

Helicobacter pylori: causation and treatment

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ABSTRACT *Helicobacter pylori* is strongly associated with chronic active gastritis, peptic ulcer disease, and gastric carcinoma. Understanding the mode of transmission of *H. pylori* is essential to limit its spread and serious associated diseases. Most infections are acquired in childhood and some risk factors associated with childhood infection include poor sanitation, overcrowding, bed sharing, and lower socio-economic status. The theory of direct person-to-person spread is now generally accepted, but the route of transmission remains open to conjecture. The evidence linking *H. pylori* with peptic ulcer disease and low-grade MALToma is extremely strong. However, the association with gastro-oesophageal reflux disease, non-ulcer dyspepsia and its synergism with NSAIDs in the causation of ulcers remains controversial. The infection can be diagnosed by invasive (endoscopic) and non-invasive testing. Current therapy is highly effective in eradicating the organism.

KEYWORDS gastric carcinoma, gastro-oesophageal reflux disease, *Helicobacter pylori*, MALT, nonsteroidal anti-inflammatory drugs, peptic ulcer disease

LIST OF ABBREVIATIONS Gastro-oesophageal reflux disease (GORD), *Helicobacter pylori* (*H. pylori*), mucosa-associated lymphatic tissue lymphoma (MALToma), non-steroidal anti-inflammatory drugs (NSAIDs), non-ulcer dyspepsia (NUD), peptic ulcer disease (PUD), proton pump inhibitor (PPI), urea breath tests (UBT)

DECLARATION OF INTERESTS No conflict of interest declared.

OVERVIEW

Introduction

Since Marshall and Warren discovered *H. pylori* in 1982, much has been learned about the association of this microorganism with chronic active gastritis, peptic ulcer disease, MALToma, and gastric carcinoma. *Helicobacter pylori* is a spiral-shaped, microaerophilic, Gram-negative bacterium. This overview discusses the epidemiology and possible mode of transmission of *H. pylori*, its association with disease states, diagnostic tests, and treatment.

Incidence, epidemiology and routes of transmission

Helicobacter pylori infection occurs worldwide, with approximately 50% of the world's population thought to be infected. In developed countries, the prevalence of infection in children under 10 years of age is approximately 5–10%, increasing to around 70% in those over 70 years of age. In contrast, much higher prevalence, of up to 80%, has been reported in developing countries with most of the population infected by the age of 10 years. The acquisition of *H. pylori* infection is rare in adults, 0.33–0.5% per person-year, be it in developed or developing countries. Therefore, the increase of prevalence with age is

unlikely to be due to progressive acquisition of the organism over time, and is more likely to be due to a cohort phenomenon. Most infections occur in childhood and the decreased prevalence in younger cohorts in developed countries may reflect improved childhood living conditions in recent years. With the gradual improvement in living standards, there is reduced transmission of the infection. The high prevalence in adults may have been due to poor socio-economic conditions prevalent in developed countries 40–50 years ago.

Features of low socio-economic status such as overcrowding, bed sharing, poor sanitation, and lack of hot water have all been shown to be risk factors for *H. pylori* infection. Children with infected parents are more likely to be infected than children without infected parents, and these children are infected by *H. pylori* strains that are genetically identical to those infecting their parents.

It is generally agreed that the organism gains entry to the stomach by ingestion of contaminated food or water. The organism survives in faeces and faecal-oral, oro-oral, and gastro-oral infections all occur. Endoscopists and endoscopy nurses are at risk of *H. pylori* infection, presumably through exposure to contaminated gastric fluids.

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CME

Evidence in support of oro-oral transmission (through kissing or pre-mastication of food as practised by mothers from some ethnic backgrounds) is derived from a variety of observations. Clustering of *H. pylori* infection has been noted among family members and spouses. *Helicobacter pylori* has been detected in saliva, dental plaque, and oral mucosae. However, transmission between spouses through kissing has not been substantiated.

Clinical associations

Colonisation of the gastric mucosa by *H. pylori* has been shown to cause PUD and possibly to predispose to gastric cancer. Antral colonisation leads to increased gastric acid secretion in some individuals who may then develop dyspepsia due to duodenal ulcers or PUD, while in others gastric acid secretion remains normal and there is mild asymptomatic antral gastritis. More extensive colonisation leads to a pangastritis with decreased acid secretion, which predisposes to gastric cancer.

Less than 20% of infected individuals develop clinical diseases such as PUD, MALToma, or gastric carcinoma, suggesting that other factors are important in determining the clinical outcome. Individuals who develop PUD may have genetically determined large parietal cell masses and thus increased acid secretion, whilst others may be prone to widespread gastric colonisation and low acid secretion leading to gastric cancer. Environmental factors such as smoking may also predispose to increased acid secretion. Finally, particular *H. pylori* strains may be important as strains with cytotoxin associated genes (*cagA*) and vacuolating cytotoxin genes (*vacA*) are associated with increased inflammatory cytokine production and higher prevalence of peptic ulcers.

H. pylori and PUD

There is compelling evidence linking *H. pylori* infection with PUD. First, with the exception of patients with gastrinomas and those taking NSAIDs, more than 95% of patients with duodenal ulcers and more than 80% of patients with gastric ulcers are infected with *H. pylori*. Second, duodenal ulcers develop far more frequently in people infected with *H. pylori* than in non-infected people. Third, eradication of *H. pylori* prevents disease recurrence.

The mechanism by which *H. pylori* contributes to PUD is now clear and relates to changes in acid secretion. *H. pylori* colonises the mucus layer covering the gastric antral epithelium, and in so doing releases a range of cytotoxins (see 1 in Figure 1). These cause antral gastritis and increased gastric secretion as a result of direct stimulation of antral G cells and by inhibiting somatostatin release from antral D cells (see 2 in Figure 1). Hypergastrinaemia (see 3 in Figure 1) then leads to increased acid secretion by gastric parietal cells, and the resulting increase in duodenal acid

concentration causes gastric metaplasia, *H. pylori* colonisation, and duodenitis, with or without duodenal ulceration (see 4 in Figure 1).

Helicobacter pylori eradication is the treatment of choice for patients with peptic ulcer disease, be it complicated or uncomplicated. For uncomplicated duodenal ulcers, one week of triple therapy is sufficient to heal ulcers and bring about symptomatic relief. For gastric ulcers or bleeding duodenal ulcer, one week of triple therapy should be followed by a further 1–2 months of PPI.

H. pylori and gastro-oesophageal reflux disease

A possible link between *H. pylori* and GORD comes from epidemiological studies that showed a higher incidence of GORD in populations with a low prevalence of *H. pylori*. *Helicobacter pylori* does not affect the lower oesophageal sphincter but it can determine the acidity of the gastric refluxate through the distribution of gastritis (see Figure 1). Individuals with body-predominant gastritis may experience onset or worsening of GORD symptoms due to higher acid secretion after *H. pylori* eradication. Several studies have shown that individuals with duodenal ulcers (and with antral-predominant gastritis and higher acid secretion) do not suffer from worsening of GORD after reduction of acid secretion following eradication of *H. pylori*.

Should *H. pylori* be eradicated in patients with GORD who do not have PUD? There is no evidence that *H. pylori* eradication causes or exacerbates GORD. There is a concern, however, that long-term PPI therapy in patients infected with *H. pylori* increases the risk of atrophic gastritis, and thus gastric cancer, but this anxiety has not been substantiated. As *H. pylori* has been classified as a Class I carcinogen, the benefits of eradication may outweigh the risk of worsening symptoms of GORD in those individuals.

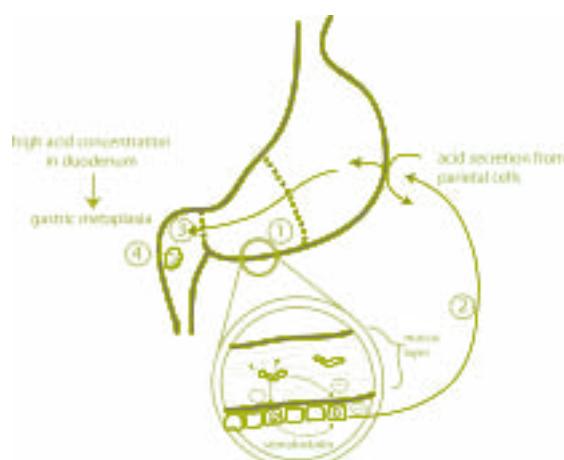


FIGURE 1 *H. pylori* and duodenal ulcer pathogenesis

who have corpus-predominant gastritis. Based on available evidence, the European *Helicobacter pylori* Study Group (EHPG) recommends *H. pylori* eradication in GORD.

H. pylori and NUD

The pathophysiology of NUD is unclear and possible factors include disorders in gastric motor function, visceral sensitivity, *H. pylori* infection, and psychosocial factors.

A clear association between *H. pylori* and NUD has not been established. *H. pylori* causes chronic active gastritis, and it is possible that this inflammatory condition could cause altered smooth muscle dysfunction and visceral sensitivity. However, this has never been confirmed in physiological studies of gastric motility and distension respectively.

Many well-designed randomised studies have produced conflicting results concerning the benefits of eradication in patients with NUD. A recent meta-analysis indicates a relative risk reduction of 9% with eradication therapy over placebo at 12 months. Though controversial, the EHPG supports eradication therapy in patients with NUD. Therapy is justifiable for patients from areas with low rates of re-infection as successful eradication may improve symptoms and reduce ulcer occurrence. However, the side-effects of eradication therapy, such as Clostridium difficile infection, interstitial nephritis, and other antibiotic-related side-effects, and the uncertain benefits should be discussed with patients.

H. pylori and gastric cancer

Gastric cancer is the second most common cause of cancer-related death in the world. In 1994, the International Agency for Research on Cancer declared *H. pylori* a Class I human carcinogen for gastric adenocarcinoma. Correa's hypothesis states that gastric carcinogenesis a multi-step process starting from superficial gastritis and progressing to chronic atrophic gastritis, intestinal metaplasia, dysplasia, and finally carcinoma. *H. pylori* causes chronic active gastritis and atrophic gastritis and has been identified in the uninvolved mucosa from stomachs with carcinoma. A large epidemiological study by the EUROCOST group showed that *H. pylori*-infected individuals have at least a sixfold increased risk of developing gastric cancer compared with non-infected individuals.

Some patients infected with *H. pylori* develop hypochlorhydria; *H. pylori* eradication results in normalisation of acid secretion. In addition, the inflammatory response produced by *H. pylori* infection could induce release of free radicals, which can cause mutation in DNA and malignant transformation. However, gastric carcinogenesis cannot be explained by *H. pylori* infection alone as there is great variation in the

incidence of gastric cancer from different geographical regions despite similar prevalence of *H. pylori* infection. Furthermore, only a small fraction of infected individuals develop gastric cancer. These observations could be explained by the finding that a particular strain of *H. pylori* (cagA strain) is more strongly associated with carcinogenic potential. Host factors could also play an important role in the progression to carcinogenesis. Infected individuals with IL-1 beta polymorphism have been found to have more gastric atrophy, lower acid secretion, and greater risk of gastric cancer.

The question remains whether eradication of *H. pylori* reduces the risk of gastric cancer. A recent study from China has shown that successful eradication caused a decrease in acute and chronic gastritis but no regression of intestinal metaplasia or gastric atrophy was noted. Data from longitudinal studies with long-term follow-up of the effect of eradication is being eagerly awaited.

H. pylori and MALToma

Lymphoma arising from the mucosa is referred to as a MALT tumour. Many studies have demonstrated an association between *H. pylori* infection and MALToma. Furthermore, several studies have demonstrated successful remission of MALToma following eradication of the infection. Complete remission is more likely in patients with tumours limited to the mucosal or submucosal layer with no lymphadenopathy or distant metastases. The degree of mucosal invasion can be assessed by endoscopic ultrasound scans.

H. pylori and NSAIDs

The effect of *H. pylori* infection on the risk of PUD in NSAID users is uncertain. A recent meta-analysis concluded that *H. pylori* and NSAIDs are independent risk factors for PUD, which act synergistically in the causation of PUD. *Helicobacter pylori* infection and NSAIDs both increased the risk of ulcer bleeding by nearly two- and fivefold, respectively, and the risk of ulcer bleeding increased to sixfold when both factors were present. Whether *H. pylori* eradication reduces the risk of ulcer bleeding in NSAID users is controversial.

Current guidelines do not recommend testing for and treating *H. pylori* before NSAIDs are prescribed. Nevertheless, it appears logical to test and eradicate *H. pylori* prior to starting NSAIDs or low-dose aspirin. In patients with a history of PUD, or complications such as bleeding or perforation, PPI therapy should be given as co-therapy to prevent ulcer complications.

Diagnostic tests

Diagnostic tests for *H. pylori* can be classed as invasive or non-invasive based on the need for endoscopy. The choice of test depends on the circumstances and economics of clinical practice. The non-invasive tests are the urea

breath test, *H. pylori* serology, and stool antigen tests.

H. pylori serology

Serological assessment using laboratory-based ELISA assays measuring IgG antibodies are both sensitive and specific (90–100%) for the diagnosis of *H. pylori* infection before as well as after eradication therapy. A 50% decrease in titre 6 months after therapy has high specificity for successful eradication. However, serological testing using near-patient kits may not be reliable and is not recommended.

Stool antigen tests for H. pylori

Most studies have shown this test to have a sensitivity and specificity close to 90% if performed before and after eradication therapy.

Urea breath tests

The UBT is based on the hydrolysis of urea to carbon dioxide and ammonia by *H. pylori* urease enzyme. Urea can be labelled with ¹⁴C or ¹³C, and after hydrolysis the labelled carbon dioxide is exhaled in the breath, where it can be detected in breath samples. An increase in the excretion of labelled CO₂ indicates colonisation by *H. pylori*. For ¹⁴C, the radioactivity of each sample can be measured by a scintillation counter. For ¹³C, the carbon dioxide can be detected by a mass spectrometer, as it is non-radioactive. The sensitivity and specificity of the test is in the range of above 95% and it can be used to determine the effect of treatment.

The EHPSG recommends the stool antigen test and the UBT as the non-invasive tests of choice. These are ideal tests for primary care physicians, but recent therapy with bismuth, PPIs, and antibiotics can cause false-negative results. Proton pump inhibitors should be stopped for at least 1 week and antibiotics for at least 4 weeks before these tests are used.

Upper gastrointestinal endoscopy

During endoscopy, biopsies are obtained from the gastric antrum to establish the presence of *H. pylori*. This can be determined by placing one or two pieces of gastric mucosa into a commercially prepared agar well containing urea and a pH reagent. Urease present in *H. pylori* will cleave urea to ammonia producing an alkaline pH and a resultant change in colour. One of the most widely used is the CLO test (Ballard Medical, Utah). The result can be read as soon as one hour after collection, though it is recommended to read the results at 24 hours. The sensitivity and specificity of biopsy urease test is approximately 95%. Obtaining antrum and body tissue and placing them into the same agar well may increase the sensitivity. False-negative results may be produced in patients who are on PPIs and antibiotics.

Other methods include specific histological staining of the biopsy material for *H. pylori* or culture under special

microaerobic conditions. Histology has sensitivity and specificity above 95% and is similar to the urease-based test, but false-negative results can occur in patients on PPIs through patchy distribution of the organism in the stomach. Microbiological culture is rarely performed but can be useful for testing antibiotic sensitivity in patients who have failed first-line therapy.

Treatment

H. pylori eradication

All PUD patients with *H. pylori* should undergo therapy to eradicate the organism as successful eradication reduces the risk of ulcer recurrence.

First-line regimens that have proven efficacy consist of a PPI and two antibiotics, amoxicillin and clarithromycin, or amoxicillin and metronidazole, given twice daily for 1 week. For those allergic to penicillin, amoxicillin can be replaced with metronidazole, though the eradication rate with this combination is lower as shown in the MACH 2 trial. In the event of treatment failure, second-line quadruple therapy can be attempted with a PPI twice daily in addition to bismuth subcitrate 120 mg 4 times daily, tetracycline 500 mg 4 times daily and metronidazole 500 mg 3 times daily for a minimum of 7 days, and preferably for 2 weeks. Early reports on new combinations, such as furazolidone-quadruple therapy and rifabutin-triple therapy, are encouraging. When eradication of *H. pylori* infection has been documented after treatment, subsequent re-infection is rare.

Non-H. pylori, non-NSAID ulcers

Over the past decade, the incidence of non-*H. pylori*, non-NSAID ulcers appears to have been increasing. Although the magnitude of this problem is uncertain, such ulcers are increasing as PUD due to *H. pylori* infection is decreasing. North American studies indicate that 11–44% of PUD is now not related to *H. pylori* infection or NSAIDs. Unreported NSAID use needs to be considered, especially given the large number of over-the-counter NSAID-containing medications available. Illicit contamination of traditional medicines with NSAID is another possibility. Other drugs capable of producing ulceration include alendronate, mycophenolate, and potassium tablets. Other conditions producing such ulcers include Crohn's disease, Zollinger-Ellison syndrome, and lymphoma.

HIGHLIGHTS

- *Helicobacter pylori* infection occurs worldwide. It is much more common in developing countries (up to 80%), where most infections occur in childhood. It is much less common in developed countries, where childhood infection is low (5–10%) and new adult infection uncommon.
- The most common method of spread is the faecal-

oral route.

- *Helicobacter pylori* infection is the most important cause of peptic ulcer disease. It is also associated with gastric carcinoma and low-grade MALTomas, but a role in gastro-oesophageal reflux and non-ulcer dyspepsia has not been established.

- The stool antigen test and the UBT are the non-invasive diagnostic tests of choice. Endoscopy and mucosal biopsy are also important.
- Treatment is by a combination of antibiotics and a PPI.

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