Helicobacter pylori

Basics and clinical overview

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ABSTRACT

The discovery of *Helicobacter pylori* (*H. pylori*) has greatly changed the approach to the management of peptic ulcer disease and gastric cancer. A sound knowledge of the basics of *H. pylori* is an important aid in the diagnosis and treatment of clinical conditions associated with this infection. Gastric carcinoma is estimated to be the world's second most common cancer as a cause of death. It is hoped that gastric cancer can be prevented by *H. pylori* eradication; however, this issue is still under investigation. Active research is ongoing to highlight the mechanisms by which *H. pylori* leads to severe gastric diseases as well as finding associations with extra-gastric diseases.

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Helicobacter pylori (*H. pylori*) has been the subject of intense investigation since its isolation and culture from a gastric biopsy in 1982.[1] The first positive culture was noted by Marshall and Warren[1] after plates had been left in the incubator for 6 days during the Easter vacation.[2] To convince the colleagues and to prove Koch's postulates of causation between *H. pylori* and gastritis, Marshall drank a suspension of the bacterium.[3] The discovered organism has been through several name changes: Campylobacter-like organism,[1] Campylobacter pyloridis,[4] Campylobacter pylori,[5] and finally *H. pylori*.[6]

Microbiology. *Helicobacter pylori* is a spiral gram-negative rod 0.3-0.5 µm in length and 0.5-0.9 µm in diameter.[7] Its ability to move through the viscous gastric mucus layer is due to the presence of 5-6 unipolar flagellae.[8] *Helicobacter pylori* is a microaerophile that grows best in an atmosphere of 5% oxygen with 5-10% CO_2 on blood containing media.[9] The cultures grow optimally at 37°C after 3-5 days of incubation.[10] There are 7 known gastric Helicobacter species, of which *H. pylori* and *Helicobacter heilmanii* (previously known as *Gastrospirillum hominis*) are the only 2 species which have been associated with human gastric diseases.[11] Deoxyribonucleic acid based typing of *H. pylori* have identified 2 important strains: vacA (vacuolating toxin gene) and cagA (cytotoxin associated gene). The cagA gene is present in 60-70% of strains[12] and cagA strains are more virulent than vacA strains.[13]

Epidemiology of H. pylori. The prevalence of *H. pylori* infection varies widely by geographic area, age, race and socio-economic status.[14] In general, the prevalence in developing countries may reach up to 70%, compared with 40% in developed countries.[15] The acquisition rate of *H. pylori* appears to be more rapid in developing than developed countries, which was attributed to the rate of acquisition of *H. pylori* in childhood.[16]

Animals and water have been implicated as potential sources of infection. Animals that have been proposed to act as a source of *H. pylori* infection include: sheep,[17] rhesus monkeys,[18] domestic cats,[19] houseflies[20] and cockroaches.[21]

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Despite an extensive search for an environmental source of *H. pylori*, there are no significant sources have been found to exist outside the human stomach.[22] The most likely mode of transmission of *H. pylori* infection is the direct person-to-person contact.[23] However, there is controversy over whether gastro-oral, oral-oral or fecal-oral spread predominates. Iatrogenic transmission of *H. pylori* by gastric endoscopy is a potential risk with reported rates of 0.4%[24] and 1.1%.[25]

Effects of H. pylori on gastric mucus layer and mucosa. (i) Helicobacter pylori and mucus gel-layer thickness. The mucus gel layer provides a protective environment for *H. pylori* to colonize the gastric epithelium.[26] The effects of *H. pylori* infection on human gastric mucus thickness have been investigated by several studies, with contradictory findings ranging from a reduction in mucus thickness [27] to no effect on thickness.[28,29] It is only with *H. pylori* associated gastric atrophy[28] or advancing patient age[30] that there is a significant reduction in mucus thickness.

(ii) Helicobacter pylori and gastric prostaglandins (PGE2). Prostaglandins have a variety of actions within the gastric mucosa that contribute to mucosal protection. Since the discovery of *H. pylori*, many studies have investigated its effect on PGE2 levels and its role in gastric diseases. Most studies suggest that PGE2 levels are increased in the presence of *H. pylori* infection.[31,32] Although Goren[33] reported that PGE2 levels decrease in the presence of *H. pylori* infection.

(iii) Helicobacter pylori and mucus hydrophobicity. The hydrophobic lining of the stomach plays an important role in protecting the gastroduodenal mucosa from acid and peptic digestion. The hydrophobicity of the gastric antral mucosa in peptic ulcer patients was found to be significantly lower than that of healthy volunteers.[34] The effect of *H. pylori* on mucosal hydrophobicity has been investigated using the contact angle technique, with most studies reporting a decrease in mucosal hydrophobicity with *H. pylori* infection compared to non-infected controls.[34-36]

Diseases associated with Helicobacter pylori infection. *H. pylori* infection has been associated with gastritis, peptic ulcer disease and gastric cancer. Moreover, it is claimed to be associated with extra-gastrointestinal disorders such as ischemic heart disease,[37] ischemic cerebrovascular disease, atherosclerosis, liver disease and skin diseases.[38] The important disease associations are discussed below.

Helicobacter pylori and gastritis. The association between *H. pylori* infection and gastritis is well documented in the literature. Individuals with antral predominant gastritis are prone to develop duodenal ulcers,[39] while those with multifocal atrophic gastritis and chronic inflammation in the body and antrum of the stomach (pangastritis) are prone to develop gastric ulcers and cancer.[40] Both atrophic gastritis and intestinal metaplasia are recognized risk factors for the development of gastric ulcers and gastric cancer.[41]

a) Helicobacter pylori and benign gastric diseases. i) Peptic ulcer disease. Covacci et al[42] reported that 90-95% of duodenal ulcers and 70-75% of gastric ulcers are due to *H. pylori* infection. The strongest evidence linking the bacteria to duodenal ulcer is the finding that the relapse rates after *H. pylori* eradication by antibiotics is lesser (2.6-7%) compared with patients in whom the bacteria is not eradicated (58-67%), or in patients treated with the traditional antisecretory drug therapy alone (68%).[43]

ii) Non-steroidal anti-inflammatory drugs (NSAIDs) peptic ulceration. Non-steroidal anti-inflammatory drugs are the most common cause of *H. pylori* negative duodenal and gastric ulcers.[44] It is controversial whether there is synergy between NSAIDs and *H. pylori* in promoting ulcer formation.[45] Nevertheless, the most cost-effective strategy in patients who are on NSAIDs and have an ulcer is to cure *H. pylori* infection, which is what is generally recommended.[46] Non-steroidal anti-inflammatory drugs decrease systemic inflammation by inhibiting the enzyme cyclooxygenase (COX), which has 2 isoforms COX-1 and COX-2. This enzyme acts on arachidonic acid to generate prostaglandins and thromboxanes.[47] Most NSAID induced-mucosal injury to the stomach and duodenum is a consequence of PGE2 reduction, which leads to a decrease in mucus secretion[47] and an alteration in the mucus layer thickness.[48]

iii) Gastroesophageal diseases. The relationship between *H. pylori* infection and gastroesophageal reflux disease (GORD) is controversial with some studies reporting an increased risk of GORD and its complications[49] while others reporting a decreased risk.[50] Chow et al[51] suggested that infection with cagA+ strains may protect against cancer of the cardia of the stomach, but this was not supported by Wu et al[52] who found no evidence for increased esophageal and gastric cardia cancer in the presence of cagA+ infection. This knowledge has imposed limitations on *H. pylori* eradication; however, the risk of not eradicating *H. pylori* and the possible development of gastric cancer have to be weighed against the risk of developing esophageal adenocarcinoma. Furthermore, eradication of *H. pylori* has no adverse effect on the relapse rate in GORD[53] and may be beneficial.

b) Helicobacter pylori and gastric cancer. i) Relationship between H. pylori and gastric cancer. Gastric carcinoma is estimated to be the

world's second most common cancer, being second only to lung cancer as a cause of death.[54] In contrast to the trend for an overall decrease in gastric cancer rates, in developed countries there has been a rapid increase in the incidence of gastric cancer localized to the cardia.[55] Gastric cancer is most common in the 50-70 years age range with a male to female ratio of 2:1.[56] Malignant tumors of the stomach are mainly (95% of cases) adenocarcinomas, with gastric lymphoma constituting 1% of gastric malignancies.[57] The adenocarcinomas are classified into 2 major histological types: well differentiated intestinal and undifferentiated diffuse.[58] The trefoil factor family (TFF) peptides have been shown to be involved in the carcinogenesis process.[59] Leung et al[60] studied the expression of trefoil peptides in the gastric tissue from cancer and non-cancer patients and suggested that TFF1 and TFF2 may possess tumor-suppressive properties. The exact relation of *H. pylori* to the trefoil peptides is yet to be clarified.

Helicobacter pylori has been designated a group one (definitive) carcinogen by the World Health Organization (WHO).[61] Two distinct gastric cancers have been associated with *H. pylori* infection: the gastric adenocarcinoma[62] and gastric lymphoma.[63] The supportive evidence for this association has come from epidemiological and experimental studies. Support for the association of *H. pylori* with gastric cancer (distal gastric adenocarcinoma) comes from 5 sources.[64] First, from epidemiological studies paralleling epidemiologic features of cancer with those of *H. pylori* infection. A review by Danesh,[65] of 34 retrospective studies and 10 prospective studies showed a risk ratio of 2.5 (95% confidence interval 1.9-3.4) for gastric cancer. Second, from cross-sectional studies, which revealed rates of *H. pylori* infection between 50% and 100% in individuals with gastric carcinoma.[66,67] Third, long-term prospective studies show a positive association between *H. pylori* seropositivity and the subsequent development of gastric cancer.[68] Fourth, experimental studies on Mongolian Gerbils have confirmed the development of gastric adenocarcinoma in *H. pylori* infected animals.[69,70] Fifth, the effect of *H. pylori* eradication on the incidence of gastric cancer: Shimizu et al[71] reported that *H. pylori* eradication could decrease the incidence of gastric carcinomas in Mongolian Gerbils. In humans, Uemura et al[72] studied 2 groups of patients who underwent endoscopic mucosal resection for early gastric cancer. Of these, one group underwent treatment to cure their *H. pylori* infection and the other did not. At 5-year follow up, no second cancer had occurred in the *H. pylori* eradicated group, whereas 9% of patients in the non-eradicated group had developed a second cancer. In addition, Wong et al[73] in their prospective, randomized, placebo-controlled, population-based primary prevention study of 1630 healthy carriers of *H. pylori* infection from a high-risk region of China in a follow up period of 7.5 years found that the incidence of gastric cancer development at the population level was similar between participants receiving *H. pylori* eradication treatment and those receiving placebo. However, in the subgroup of *H. pylori* carriers without precancerous lesions (988 participants) the eradication of *H. pylori* significantly decreased the development of gastric cancer. Further research is clearly required to show whether *H. pylori* eradication could prevent gastric cancer in humans.

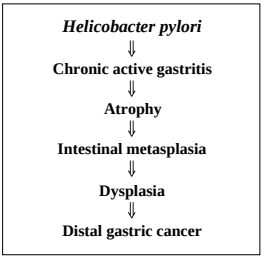

Figure 1 - Correa's multi-step model of *Helicobacter pylori* leading to gastric cancer.

Mucosa associated lymphoid tissue (MALT) lymphoma constitutes 1% of gastric cancers.[57] *Helicobacter pylori* infection has been associated with the low grade B-cell lymphoma, with the organism being detected in 58-98% of gastric biopsies from patients with gastric low grade MALT lymphoma.[74] The relationship between gastric MALT lymphoma and cagA+ infection has been studied by Eck et al,[75] who reported a 98.5% cagA+ seropositivity in 68 patients with gastric MALT lymphoma.

ii) Models of gastric carcinogenesis. Correa[76] proposed that *H. pylori* infection is one of the triggering factors in the progressive processes of increasingly severe gastric lesions (**Figure 1**). Al-Marhoon et al[77] have found that cagA+ *H. pylori* infection has the potential of increasing gastric mucus thickness and hydrophobicity through increased levels of PGE2 and proposed a model indicating the initial changes induced by cagA+ infection that possibly play a role in protecting the organism and enhancing its colonization that may lead to gastric cancer.

Helicobacter pylori may cause gastric carcinomas by the following mechanisms: 1) collateral damage of inflammatory by-products causing mutational events in gastric epithelial cells, for example production of reactive oxygen intermediates that can induce DNA damage with DNA mutations

Table 1 - Comparison between different methods of *Helicobacter pylori* (*H. pylori*) diagnosis.

Feature	Histology	Culture	Rapid urease test (CLO)	Serology (ELISA)	Urea breath test	Stool antigen test	PCR
Sensitivity (%)	90	86	88 - 92	90-100	95-100	91	93-96
Specificity (%)	88	100	92 - 100	91-100	95-100	93	100
Invasive	+	+	+	-	-	-	-
Expensive	+	+	-	-	-	-	+
Results within 24 hours	-	-	+	-		+	+
Can confirm eradication of *H. pylori*	-	-	-	-	+	-	+
Accuracy affected by recent treatment with antibiotics or PPIs	+	+	+	-	+		-

+ = yes, - = no, PCR - polymerase chain reaction, PPIs - proton pump inhibitors,
CLO - Campylobacter like organism, ELISA - enzyme-linked immunosorbent assays.

contributing to the pathogenesis of gastric cancer.[78] Farinati et al[79] showed that cagA+ patients had higher oxidative DNA damage than cagA- and *H. pylori* negative patients as assessed by the tissue concentrations of 8-hydroxydeoxyguanosine (8OHdG) levels, which is responsible for DNA base mutation induced by reactive oxygen metabolites; 2) direct toxic effects on epithelial cells, *H. pylori* is known to produce damaging enzymes such as phospholipase A2 and cytotoxins such as vacA; and 3) alterations in the balance between apoptosis and proliferation. *Helicobacter pylori* produces an apoptosis-inducing protein that was found to have gamma-glutamyl transpeptidase activity.[80]

Diagnosis of H. pylori. The presence of *H. pylori* infection in the stomach is detected by several invasive and non-invasive methods. Culture, histology and the rapid urease test are invasive as it requires mucosal biopsy specimens obtained by endoscopy. Serology, urea breath test (UBT), stool antigen test, and polymerase chain reaction (PCR) are non-invasive tests. A comparison between the different tests is presented in **Table 1.**[81-84] The choice of the test used is determined by the accuracy, cost, availability and whether the patient will be undergoing endoscopy. Currently, none of the available tests alone can be used for a definitive diagnosis of *H. pylori,* because none, including PCR, is ideal.[85] Stool antigen tests are increasingly being used as simple non-invasive methods for *H. pylori* diagnosis.[86]

Treatment of H. pylori. It is not possible to eradicate *H. pylori* infection using only one drug; hence, a number of drug combination regimes have evolved. These include: Bismuth-based triple therapy (such as Bismuth plus Nitroimidazole plus Amoxicillin or Tetracycline); and therapies based on acid inhibitory drugs (such as H2-antagonist, proton pump inhibitors (PPI) or Bismuth-Ranitidine) combined with antibiotics (such as Nitroimidazole, Amoxicillin, Clarithromycin and Azithromycin) as a dual, triple or quadruple therapy.[87] The European *Helicobacter pylori* Study Group (EHPSG), in the Maastricht 2-2000 consensus report,[88] outlined the current recommended first line regime for *H. pylori* treatment that gives a high eradication rate of 80-90%. This regime is a PPI-triple therapy, which consists of Omeprazole 20 mg twice daily, Clarithromycin 500 mg twice daily and Amoxicillin 1 g twice daily or Metronidazole 400 mg twice daily for 7 days. Many drug regimes are currently under investigation and the treating physician should keep updated on new developments.

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