therapy and the role of H. pylori eradication to prevent gastric cancerare controversial. Fourteen-day regimens are most effective. Shorter duration of therapy with currentagents available has high recurrence rates. Dual-therapy regimens are not recommended because oferadication rates of less than 80%. A number of combinations are available (*Table*). Tripletherapyregimens (one antacid plus two antibiotics) for 14 days have an eradication rate of 85–90%.Antibiotic resistance is the most common cause of failure to eradicate in compliant patients. Unfortunately, there is no currently available test for H. pylori sensitivity to direct therapy. Quadrupletherapy should be reserved for patients with failure to eradicate after an effective initial course.

Table

Regimens Recommended for Eradication of H. Pylori Infection

Drug	Dose
Triple Therapy	
1. Bismuth subsalicylate *plus* Metronidazole *plus* Tetracycline[a]	2 tablets qid 250 mg qid 500 mg qid
2. Ranitidine bismuth citrate *plus* Tetracycline *plus* Clarithromycine or metronidazole	400 mg bid 500 mg bid 500 mg bid
3. Omeprazole (lansoprazole) *plus* Clarithromycine *plus* Metronidazole[b] *or* Amoxicillin[c]	20 mg bid (30 mg bid) 250 or 500 mg bid 500 mg bid 1 g bid
Quadruple Therapy	
Omeprazole (lansoprazole)	20 mg (30 mg) daily
Bismuth subsalicylate	2 tablets qid
Metronidazole	250 qid
Tetracycline	500 mg qid

[a]Alternative: use prepacked Helidac.
[b]Alternative: use prepacked Prevpac.
[c]Use either metronidazole or amoxicillin, not both.

3. *The answer is C.* Fasting gastrin levels can be elevated in a variety of conditionsincluding atrophic gastritis with or without pernicious anemia, G-cell hyperplasia, and acidsuppressive therapy (gastrin levels increase as a consequence of loss of negative feedback). Thediagnostic concern in a patient with persistent ulcers following optimal therapy is Zollinger-Ellisonsyndrome (ZES). The result is not sufficient to make a diagnosis because gastrin levels may be elevatedin a variety of conditions. Elevated basal acid secretion also is consistent with ZES, but up to 12% ofpatients with peptic ulcer disease may have basal acid secretion as high as 15 meq/h. Thus, additionaltesting is necessary. Gastrin levels may go up with a meal (>200%), but this test does not distinguish Gcellhyperfunction from ZES. The best test in this setting is the secretin stimulation test. An increase ingastrin levels greater than 200 pg within 15 minutes of administering 2 μg/kg of secretin by IV bolus hasa sensitivity and specificity of greater than 90% for ZES. Endoscopic ultrasonography is useful inlocating the gastrin-secreting tumor once the positive secretin test is obtained. Genetic testing formutations in the gene that encodes the menin protein can detect the fraction of patients with gastrinomasthat are a mani festation of multiple endocrine neoplasia type I (Wermer's syndrome). Gastrinoma is thesecond most common tumor in this syndrome following parathyroid adenoma, but its peak incidence isgenerally in the third decade.

(**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 18th Edition Ed. Dan L. Longo , 2012, (Chap. 293)).

CONTENTS