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A Literature Review on Helicobacter Pylori Management

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***Abstract*: Helicobacter pylori (H.pylori) infection is highly associated with main symptoms and death that are recently affecting 50-75% of the population in the world. But past few years' efforts, H. pylori treatment is more difficult and it is still standing challenges for medical practitioner due to antibiotic resistance and patient compliance, as there are no regimens can achieve the desired eradication rate. In fact, no new drug has been developed for H. pylori only using different mixtures of antibiotics and anti-secretory agents. Nowadays, antibiotics are frequently prescribed for this infection that is declining their effectiveness as a result of which growing antibiotic resistant worldwide. At present, standard therapy has been regarded as the first line treatment of H. pylori in many guidelines, but the eradication rate has decreased to unacceptable levels. Therefore, standard triple therapy is left due to increase in antibiotic resistance consequences low eradication rate. Alternative treatment regimens such as sequential, quadruple, concomitant, and levofloxacin therapies are most recommended eradicating H. pylori compare to triple therapy; one of them levofloxacin therapy is most excellent therapy for eradicating H. pylori infection in antibiotic resistant patients. Herein, this review discussed recent data focusing on diverse eradication regimens so as to emphasize the current H. pylori treatment and the significance of considering the occurrence of antibiotic resistance at a regional level when choosing a suitable therapy.**

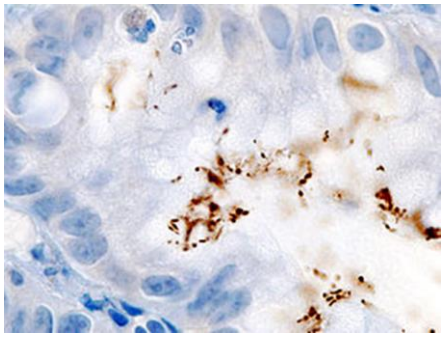
***Keywords*: antibiotic, resistance, regimens, eradication, anti-secretory, unacceptable.**

1. Introduction

Helicobacter -associated gastritis is a primary infection of the stomach caused by *Helicobacter* bacteria. The most frequent *Helicobacter* species found in patients with active gastritis is *Helicobacter pylori* (*H pylori*). *H pylori* is also the primary cause of chronic gastritis. [1] A small number of cases of chronic gastritis are associated with *Helicobacter heilmannii*.

Helicobacter pylori, previously known as Campylobacter pylori, is a Gram-negative micro aerophilic bacterium usually found in the stomach. It was identified in 1982 by Australian doctors Barry Marshall and Robin Warren, who found that it was present in a person with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial Cause. [2] Helicobacter pylori (*H. pylori*) is a type of bacteria. These germs can enter your body and live in your digestive tract. After many years, they can cause sores, called ulcers, in the lining of your stomach or the upper part of your small intestine. For some people, an infection can lead to stomach cancer. [3] Infection with *H. pylori* is common. About two-thirds of the world's population has it in their bodies. For most people, it doesn't cause ulcers or any other symptoms. If you do have problems, there are medicines that can kill the germs and help sores heal. As more of the world gets access to clean water and sanitation, fewer people than before are getting the bacteria. With good health habits, you can protect yourself and your children from *H. pylori*. However, over 80% of individuals infected with the bacterium are asymptomatic, and it may play an important role in the natural stomach ecology [4].

Helicobacter pylori:



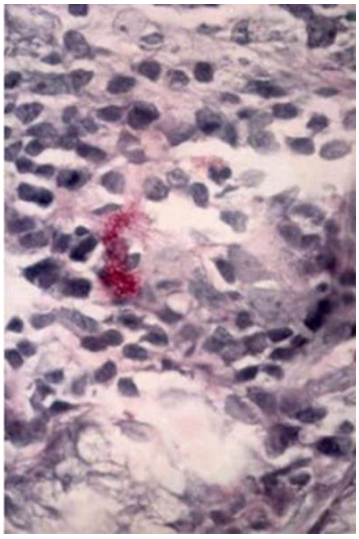
Immuno histochemical staining of H. Pylori from a gastric biopsy.

Other name: campylobacter pylori

2. Background

Helicobacter pylori, a gram-negative, helical bacilli that live in the gastric epithelium was first isolated in 1983. It was discovered by Marshall and Warren who cultured Campylobacter pylori is which was later reclassified as Helicobacter pylori. It is transmitted via the fecal-oral, gastro-oral, or oral-oral routes. H. pylori is able to thrive in the gastric environment due to urease, motility, and adherence to gastric epithelium, which allow it to neutralize gastric acid, penetrate

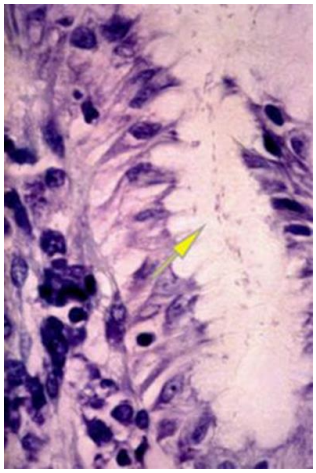
through the mucus layer to the gastric epithelium, and colonize. It induces inflammation, leading to peptic ulcer disease (PUD), gastric cancer, and gastric mucosa associated lymphoid-tissue (MALT) lymphoma. Although infection with H. pylori persists without treatment, the majority of infections do not lead to symptoms or gastrointestinal disease [5]. The association of chronic H pylori infection with alterations in the gastric mucosal cell proliferation is recognized worldwide. In addition, H pylori can produce and release several bioactive factors that may directly affect the stomach's parietal cells, which produce hydrochloric acid, and entero chromaffin like (ECL) cells (i.e., G cells and D cells), which produce gastrin and somatostatin, respectively. Evidence suggests that H pylori inhibits D cells and stimulates G cells. H pylori has some control mechanisms that are able to switch on or off the transcription of different genes when needed. Two histology images are presented below.



Helicobacter pylori infection. Lamina propria of the stomach is shown with 2 mast cells overlapping each other. Note the upper part shows the degranulating process with the release of granules of inflammation mediators (Giemsa staining, 250X). Courtesy of Pantaleo Bufo, University of Foggia, Italy.

A strong association has been reported between H pylori infection and gastric lymphoma and adenocarcinoma of the body and antrum of the stomach. Some cofactors may play a key role in determining such diseases. Whether H pylori eradication can decrease the risk of cancer remains unknown.

H pylori infection occurs more frequently in developing countries than in industrialized countries. H pylori strains differ in their potential to cause diseases. Although anyone can develop a microscopic gastritis, only a minority of infected persons develop ulcers or other diseases. H pylori gastritis is considered an infectious condition, even in the setting of asymptomatic patients and regardless of whether peptic ulcers or gastric cancer is present. Some Helicobacter -like organisms (HLOs) have been detected by specific polymerase chain reaction tests. The first of these HLOs was described in ferrets and is called Helicobacter mustelae. Helicobacter hepaticus has been described in Syrian hamsters. These HLOs are useful for researching H pylori infection modalities [6, 7].



An antral gland of the stomach with a large Giemsa-stained colony of Helicobacter pylori in the lumen (arrow) at 250X power. Courtesy of Pantaleo Bufo, University of Foggia, Italy.

3. Pathophysiology

The most common route of H pylori infection is either oral-to-oral (stomach contents are transmitted from mouth to mouth) or fecal-to-oral (from stool to mouth) contact [8]. Parents and siblings seem to play a primary role in transmission.

In a susceptible host, H pylori results in chronic active gastritis that may lead, in turn, to duodenal and gastric ulcer disease, gastric cancer, and MALTomas. H pylori infection causes chronic active gastritis, which is characterized by a striking infiltration of the gastric epithelium and the underlying lamina propria by neutrophils, T and B lymphocytes, macrophages, and mast cells. Mast cells, usually responsible for the immune response balance, may be important effector cells in the pathogenesis of gastritis. However, H pylori does not seem to invade the gastric mucosa, although evidence suggests that the mucus layer provides a niche wherein the germ is protected from gastric secretions.

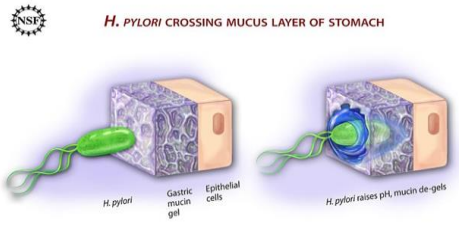


Diagram showing how H. pylori reaches the epithelium of stomach.

To avoid the acidic environment of the interior of the stomach (lumen), *H. pylori* uses its flagella to burrow into the

mucus lining of the stomach to reach the epithelial cells underneath, where it is less acidic. *H. pylori* is able to sense the pH gradient in the mucus and move towards the less acidic region (chemotaxis). This also keeps the bacteria from being swept away into the lumen with the bacteria's mucus environment, which is constantly moving from its site of creation at the epithelium to its dissolution at the lumen interface [9].

The release of host cytokines after direct contact of H pylori with the epithelial cells of the gastric lining could recall the inflammatory cells in the infected area. One study demonstrated that the gastric epithelium, when infiltrated by neutrophils and macrophages in the lamina propria, highly expresses two neutrophil chemotactic factors: gro-alpha and interleukin-8. In addition, the interferon-gamma inducible protein–10 (IP-10) and the monokine induced by interferon-gamma (MIG), 2 selective chemotactic factors for T lymphocytes, are expressed by the endothelium and mononuclear cells of the gastric mucosa in patients with H pylori -related gastritis. According to the same study, gro-alpha and interleukin-8 may have a central role in neutrophils trafficking from the vessels to the mucosal epithelium, while IP-10 and MIG determine T lymphocyte recruitment into the mucosa. Another hypothesis states that H pylori may recall immune cells from afar because of its own molecules, such as urea or lipopolysaccharide (LPS). Outer-membrane permeability is a function mediated by LPS. Despite the presence of bacterial LPS in biologically active quantities in the gastric mucosa, the mechanisms by which it may recall the immune cells are still unknown. According to one hypothesis, H pylori may induce the production of autoantibodies against the host's gastric lining. The LPS of H pylori shows certain blood group antigens, such as Leb, Lex, Ley, and H-type I. Such antigens are thought to represent important virulence factors involved in the adhesive process of the germ. Leb constitutes an adhesion, and differences exist in the Le compositions of adherent and no adherent bacteria. This, perhaps, accounts for a relationship between adhesion and Le expression. Hage and colleagues identified the BabA protein (Blood group antigen-binding Adhesin) in H pylori that interacts with gastric mucus binding Leb antigens, confirming the relationship [10]. As a consequence, H+ bridges may be formed, strongly anchoring the bacterium to the gastric mucosa. In addition, any Le antigen shows phase variation leading to the spontaneous and random switching on and off of the expression of these antigens. For example, the H-type I antigen seems to be the result of a reversible singular nucleotidic deletion/insertion in a tract of a glycosyl transferase gene. The LPS of the H pylori also seems to influence tumoral proliferation of ECL cells, stimulating the intracellular polyamine biosynthesis pathway and ornithine decarboxylase activity by the activation of a CD14 receptor on the ECL cell.

In 1997, Tomb and coworkers completely sequenced the H pylori genome, and some differences were found in gene encoding factors that are likely to interact with the host, such as surface proteins [11]. Two of the most important genes of H pylori are VACA and CAGA. The VACA gene codes for the Vac-A cytotoxin, a vacuolating toxin. Most H pylori strains (60%), by unexplained causes, do not produce this protein. The CAGA gene codes for the Cag-A protein, which seems to stimulate the production of chemotactic factors for the neutrophils by the gastric epithelium of the host. A certain proportion of H pylori strains (40%), by unexplained causes, does not produce this protein.

After the exposure to CAGA -positive H pylori strains, an increase in catalase, glutathione peroxidase, and superoxide dismutase activity has been reported. This increase is associated with fewer DNA adducts and reduced susceptibility of the gastric cells to the irreversible injuries from reactive oxygen species (ROS) compared with exposure to CAGA -negative H pylori strains. Such alterations of the ROS scavenging enzymes may partly account for the increased risk of gastric cancer in individuals with H pylori infection.

In addition, H pylori up-regulate caspases 3, 6, 8, and 9. Caspases 3 and 9 in epithelial cells are fundamental in inducing apoptosis. The expression of some bacterial genes is acid-regulated, as reported for the FILA gene (responsible for the H pylori motility) that codes for a sigma factor required for transcription of the flagellin gene FLAA. Flagella and urease are very important for the colonization of the gastric mucosa by the bacterium.

4. Etiology

The genus *Helicobacter* was established in 1989 with *H pylori* representing the type species. [12]

Infection of the stomach by *H pylori* persists lifelong and causes gastric inflammation. A small proportion of infected patients develop peptic ulceration (approximately 15%) or gastric adenocarcinoma (0.5%-2%) and gastric mucosa–associated lymphoid tissue (MALT) lymphoma.

Several factors affect the patterns of disease outcome associated with *H pylori* infection, including: (1) the virulence of the strain; (2) host genetic susceptibility factors and host immune response to infection; and (3) modulating environmental factors such as diet or smoking. [13]

In North America and Europe, the prevalence of *H heilmannii* infection ranges from 0.3% to 1.1% in the general population. *H heilmannii* infection has been reported in association with the full spectrum of gastric diseases related to *H pylori* infection, including gastric cancer and MALT lymphoma. Biopsies from infected patients with chronic gastritis reveal similar, albeit less severe features than in *H pylori* gastritis. [14]

Once *H pylori* enter the host stomach, it uses urease activity to neutralize the gastric acidic environment. [15] Then, the organism utilizes flagella-mediated motility to move toward the gastric epithelium cells. Thereafter, interactions between bacterial adhesions and host cell receptors result in successful colonization and persistent infection. Finally, *H pylori* release

several toxins, leading to host tissue damage. [16]

H pylori infection causes atrophic and even metaplastic changes in the stomach. The bacterial adhesion appears to result in tyrosine phosphorylation and is specific for gastric cells. The adhesion of H pylori to the gastric cells causes a direct decrease in mucosal levels of glutathione, a fundamental molecule in the maintenance of the cellular redox status and in the molecular regulation of host immune responses. However, the LPS of H pylori may induce the production of autoantibodies that are able to worsen the atrophy in the corpus mucosa and cause a concomitant increase in parietal cell antibodies. Such events are accompanied by a decrease in anti-H pylori immunoglobulin titers. This process leads to a scenario of severe atrophy without bacterial colonization combined with high levels of autoantibodies against gastric parietal cells. A number of reports show the close association between H pylori infection and low-grade gastric MALTomas. Giannakis and colleagues demonstrated that H pylori may adapt to gastric stem cells, influencing their biology and contributing to tumorigenesis of the stomach [17].

5. Epidemiology

United States statistics

The frequency of H pylori infection may be linked to race and low socioeconomic status. White persons account for 29% of cases, and Hispanic persons account for 60% of cases.

International statistics

H pylori is a ubiquitous organism. At least 50% of all people are infected, but an exact determination is not available, mostly because exact data are not available from developing countries. H pylori may be detected in approximately 90% of individuals with peptic ulcer disease; however, less than 15% of infected persons may have this disease.

Race, sex, and age-related statistics

The pathogenetic role of H pylori may differ depending on the geography and race. White persons are infected with H pylori less frequently than persons of other racial groups. The prevalence rate is approximately 20% in white persons, 54% in African American persons, and 60% in Hispanic persons.

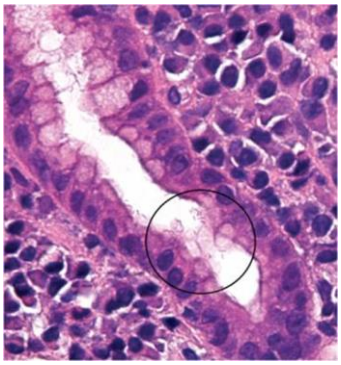
No sex predilection is known; however, females have a higher incidence of reinjection (5%-8%) than males.

H pylori infection may be acquired at any age. According to some epidemiologic studies, this infection is acquired most Frequently during childhood. Children and females have a higher incidence of reinjection (5%-8%) than adult males [18].

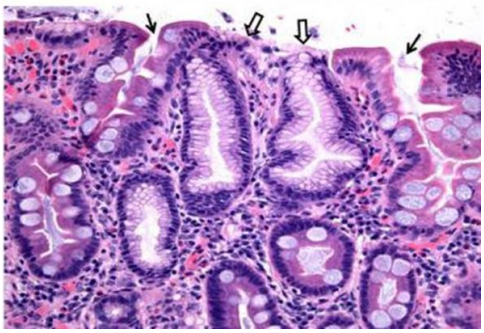
6. Microscopic finding

In addition to recommendations that *H pylori* gastritis be categorized by gastric sub sites, it is also advised that *H pylori* gastritis be categorized on the basis of histology (extent/severity of inflammation/atrophy) owing to the risk of development of gastric cancer. Moreover, gastric erosions should not only be reported separately from gastritis but the etiology, natural history, and clinical significance of gastro duodenal erosisions should also be evaluated.

H pylori infection of the stomach is associated with bacterial colonization primarily localized to the mucous layer that covers the gastric surface epithelium and the upper portions of the gastric foveolae (see the following images). *H pylori* may be dispersed or cluster as groups of bacteria in the mucus and adherent to 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.



Helicobacter pyloribacteria can be identified on hematoxylin and eosin stains, as shown in the circle. Other H pylori forms are also seen elsewhere in the picture, albeit more sparsely. The bacteria characteristically are adherent to the surface of the gastric epithelial cells or within the mucus layer that lines the luminal surface of the gastric mucosa. Original magnification (400X).

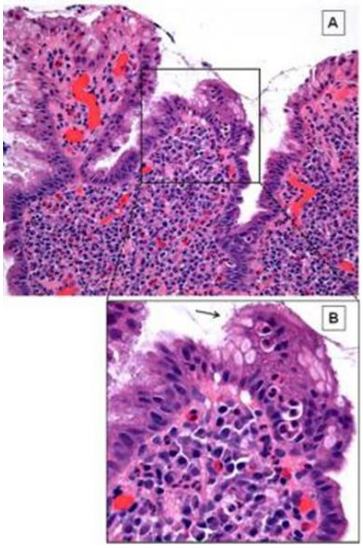


Intestinal metaplasia in gastric antral mucosa. The open arrows point to residual antral type epithelium, whereas the solid arrows point to the intestinal metaplasia associated areas that have replaced the normal antral type glandular epithelium. Hematoxylin and eosin stain, original magnification 200X.

View Media Gallery

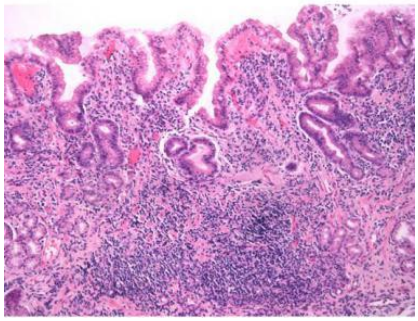
H pylori bacteria can be found in the deeper glands, namely those of the oxyntic mucosa of the body and fundus, in particular in those patients who are under treatment with proton pump inhibitors (PPIs). [15] The presence of *H pylori* bacteria leads to inflammatory response of the underlying gastric mucosa, characterized by a combination of active and chronic

gastritis. The chronic inflammatory host response to *H pylori* and bacterial products is composed of T- and B-cell lymphocytes, plasma cells, rare eosinophils, and mast cells that primarily expand the lamina propria, as well as infiltration of the lamina propria and gastric epithelium by polymorphonuclear leukocytes that eventually phagocytize the bacteria (see the image below).

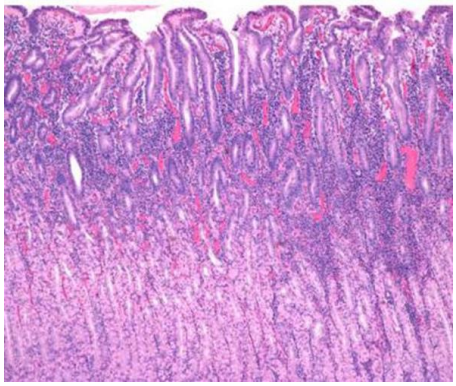


Biopsy of gastric antral mucosa of patient with Helicobacter pylori-associated chronic active gastritis. Note the presence of superficially oriented inflammation, including chronic inflammation (plasma cells and lymphocytes) and acute inflammation (neutrophils). The presence of neutrophils in the mucosa, with neutrophil permeation into and through the gastric epithelium indicates active disease (B: inset). H pylori bacteria are seen adherent to the surface of gastric epithelial cells, as minute linear to punctuate purple forms (arrow). Hematoxylin and eosin stain, original magnification (100X).

Patients with typical cases of infection develop chronic active gastritis in which *H pylori* are initially observed in both the antrum and corpus, but the organisms are usually more numerous in the antrum (see the following images).

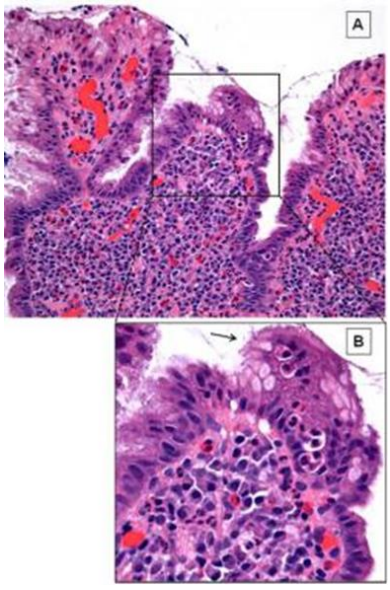


Biopsy of gastric antral mucosa of patient with Helicobacter pylori-associated chronic active gastritis. Note the presence of scattered lymphoid aggregates in the lamina propria, including superficially oriented inflammation involving the lamina propria underlying the gastric surface and foveolar epithelium. Hematoxylin and eosin stain, original magnification (100X).



Biopsy of oxyntic mucosa from the gastric body of patient with Helicobacter pylori-associated chronic active gastritis. Note the presence of superficially oriented inflammation involving the lamina propria underlying the gastric surface and foveolar epithelium. Hematoxylin and eosin stain, original magnification (100X).

Polymorphonuclear leukocytes (neutrophils) infiltrate the lamina propria, glands, surface epithelium, and foveolar epithelium, occasionally spilling into the lumen and forming small microabscesses (see the image below).



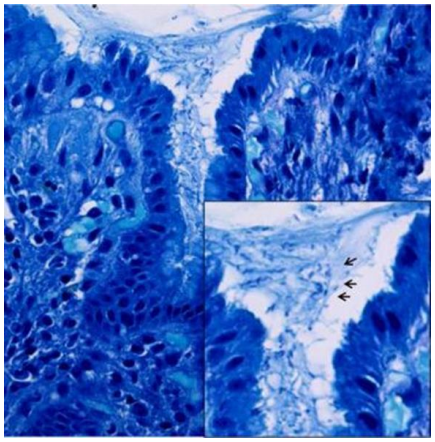
Biopsy of gastric antral mucosa of patient with Helicobacter pylori-associated chronic active gastritis. Note the presence of superficially oriented inflammation, including chronic inflammation (plasma cells and lymphocytes) and acute inflammation (neutrophils). The presence of neutrophils in the mucosa, with neutrophil permeation into and through the gastric epithelium indicates active disease (B: inset). H pylori bacteria

are seen adherent to the surface of gastric epithelial cells, as minute linear to punctuate purple forms (arrow). Hematoxylin and eosin stain, original magnification (100X).

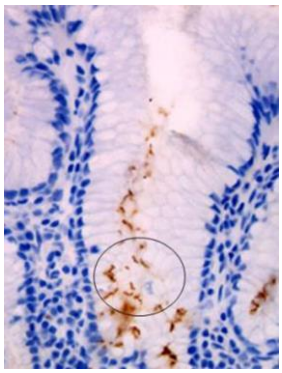
The presence of neutrophils in a background of chronic inflammation is diagnostic of active gastritis, and this may be graded as mild, moderate, or severe, based on the numbers of neutrophils in the mucosa and epithelium. Neutrophil infiltrates appear to be most susceptible to eradication therapy, followed by eosinophils. The numbers of lymphocytes and plasma cells tend to decline at slower rates.

7. Immuno histochemistry

Identification of *H pylori* in tissues can be easily done by examination of Hematoxylin and eosin (H&E) – stained slides in about 70%-80% of infected patients. Special stains, including Gram stains, silver stains, Giemsa, Diff-quick, thiazine, and immuno histochemical stains, can detect the remaining 10%-20% (see the images below). Immunohistochemical stains for *H pylori* can also be performed and are particularly helpful in the detection of coccoid forms of the bacterium and in cases with low bacterial density, such as in treated patients or in cases with intestinal metaplasia. [8]



Helicobacter pylori bacteria can be identified on thiazine stains. Arrows point out the group of H pylori within the mucus layer that lines the luminal surface of the gastric mucosa. Original magnification (400X).



Helicobacter pylori bacteria can be identified by immuno histochemistry. A group of H pylori(highlighted by the brown stain) adherent to the surface of the gastric epithelial cells and in the mucus layer that lines the luminal surface of the gastric mucosa can be appreciated within the circle. Other H pylori forms are also seen elsewhere in the picture adherent to the foveolar epithelium. Original magnification (400X)[19].

Causes:

Exact cause is unknown but H.pylori bacteria may be passed from person to person through direct contact with saliva, vomit or fecal matter. H.pylori may also be spread through contaminated food or water.

Symptoms:

If you have an ulcer, you may feel a dull or burning pain in your belly. It may come and go, but you'll probably feel it most when your stomach is empty, such as between meals or in the middle of the night. It can last for a few minutes or for hours. You may feel better after you eat, drink milk, or take an antacid.

Other signs of an ulcer include:

- Bloating
- Burping
- Not feeling hungry
- Nausea
- vomiting
- weight loss for no clear reason

Ulcers can bleed into your stomach or intestines, which can be dangerous to your health. Get medical help right away if you have any of these symptoms:

- Stool that is bloody, dark red, or black
- Trouble breathing
- Dizziness or fainting
- Feeling very tired for no reason
- Pale skin color
- Vomit that has blood or looks like coffee grounds
- Severe, sharp stomach pain

It's not common, but *H. pylori* infection can cause stomach cancer. The disease has few symptoms at first, such as heart burn. Over time, you may notice:

- Belly pain or swelling
- Nausea
- Not feeling hungry
- Feeling full after you eat just a small amount
- vomiting
- Weight loss for no reason

Treatment

The first line, Food and Drug Administration (FDA) approved drug regimens for the treatment of H. pylori are listed in table 2. These therapies include proton pump inhibitor (PPI) and two antibiotics or bismuth subsalicylate, acid suppressor, and two antibiotics. However, eradication rates using these regimens are a disappointing 75% in the United States due to increased H. pylori resistance to standard antibiotics [20]. Clarithromycin and metronidazole show the highest rates of

resistance and the factors associated with resistance include geographic region, sex, ethnicity, age, and active versus inactive ulcer disease [21]. As a result of the declining eradication rates, other.

Table 1

Therapy	Duration (days)	Eradication Rates	Comments
PPI twice a day clarithromycin 500mg twice a day , amoxicillin 1g twice a day	10-14	70-85%	Not allergic to penicillin and have not received a macrolide.
PPI twice a day , clanthromycin 500mg twice a day, metronidazole 500mg twice a day.	10-14	70-85%	Allergic to penicillin and have not received macrolide.
Bismuth subsalicylate 525 mg four times a day, PPI twice a day for 2 weeks, or H2RA for 4 weeks.	10-14	75-90%	Those allergic to penicillin or failed triple therapy or prevalence of macrolide-resistance is greater than20%

A. Helicobacter pylori Infection Treatment

Regimens for eradication of Helicobacter pylori infection are typically chosen empirically, on the basis of regional bacterial resistance patterns, local recommendations, and drug availability. Health care providers should ask their patients about any prior antibiotic use or exposure, and take that information into consideration before choosing a treatment regimen. The following regimens are described below:

- Triple therapy
- Non bismuth quadruple therapy
- Bismuth-based therapy
- Levofloxacin-containing therapy
- Concomitant bismuth and levofloxacin-containing therapy
- Second-line therapy
- Rescue or third-line therapy

B. Triple therapy

Triple therapy for *H* pylori infection remains an option for first-line therapy in areas of low (< 15%) clarithromycin resistance and consists of the following:

1. Proton pump inhibitor (PPI) (eg, omeprazole 20 mg BID, lansoprazole 30 mg BID, esomeprazole 40 mg QD, pantoprazole 40 mg QD, rabeprazole 20 mg BID) *plus.*
2. Clarithromycin 500 mg BID (first-line and continues to be recommended in areas where *H pylori* clarithromycin resistance is less than 15% and in patients without previous macrolide exposure) or metronidazole 500 mg BID (when clarithromycin resistance is increasing) *plus*
3. Amoxicillin 1000 mg BID or metronidazole 500 mg BID (if not already selected)

Duration

A Cochrane meta-analysis of 55 studies concluded that 14 days is the optimal duration of triple therapy, achieving an *H pylori* eradication rate of 81.9%, whereas 7 days attains an eradication rate of only 72.9%. In more recent studies, however, the eradication rate with 14-day triple therapy is not significantly different from that with 10-day sequential therapy (amoxicillin and a PPI for 5 days followed by a PPI, clarithromycin and metronidazole for another 5 days) or 10-day concomitant non bismuth quadruple therapy.

C. Non bismuth quadruple therapy

Non bismuth quadruple therapy may be given sequentially or concomitantly.

Sequential therapy

Sequential therapy (a suggested first-line option) is superior to standard triple therapy, according to two systematic reviews, consists of the following:

1. PPI plus amoxicillin for 5-7 days (eg, pantoprazole 40 mg BID and amoxicillin 1 g BID for 7 days), *then*
2. PPI plus 2 other antibiotics for the next 5-7 days; clarithromycin and metronidazole are the antibiotics usually chosen, but levofloxacin-based regimens (see below) and tetracycline-based regimens (eg, pantoprazole 40 mg BID, tetracycline 500 mg QID, and metronidazole 500 mg BID) are superior to 14-day triple therapy, based on a meta-analysis of 21 trials

Eradication rates with different durations of sequential therapy are as follows:

- 14 days: 90.7-92.5% eradication rates
- 10 days: 87% eradication rate

Concomitant therapy

Concomitant therapy (an alternative first-line option) consists of the following (using dosages similar to those in triple therapy; or all drugs BID in one study):

- PPI *plus*
- Amoxicillin *plus*
- Clarithromycin (1 g modified-release tablet QD in one study) *plus*
- Metronidazole (500 mg TID in one study)

Duration of concomitant therapy is 10-14 days.

Concomitant therapy is better for clarithromycin-resistant strains, and 14 days of concomitant therapy is superior to 14-day triple therapy, with cure rates of ≥90%.

Hybrid therapy

Hybrid therapy is a combination of sequential and concomitant therapy, as follows:

1. PPI plus amoxicillin for 3 - 7 days (the latter recommended as another suggested first-line option in the 2017 American College of Gastroenterology Guideline), *then*
2. PPI plus amoxicillin plus 2 other antibiotics (usually, clarithromycin and metronidazole) for 7 days

There is evidence that the eradication rates with 10-day, 12-

day and 14-day regimens are comparable at 95.0%, 95.1%, and 93.4%, respectively. This suggests that the optimal duration of hybrid therapy is 12 days, since high rates of eradication are still achieved.

Reverse Hybrid

Reverse hybrid therapy is a combination of sequential and concomitant therapy, using the same drugs as hybrid therapy, but in reverse sequence, as follows:

1. PPI plus amoxicillin plus 2 other antibiotics (usually, clarithromycin and metronidazole) for 7 days *then*
2. PPI plus amoxicillin for 3–7 days

The eradication rate achieved with 12 days of reverse hybrid therapy is similar to that with 12 days of hybrid therapy (95.7% vs. 95.1%, respectively).

Novel concomitant therapy

Novel concomitant therapy consists of the following:

1. PPI (eg., rabeprazole 20 mg TID) for 10 days *plus*
2. Amoxicillin 1 g TID for 10 days (or, if penicillin allergic, bismuth sub citrate 240 mg QID for 10 days) *plus*
3. Rifabutin 150 mg BID for 10 days *plus*
4. Ciprofloxacin 500 mg BID for 10 days

The regimen with amoxicillin eradicated *H pylori* in 95.2% of cases, while the one with bismuth sub citrate achieved an eradication rate of 94.2%.

D. Bismuth-based therapy

Bismuth-based therapy is an alternative first-line therapy (in areas with high clarithromycin and metronidazole resistance, and in patients with prior macrolide exposure or penicillin-allergic) [4] or second-line therapy (see below). It consists of the following:

1. PPI or H2 receptor antagonist (eg, lansoprazole 30 mg BID or ranitidine 150 mg BID) *plus*
2. Bismuth subsalicylate 525 mg QID (or bismuth tripotassium dicitrate 300 mg QID) *plus*
3. Metronidazole 250 mg QID or 500 mg TID (or levofloxacin) *plus*
4. Tetracycline 500 mg QID

Duration is 10-14 days. The eradication rate was 90.4% for 10 days of bismuth quadruple therapy,

while extending therapy to 14 days achieved an eradication rate of 97.1%

Chinese researchers reported that the following regimen provides effective first-line treatment in a population with high antibiotic resistance:

- Rabeprazole 10 mg BID *plus*
- Bismuth potassium citrate 220 mg BID *plus*
- Amoxicillin 1000 mg BID *plus*
- Clarithromycin 500 mg BID

Duration is 10 days. Rabeprazole and bismuth were given 30 min before the morning and evening meals. Antibiotics were given 30 min after the morning and evening meals.

Researchers in Turkey, however, reported that a 14-day regimen of lansoprazole 30 mg BID, amoxicillin 1000 mg BID, clarithromycin 500 mg BID, bismuth subsalicylate 600 mg BID was not significantly superior to a 7-day regimen (81.4% vs. 80%).

E. Levofloxacin-containing therapy

This is an alternative first-line regimen and consists of a PPI plus amoxicillin 1 g BID plus levofloxacin 500 mg QD.

Duration options are as follows:

- 7 days (eradication rates of up to 80.9%)
- 10 days (eradication rates of up to 83.1%)
- 10-14 days is recommended by the 2017 American College of Gastroenterology Guidelines

Sequential therapy, an alternative first-line regimen, is as follows (eradication rates of up to 86.5%):

1. PPI (esomeprazole 20 mg or 40 mg BID) plus amoxicillin (1 g BID) for 5-7 days, *then*
2. PPI (esomeprazole 20 mg or 40 mg BID) plus levofloxacin (250 mg or 500 mg BID) plus a nitroimidazole antibiotic (eg, tinidazole 500 mg BID) for 5-7 days

A randomized trial investigated the role of bismuth in levofloxacin-containing 14-day sequential therapy, and concluded that adding bismuth did not significantly improve eradication rates (85.2% vs. 82.6%).

Concomitant therapy, another alternative first-line regimen, is as follows (eradication rates of up to 96.5%):

- PPI (esomeprazole 40 mg BID) plus amoxicillin (1 g BID) plus levofloxacin (500 mg QD) plus another antibiotic (eg, tinidazole 500 mg BID) for 5 days

F. Concomitant bismuth and levofloxacin-containing therapy

A group of Chinese researchers reported that the following regimen also provided satisfactory eradication rates in a population with high antibiotic resistance:

- Esomeprazole 20 mg BID *plus*
- Levofloxacin 500 mg BID *plus*
- Bismuth 220 mg BID *plus*
- Amoxicillin 1000 mg BID *OR* cefuroxime 500 mg BID

Duration: 14 days. Eradication rates were not scientifically different between the amoxicillin and cefuroxime groups (83.5% vs. 81%).

An open-label, randomized trial conducted in China reported acceptable eradication rates even for the following 1-week bismuth-containing regimen:

- Esomeprazole 20 mg BID *plus*
- Colloidal bismuth pectin 200 mg BID *plus*
- Amoxicillin 1000 mg BID *plus*
- Levofloxacin 500 mg OD *OR* clarithromycin 500 mg BID

The above levofloxacin-based concomitant quadruple regimen demonstrated a higher eradication rate (86.66% vs 76.22%).

G. Second-line therapy

Second-line therapy should avoid repeating first-line regimens that were already used, and should incorporate at least one different antibiotic. Bismuth-based therapy or levofloxacin-containing triple therapy can be used (same regimens as above, if not used previously).

H. Rescue or third-line therapy

Send ulcer biopsy specimen for antimicrobial culture and susceptibility before treatment. It is essential to avoid antimicrobials that have previously been used. The preferred treatment for patients who have received a clarithromycin-containing first-line regimen are bismuth quadruple therapy or levofloxacin-salvage combination therapy. In general, clarithromycin triple therapy is not recommended for salvage treatment.

Bismuth-based quadruple therapy (with amoxicillin, tetracycline, furazolidone, or metronidazole) is used for 14 days and comprises the following (eradication rates for all combinations below were above 90%):

1. PPI (lansoprazole 30 mg BID) *plus*
2. Bismuth potassium citrate 220 mg BID *plus*
3. Tetracycline 500 mg QID or amoxicillin 1 g TID *plus*
4. Furazolidone 100 mg TID or tetracycline 500 mg QID (if not already selected) or metronidazole 400 mg QID

For patients who already received bismuth quadruple therapy as first-line treatment, clarithromycin or levofloxacin-containing salvage regimens are preferred.

Levofloxacin-based sequential therapy is superior to clarithromycin- and tetracycline-based therapies and consists of the following (eradication rates of up to 92.2%, as long as the *H pylori was* susceptible to levofloxacin):

1. PPI (esomeprazole 40 mg BID) + amoxicillin (1 g BID) for 7 days, *then*
2. PPI (esomeprazole 40 mg BID) + metronidazole (500 mg BID) + levofloxacin (250 mg or 500 mg BID, with the former surprisingly achieving higher cure rates [13]) for another 7 days

Other salvage regimens that can be recommended are the following:

1. Triple therapy (which includes levofloxacin) is also a recommended salvage regimen (see above)
2. Concomitant therapy as described above
3. 10-day Rifabutin triple salvage regimen (PPI plus amoxicillin plus Rifabutin)
4. High-dose dual therapy (PPI plus amoxicillin for 14 days) [22].

I. Management

Only treat patients with a positive test result for *H pylori* infection. It is important to consider possible antibiotic resistance when selecting the treatment regimen.

Pharmacotherapy

The US FDA and international organizations have approved several triple therapy regimens for the treatment of *H pylori* infection in patients with gastric and duodenal peptic ulcer disease, as follows:

- Omeprazole, amoxicillin, and clarithromycin (OAC) for 10 days
- Bismuth subsalicylate, metronidazole, and tetracycline (BMT) for 14 days
- Lansoprazole, amoxicillin, and clarithromycin (LAC), for either 10 days or 14 days

All the eradication treatments have a high incidence of certain adverse effects (eg, nausea, metallic taste). If skin rash, vomiting, or diarrhea occurs, discontinue treatment.

Other medications used in the management of *H pylori* infection include the following:

- Anti diarrheal (eg, bismuth subsalicylate)
- Proton pump inhibitors (eg, lansoprazole, omeprazole)
- H2-receptor blockers (eg, ranitidine, famotidine)

Surgical option

Surgical intervention is not required for patients with *H pylori* infection, but it may be a consideration for patients with severe complications, such as cancer.

J. Prevention

You can protect yourself from getting an H.pylori infection with the same steps you take to keep others germs at bay:

- Wash your hands after you use the bathroom and before and before you prepare or eat food. Teach your children to do the same.
- Avoid food or water that's not clean.
- Don't eat anything that isn't cooked thoroughly.
- Avoid food served by people who haven't washed their hands.

Though stress, spicy foods, alcohol, and smoking don't cause ulcers, they can keep them from healing quickly or make your pain worse. Talk to your doctor about ways to manage your stress, improve your diet, and, if you smoke, how you can get help to quit.

8. Conclusion

In summary, patients should be evaluated for H. pylori when they have PUD or gastric cancer and the treatment of choice is either triple or quadruple therapy with subsequent documentation of eradication of infection. However, in the era of antibiotic resistance these treatment options could soon become obsolete; thus new research is focusing on other antibiotic regiments along with vaccine development to combat this pathogen [23]. Other areas of study are attempting to elucidate the oncogenesis of H. pylori, finding that strains that carry cytotoxin-associated antigen A (cagA) gene are associated with gastric carcinoma [24]. The new frontiers in H. pylori research will provide for better understanding of its impact on human health and allow for the development of targeted therapies.

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