**Journal of Mind and Medical Sciences**

Volume 3 | Issue 2 Article 7

2016

# Helicobacter pylori: types of diseases, diagnosis, treatment and causes of therapeutic failure

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**Cover Page Footnote**
This study was financially supported by the project: "The role of Helicobacter pylori infection in upper gastrointestinalnon-variceal bleedings. A clinical, endoscopic, serological and histopathological study" sponsored by "The Medical Center Amaradia"(Contract No. 723/ 25.06.2014, partner of UMF of Craiova)

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*J Mind Med Sci.* 2016; 3(2): 150-161. ▸ **Review Article**

# Helicobacter pylori: types of diseases, diagnosis, treatment and causes of therapeutic failure

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**Abstract**

Acute upper gastrointestinal lesions have a multifactorial etiology but, regardless of the cause, they are related to mucosal barrier destruction. Since Helicobacter pylori induces a superficial chronic gastritis with the infiltration of neutrophils in the mucosa, it was speculated that Helicobacter pylori infection could also cause bleeding lesions. The diagnosis, the proper treatment and the revaluation of its effectiveness actually represent the prophylaxis of some diseases such as peptic ulcer, gastric lymphoma or mucosa-associated lymphoid tissue (MALT) and gastric cancer. These diseases and their severe complications are life-threatening for the patient. Periodic renewal of the treatment and knowing the real causes of Helicobacter pylori resistance to various antibiotics must always be understood by the clinician. Although Helicobacter pylori treatment fails in about 20% of cases, moral support of the patient by the clinician, information about possible evolutional complications of Helicobacter pylori infection, and periodic evaluation of the patient during therapy, are important tools on which the therapeutic success depends.

**Keywords**: helicobacter pylori, diagnosis, bleeding, treatment resistance

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## Introduction

Helicobacter pylori bacterium (H. pylory) is the first officially recognized carcinogen. Over half the world's population is colonized with this bacterium, being the best known gram negative bacteria. Because histopathological changes induced gastric mucosam, the Helicobacter pylori infection represents a determining factor in the occurrence of the gastrointestinal disease that can range from chronic gastritis without clinical symptoms to serious neoplastic diseases. In many cases, the clinical signs of upper gastrointestinal bleeding is the first symptom of gastrointestinal infection with Helicobacter pylori.The disease is the result of complex interactions between host and bacteria (1).

*History*

Barry Marshall and Robin Warren were first to describe the isolation and culture of a bacterium in the human stomach, later known as H. pylori (2). Their experiments on themselves using self-ingestion (3, 4) and those on volunteers showed that bacteria can colonize the human stomach and can induce inflammation of the stomach mucosa (5).

Later research has shown that colonization of H. pylori can cause chronic gastritis, peptic ulcers, as well as gastric lymphoma mucosa associated lymphoid tissue (MALT) or gastric cancer.

*Morphology*

H. pylori is a gram negative bacterium, measuring 2 to 4 pm in length and 0.5 to 1 pm in width. The body has 2 to 6 flagella and the motility of the flagella confers and allows rapid movement in viscous solutions, such as the mucus layer of the gastric epithelial cell (6). Unlike many other gastrointestinal tract pathogens, Helicobacter pylori does not have fimbriae adhesins. The growth occurs at a temperature of 34 - 40° C, with an optimum of 37º C. Although its natural habitat is the acid gastric mucosa, H. pylori is considered to be a neutrophil. The bacterium survives to pH < 4 exposure, but the growth occurs only in relatively narrow pH range of 5.5 to 8.0, with optimal growth at neutral pH (7, 8).

*Geographical distribution*

A high diversity in prevalence of H. pylori infection among adults in Europe was registered in 2000, with a global prevalence in adulthood of 18.3-82.5%, with variations from country to country. The highest prevalence, 82.5% for adults older than 18 years old, was measured in Turkey, on a nationally representative population; and the lowest prevalence, 18,3%, was found in Denmark (9). H. pylori prevalence shows large geographical variations. In various developing countries, more than 80% of the population is H. pylori positive, even at young ages. H. pylori prevalence in industrialized countries remains generally below 40% and is significantly lower in children than in

adults and the elderly. In geographical areas, the prevalence of H. pylori correlates inversely with socioeconomic status, particularly regarding living conditions during childhood (10).

H. pylori colonization is not a disease itself, but it influences the relative risk of developing different clinical conditions of the gastrointestinal tract and possibly the hepatobiliary tract. Therefore, routine or random testing for H. pylori has no benefit, but testing should be performed in order to find the cause of diseases such as peptic ulcer, or, for the prevention of diseases, such as in subjects with family history of gastric cancer. In these cases, a positive test result justifies a treatment and a negative result may indicate the need to search for other etiological factors and preventive measures. For these reasons, a correct understanding of disorders associated with H. piloryis needed.

*Types of diseases*

Gastritis lesions occur in all H. pylori infected subjects, but only a minority develop clinical signs of this colonization. It is estimated that H. pylori positive patients have a risk of 10-20% of developing peptic ulcer and 1-2% of them have a risk of developing gastric cancer (11, 12, 13). The emergence of these disorders depends on the type and severity of gastritis.

In acute and chronic gastritis, due to H. pylori infection, the infiltration of gastric mucosa most frequently appears in the antrum and gastric body with mononuclear and neutrophil cells. Active chronic gastritis is the main condition linked to the colonization with H. pylori, and other disorders associated with H. pylori results in particular because of the chronic inflammatory process (1).

Causes of gastritis, other than H. pylori infection are: excessive consumption of alcohol and nonsteroidal antiinflammatory drugs (NSAIDs), cytomegalovirus infections, and chronic idiopathic diseases (Crohn's disease and pernicious anemia).

Gastric and duodenal ulcers (commonly referred to as peptic ulcers) are defined as mucosal defects with a diameter of at least 0.5 cm penetrating the mucous and/or muscular tunica. Gastric ulcers occur mainly along the lesser curvature of the stomach, particularly in the mucosa in the lining of the boundary between the body and antrum (1), the duodenum being the most exposed area to gastric acid.

The initial worldwide reports, in the first decade after discovering H. pylori, associated this infection with about 95% of duodenal ulcers and 85% of gastric ulcers (14). H.pylori eradication has changed the natural history of ulcer disease and ulcer recurrence was prevented almost completely (15). These data show that gastric and duodenal ulcers seem to be strongly linked by H. pylori infection. However, recurrent ulcers can be registered after H. pylori eradication therapy

because of the persistence or reinfection with H. pylori, NSAID use, or in case of idiopathic ulcer.

The most common complication of ulcer is bleeding and perforation, followed by stomach obstruction. It is estimated that 15-20% of peptic ulcers are complicated by hemorrhage and that approximately 40% of patients who develop upper gastrointestinal bleeding are also suffering of ulcer (1).

The primary treatment for bleeding in ulcerous disease is endoscopic therapy, which is mandatory in order to establish the bleeding cause, to estimate its gravity, and to reduce the risk of recurrent bleeding. H. pylori eradication markedly reduces the risk of ulcer as wekk as the risk of re-bleeding for those patients whose bleeding was caused by H. pylori infection (16). In general, a small percentage of bleeding ulcers requires very careful management, and the indications for emergency surgery in such cases are: hemodynamic instability, failure in performing endoscopic hemostasis, and bleeding recurrences despite endoscopic attempts to stop it. Regarding the third indication, many doctors indicate surgery after two failed endoscopic attempts to stop the bleeding (17). Several studies have shown that some perforated peptic ulcers can be treated conservatively, but in any patient with a perforated peptic ulcer, showing peritoneal signs, surgery is required, and then it is necessary to decrease the acid secretion and antibacterial therapy in H. pylori-positive patients. Chronic ulcer, especially in the pyloric and bulbar regions, can lead to hypertrophic scars and stenosis, impairing the gastric eviction process. In these patients, malignancy as a cause of obstruction must first be ruled out. Most benign obstructions associated with H. pylori respond well to the eradication therapy, due to the reduction or disappearance of inflammation and edema. In refractory patients, local reconstruction surgery, or a distal gastric resection is mandatory (1).

*Atrophic gastritis, intestinal metaplasia and gastric inflammation, cancer.*

In histopathogic terms, in chronic gastritis induced by H. Pylori, studies have shown a loss of the normal architecture through the destruction of the gastric mucosa and gastric glands, with normal mucosa replaced by areas of fibrosis and intestinal epithelium. These changes occur in areas of the gastric or duoudenal mucosa, with that inflammation being more severe in 50% of subjects aproximativ H. pylori positive (18). The risk of atrophic gastritis depends on the distribution and the chronic active inflammation model; therefore, subjects with decreasing acid production show a faster progression to atrophic gastritis (19).

Various studies have shown that H. pylori positive subjects have increased risk of developing

gastric cancer compared to uninfected persons by sequence of atrophy and metaplasia (20). This idea is supported by studies showing links between geographic prevalenceof H. pylori and incidence of stomach cancer (21). Factors that influence the occurrence of gastric atrophy and later, of stomach cancer in H. pylori positive subjects are both linked to host and bacteria, by the severity of chronic inflammatory response caused by them. Therefore, the risk of developing gastric atrophy is increased in subjects with strains CagA positive (22), but also in those with a genetic predisposition to high yields of IL-1, as a result of the response to the colonization of the bacteria (23).

Although lymphoid tissue is not normally present in the gastric mucosa, MALT almost always occurs in response to infection with H. pylori. This tissue may give birth to a population of B monoclonal cells from which can proliferate and form a MALT lymphoma. Almost all patients with a MALT lymphoma are H. pylori-positive (24) and H. pylori positive subjects have a significantly increased risk of developing gastric MALT lymphoma (25). Different series of "case-reports" have shown that H. pylori eradication may lead to complete remission in patients with MALT lymphoma stage IE confined to the stomach (26, 27). Generally, about 60 to 80% of these patients achieve complete remission after H. pylori eradication, about 10% continue to have signs of residual disease, while the rest show no response (1).

There have been cases where the disease evolution depends on the correct guided therapy for H.pilory. For example, two subjects from the same family colonized with H. pyloriwho manifested clinical signs of disease and had positive laboratory tests (the mucosal lesions are highlighted by upper gastrointestinal endoscopy). One of them received the correct treatment to eradicate H. Pylori and had symptoms remission, while the other, who did not receive treatment, developed a hemorrhagic MALT lymphoma 10 years after the diagnosis.

*Diagnose: specificity and sensitivity. Invasive and/ or non-invasive tests.*

Various tests have been developed for H. Pylori detection, each with advantages and disadvantages. The available tests are generally divided into invasive tests, based on gastric specimens for histology, culture, or other techniques and non-invasive tests, based on peripheric evidence, such as blood samples, respiratory tests, feces, urine or saliva for antibodies or bacterial antigens detection.

*Invasive methods:*

1. The histological methods are the "gold standard" for diagnosing H. pylori infection, providing information not only about the inflammation, but also the degree of atrophy

induced by the bacteria. The need for an experienced pathologist and the invasive method represent a disadvantage. It has a higher sensitivity and specificity of about 95%.

2. Helicobacter pylori cultures are the alternative to the "gold standard"; with similar specificity and sensitivity, they also allow testing for antimicrobial susceptibility.

3. The rapid urease test is used for the qualitative detection of Helicobacter pylori in the urease from the biopsy sample obtained after gastroscopy. With a specificity and sensitivity of more than 90% and with good cost-effectivness, the urease test is a quick method of diagnosis (3 minutes), being the most common invasive method. It requires an additional test to confirm H. pylori infection.

*Non-invasive methods.*

1. Testing the urea in the exhaled air is an alternative to the "gold standard" with a similar specificity and sensitivity, the most accurate non-invasive method of diagnosis. It is also a reliable test to evaluate the success of H. pylori eradication therapy. The major disadvantage is the high cost of the equipment.

2. Antigen testing in stool samples, with a sensitivity greater than 90%, gas not been used widely, but it can be reliable for assessing the success of H. pylori eradication treatment.

3. Serology (with a sensitivity of 80-90%), is mainly used for epidemiological studies; it cannot verify the evolving infection due to immunologic memory.

Invasive methods cause discomfort in patients during diagnosis, the reason many patients refuse upper gastrointestinal endoscopy, especially during the check-up performed 4 weeks after treatment. Non-invasive methods of diagnosis are recommended as an alternative for patients under 45 years of age who do not show symptoms such as: unexplained weight loss, digestive bleeding or repeated vomiting. Patients experiencing these symptoms require upper gastrointestinal endoscopy.

When patients present acute gastroesophageal bleeding or are under treatment with proton pump inhibitors, histamine antagonists or antibiotics, most diagnostic tests for H. pylori infection may show false negative results. Because of this, it is mandatory that the treatment with inhibitors of proton pump or histamine antagonists should be stopped two weeks before the diagnosis test, and if the patients are receiving antibiotic treatment, it should be discontinued at least four weeks before testing (28).

Blood presence in the gastric lumen can lead to false results due to the buffering effect it has on the gastric pH. If there is upper gastrointestinal bleeding or extended mucosal atrophy, serological tests can be useful, as they indicate a history of

exposure to H. pylori, although they do not confirm the presence of infection; so, it is necessary to repeat a non-invasive diagnostic test (if the initial test result was negative) 4-8 weeks after the hemorrhagic event (28).

*Treatment*

Helicobacter pylori eradication methods have continued to evolve over the last 20 years. Originally, the treatment used H-2 histamine receptor antagonists and an antibiotic with a success rate of 73-84% (29). In time, this therapy has been used less frequently, thanks to new treatment regimens having much better results. Currently, triple therapy based on proton pump inhibitors is the most commonly used method. This system includes the use of PPIs in combination with amoxicillin and clarithromycin.

*Eradication therapy*

1.The PPI-based triple therapy consists of Esomeprazole 20 mg twice a day, or 20 mg of omeprazole twice a day, Amoxicillin 1 g twice a day and Clarithromycin 500 mg twice a day. The treatment must be taken for 7 days; this therapy is highly recommended in Australian guidelines (30).

2.The quadruple therapy includes Omeprazole 20mg per day subsalicylate 120 mg four times a day, metronidazole 400 mg three times a day, tetracycline 500 mg four times. The treatment is prescribed between 7 and 14 days (30).

*Therapy control*

Because treatment of H. pylori fails for approximately 20% of cases for any number of different reasons, verifying eradication of infection after treatment is required in patients at risk. The same control is mandatory in patients with peptic ulcers, with MALT, and if patients whose dyspeptic symptoms are persistent. For efficacy evaluation of the treatment, 13 C marked urea or feces antigen tests are reccomended. Testing of urea in the patient's exhaled air has a precision higher than the antigen in feces and is preferred in these cases (28).

*Causes of treatment failure*

*1. Antibiotic resistance of Helicobacter pylori strains.*

Diabetes can be a risk factor for resistance to antibiotics used for Helicobacter pylori eradication. Although in a study in Taiwan, a better rate of H. pylori eradication in patients with diabetes was observed (31), several studies have shown opposite results. Impaired microvascular gastric absorption lowering drugs, gastroparesis and the use of antibiotics for recurrent urogenital infections, respiratory infections, and skin resistance represent the main causes of H. pylori resistance to standard treatment in patients with diabetes. Diabetic gastroparesis affects approximately 40% of patients with diabetes type 1 and 30% of patients with diabetes type 2, especially those with long-term

illness. In a study published by Ojetti et al. (32), H. pylori eradication rate is lower in diabetic adults than in children, probably due to more frequent infections and antibiotic therapies. Bismuth-based therapy has better results for H. pylori eradication in these patients, compared with the triple therapy (33).

The treatment of recurrent respiratory infections or urogenital tract, often treated with antibiotics, is another cause of bacteria resistance to the drugs used in different regimens for H. pylori eradication. Amoxicillin, clarithromycin, metronidazole and tetracycline are antibiotics used in first-line treatment of various respiratory or urogenital tract infections; in many cases, patients undergoing treatment for H. pylori eradication have used these antibiotics regimen for treating other infections.

Increased resistance to levofloxacin in several European countries is also worrying because it opposes its use of empirical anti-H pylori treatment regimens without prior sensitivity tests (34). In the same study published by Megraud F, a significant positive association was shown between the use of antibiotics in the ambulatory and the primary degree of resistance observed in antimicrobial key agents used for the eradication of H pylori. Knowledge about the antibiotics used in a particular region or by every patient can provide information regarding the sensitivity or the resistance of H pylori not only to quinolones and macrolides, but also to other antibiotics, and thus the rehabilitation of the treatment strategies where the tests of sensitivity of H .pylori strains, isolated from the patient, are not available.

H. pylori strains that grow in the presence of cholesterol are more resistant to multiple antibiotics (35). The antibiotics with this kind of resistance from the patients, in relation with cholesterol, are included in some treatment schemes used for to treat H. pylori infections, with recent work showing that H. pylori has a resistance dependent on bile salts cholesterol (36). This suggests that H. pylori can use the cholesterol modifying its envelope so as to resist to multiple antibiotics (37).

Clarithromycin and tetracycline are antibiotics which inhibit protein synthesis and are used to treat H. pylori infection. A study based on the effect of antibiotics on the viability of H. pylori cultivated in the presence or absence of cholesterol showed how cholesterol substantially increased H. pylori resistance to tetracyclin and clarithromycin.

Ciprofloxacin and Metronidazole inhibit the DNA replication, and they are also used for the treatment of H. pylori infections. However, H. pylori grown with cholesterol was more resistant to ciprofloxacin than H. pylori grown without cholesterol. H. pylori grown with cholesterol showed a modest increase resistance to

metronidazole (about 10 to 30 times). For antibiotics that inhibit the biosynthesis of the cell wall, i.e., ampicillin and amoxicillin, there were similar results: H. pylori strains grown on the medium with cholesterol levels were up to 1,000 times more resistant to antibiotics than those grown without cholesterol. Bismuth compounds are part of the regimen of H. pylori infection in some countries. H. pylori cultivated with cholesterol was significantly more resistant to bismuth (up to 107), than H. pylori bacteria grown without cholesterol. H. pylori grown without cholesterol was also more susceptible to rifampicin than H. pylori grown with cholesterol (35).

*2.Patient non-cooperation. Quitting the initial treatment.*

Many patients abandon treatment and the therapeutic scheme after being diagnosed with H. pylori infection, typically for two reasons: improvement and disappearance of symptoms of peptic ulcer; or the side effects of the treatment. The recurrence of symptoms at some time after giving up the initial treatment requires H. pylori culture, allowing thus antimicrobial susceptibility testing. The patient's support by the clinician about the awareness of the disease, information about the possible complications of this disease, and periodic evaluation during therapy is important for patient compliance to treatment and therapeutic success.

**Conclusions**

Helicobacter pylori infection is still a global concern, its diagnosis and treatment may raise serious challenges. The diagnosis, the effective treatment and the revaluation of its effectiveness represents the prophylaxis of some diseases such as peptic ulcer, gastric lymphoma of mucosa-associated lymphoid tissue (MALT) and gastric cancer. These diseases and their severe complications (bleeding, perforation) are life-threatening for the patient. Treatment failure is due to the patient’s non-cooperation or his/her resistance to antibiotics; it varies depending on the patient’s country of origin, the patient him/herself, and previous prescriptions of antibiotics for other conditions. If the second treatment (as recommended by regional doctors) also fails, an endoscopy is required in order to have a biopsy sample from which to perform culture and DST. Although H. pylori treatment fails in about 20% of cases, moral support for the patient by the clinician, information about possible evolutional complications of H. pylori infection, and periodic evaluation of the patient during therapy, are important tools on which the therapeutic success depends.

**Acknowledgment:**

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