Review Article

The current status of *Helicobacter pylori*

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ABSTRACT

We present a review of the current status of *Helicobacter pylori* infection, and focus on the clinical issues facing physicians with regards to its pathogenicity, diagnosis and treatment. We have attempted to address the important clincial issues relevant to the subject, and summarize the currently accepted concepts concerning *Helicobacter pylori*. Our knowledge regarding *Helicobacter pylori* biology is enormous, but detailed knowledge on its transmission is still far from clear. *Helicobacter pylori* is mainly involved in gastrointestinal and possibly in other extra-intestinal disorders. There are differences in the clinical presentation in various geographical regions resulting from variations in the genetic make-up of *Helicobacter pylori*. There is still need for more simple, cost-effective, accurate and less invasive diagnostic techniques. The gold standard treatment is the one-week proton pump inhibitor-based triple regimen as first line, with quadruple therapy as a 2nd line. *Helicobacter pylori* resistance to the main antimicrobials needs to be defined in particular geographical areas.

Keywords: *Helicobacter pylori*, review, gastritis.

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The discovery of *Helicobacter pylori (H.pylori)* by Warren and Marshall in 1983 brought a dramatic change to medicine.[1] In the past most peptic ulcers were considered idiopathic; but since this historic discovery it became clear that most ulcers results from infection with *H.pylori* or the use of non steroidal anti-inflammatory drugs (NSAIDs) or both.[2] Although a decline in the prevalence of peptic ulcers has been noticed in developed countries, the rate of complications which results from these ulcers remain relatively stable. This fact primarily points to 3 factors: The decreasing prevalence rate of *H.pylori* in developed countries, the increase ingestion of NSAIDs, and the change in rates of smoking.[2]

Helicobacter pylori and gastrointestinal diseases. Infection with *H.pylori* is the most frequent infection worldwide as more than half of the world's population are infected.[3] *Helicobacter pylori* is a well known factor in the pathogenesis of chronic active gastritis, atrophic gastritis, peptic ulcer disease, gastric polyps, mucosa associated lymphoid tissue (MALT) lymphoma and gastric cancer.[4-18] Although the majority of *H.pylori* infected individuals are asymptomatic, approximately 16% of them develop peptic ulcer disease, and each year 1%-2% of these will experience a major ulcer related complication.[19]

Several observations support the causal role of *H.pylori* in peptic disease. First, there is a strong association between the presence of *H.pylori* and chronic active gastritis histologically. Second, most patients with peptic ulcers are infected with *H.pylori,* since it is found in more than 70% of gastric and in over 90% of duodenal ulcer patients. Third, the eradication of the organism has been associated with histological improvement of gastritis, decrease in ulcer relapse rate and in risk of bleeding from duodenal ulcer.[4] The mechanism by which *H.pylori* causes gastric mucosal damage and peptic ulcer is not fully elucidated, but it is clear that it involves several *H.pylori* virulence factors enabling it to survive the strong gastric acid. In addition, host-dependent noxious substances lead to progressive damage to the gastric mucosa, deregulation of acid production, induction of gastric metaplasia, and development of chronic gastritis. These *H.pylori*

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virulence factors and host noxious substances include cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), ammonia, lipopolysaccharide (endotoxin), platelet activating factor, nitric oxide and interleukin-8.[20,21] The type of pathology induced by *H.pylori* (gastritis, peptic ulcer, gastric lymphoma and adenocarcinoma) depends on the interactions between the *H.pylori* infected host and the environment. Haruma et al[22] investigated the grade of fundus atrophic gastritis (FAG) and gastric acid secretion in association with *H.pylori* infection. While the advance in age had no influence on gastric acid secretion in *H.pylori*-negative subjects, it greatly decreased the gastric secretion in *H.pylori*-positive subjects due to the increase in the prevalence of FAG with age. Similarly, Ohkuma et al,[8] suggested that atrophic gastritis is not a normal aging process, but instead is likely to be the result of *H.pylori* infection, while intestinal metaplasia is caused by both the aging process and *H.pylori* infection. One of several possible initial manifestations of *H.pylori* acquisition in adults may be acute gastritis with hypochlorhydria, while *H.pylori* colonization usually persists, hypochlorhydria resolves in most subjects.[23] *Helicobacter pylori* infection is also associated with increased Pepsinogen 1 levels.[24]

Helicobacter pylori and extra-gastrointestinal diseases. There is a growing body of literature linking *H.pylori* to extra-digestive disorders such as ischemic heart disease, ischemic cerebrovascular disease, atherosclerosis, autoimmune thyroid diseases, migraine, and skin diseases.[25-28] There is a suggested role of autoimmune processes in the pathology of *H.pylori* infections.[26] If these associations are adequately proven, then the eradication of *H.pylori* must have a great beneficial impact on human health.[4] On the other hand, there is evidence against the association between *H.pylori* infection and extra-digestive disorders.[28] Since *H.pylori* infection is very common, caution must be taken not to accuse *H.pylori* in every disease. Different reports suggested that *H.pylori* infection is not strongly related to the incidence of coronary heart disease, and CagA-positive strains appeared to be no more strongly related to the disease than other strains. However, further studies are required to confirm or refute the existence of any moderate associations.[29,30]

Clinical and geographical variations of Helicobacter pylori. There is a variable geographic distribution for different strains of *H.pylori* that differ in the genomic structure and in the virulence factors.[31] Some strains are endowed with greater pathogenicity such as the *H.pylori* type I CagA-positive strains, which induce a higher release of proinflammatory substances by the gastric mucosa that trigger systemic vasospasm.[27] The majority of infected individuals remain asymptomatic, and even when symptoms develop, they are not specific. It is not known why only a small proportion of infected individuals develop peptic ulcer disease and even fewer develop gastric cancer. The variation in the clinical picture related to *H.pylori* infection is probably due to differences in the virulence factors.[31-35] Mukhopadhyay et al[35] suggested that *H.pylori* genomic structure differ regionally and they emphasized the potential importance of studying non-Western *H.pylori* populations in order to develop a global understanding of *H.pylori* and its associated diseases.

Virulence factors. Two major markers of virulence in *H.pylori* have been described.[36] The first is a secreted protein VacA that is toxic to human cells in tissue culture. This cytotoxin causes vacuolation and damage of epithelial cells. The 2nd is a pathogenicity island for which the gene CagA is a marker. Approximately 60% of *H.pylori* that isolates in western countries are CagA+.[36] In that study Perez et al[36] suggested that there is a correlation between the prevalence of CagA seropositivity on one hand and peptic ulcer disease and distal gastric cancer on the other. They found a clear negative association between the presence of positive CagA and esophageal diseases.[36] Therefore, CagA seropositivity is associated with increased risks of certain diseases (involving the lower stomach and duodenum) and decreased risks of gastroesophageal reflux disease (GERD) and its sequelae.[36] They suggested that this apparent paradox can best be explained by differences in the interaction of CagA+ and CagA- strains with their hosts.[36]

Although *H.pylori* infection is associated with various gastroduodenal diseases, it plays a protective role rather than a promoting factor for reflux esophagitis and GERD. Various reports showed lower prevalence of *H.pylori* infection in reflux esophagitis and Barrett's esophagus compared to controls.[37,38] However, the relationship between *H.pylori* infection and reflux esophagitis has not been made clear as it remains controversial whether eradicating *H.pylori* in duodenal ulcer or functional dyspepsia increases the risk of subsequent development of reflux esophagitis and GERD.[39] There is an association between cytotoxic strains and the severity and activity of histological gastritis where the cytotoxic strains were more common in subjects with severe histological gastritis than in those with normal mucosa or mild gastritis and the prevalence of cytotoxic strains was also higher in subjects with active gastritis than in those without.[40] The CagA gene is more closely associated with duodenal ulcer than with gastric ulcer and the VacA s1a/m2 strain is more closely associated with active chronic and atrophic gastritis than with chronic gastritis.[41] Matsui et al[42] suggested that the recurrence of gastric ulcer depends upon strain differences of *H.pylori* in urease B gene. They studied 32 patients with benign gastric ulcers, and

found that the rate of recurrence was significantly lower in patients with type II than in patients with types I, III, and IV.[42] They also showed that the occurrence of gastric ulceration was significantly lower in type II compared with types I and III.[42] This data indicated that in the context of ulcer recurrence, it is not necessary to eradicate *H.pylori* during infection with type II.[42]

Transmission. *Helicobacter pylori* is mainly a human bacterium.[43] It colonizes the human stomach, especially during childhood but the precise mode of transmission and the natural reservoir for *H.pylori* remains unclear. In one study, *H.pylori* was present in the oral cavity of 97% of tested individuals, with a characteristic distribution that was independent of the infection status of the stomach, which means that it may belong to the normal oral microflora.[44] Transmission is thought to be mainly through the oral-oral route, but fecal-oral and waterborne transmissions are other suspected modes.[5,45] In developing countries, feco-oral transmission, either direct or via the water supply might be a significant mechanism of human contamination both for primary infection in children and perhaps, reinfection in adults, although it seems to be rare in the west.[45] Transmission of *H.pylori* from beef and beef products is not a primary factor in humans.[43]

Prevalence and risk factors. It is estimated that 0.4-1.0% of uninfected adults acquire *H.pylori* each year, and the incidence of *H.pylori* infection tends to increase with age.[5,46,47] However, detailed information on the prevalence of the bacteria in developing countries and on the factors that may influence the pattern of distribution remains scanty. In developing countries the prevalence of *H.pylori* ranges between 70%-90%[6,48,49] while in developed countries it is 50%.[5] The main risk factors for *H.pylori* acquisition are childhood, low socio-economic status, the presence of *H.pylori*-positive family members, and poor sanitation.[45,47] *Helicobacter pylori* infection is essentially acquired during childhood; changes in infection status with time are rare in adults as only few adults become infected with *H.pylori*.[50]

There is controversy regarding the relation of smoking, alcohol, and other life style factors to *H.pylori*[49,51-54] Ponzetto et al[55] reported a high prevalence of *H.pylori* in patients with hepatitis B virus-related cirrhosis compared to controls, they suggested that this might explain the frequent occurrence of gastroduodenal ulcer in cirrhotic patients. To assess the benefits of intervention programs against *H.pylori* infection, Rupnow et al[56] published a report regarding a dynamic transmission model for predicting trends in *H.pylori* and associated diseases in the United States of America (USA). They suggested that in the USA, transmissibility of *H.pylori* has decreased to values so low, that should this trend continue, the organism would disappear from the population without targeted intervention. This process, however, will take more than a century. The prevalence of *H.pylori* infection is decreasing in the developed countries as a result of the progressive improvement of socio-economic and environmental conditions. As a result of this decrease, the incidence of peptic ulcer disease not related to anti-inflammatory drugs will fall, allowing the relative frequency of *H.pylori* negative ulcer disease to increase, but the extent to which *H.pylori* disappearance is responsible for decreasing prevalence of gastric cancer remains speculative.[57]

Diagnosis. Identification of *H.pylori* as the major etiological factor for peptic ulcer disease has dramatically changed management of this disease. Given the high prevalence of *H.pylori* infection, particularly in the developing countries, diagnosis of *H.pylori* infection has become increasingly important and this has stimulated the search for developing simple, cost-effective, accurate and less invasive diagnostic techniques. The diagnostic tests available so far are invasive such as histology, culture, urease test, and polymerase chain reaction and non-invasive such as urea breath test using Carbon 13 (C13) or Carbon 14 (C14), serology and tracing *H.pylori*-antigens in feces. The decision to chose a particular test depends on the prevalence of *H.pylori,* clinical situation, sensitivity and specificity of the test. Endoscopy with multiple site biopsy, particularly where atrophic gastritis is also prevalent is the key to diagnosis, allowing direct assessment of *H.pylori* infection. The golden standard technique is culture of gastric biopsies while serological tests have a low specificity and sensitivity especially during childhood. On the other hand, although the C14 urea breath test is a reliable and cheaper test than C13 test, it has small radioactivity risk, which limits its usage. Carbon-13 urea breath test remains the non-invasive test of choice and it is especially useful during follow-up.[34] The diagnosis using stool analysis for *H.pylori* antigen has been recently approved, it is rapid and easy to perform, cost-effective, with a high specificity and sensitivity and is a good alternative for the urea breath test in monitoring the response to therapy.[58,59]

Treatment. The main goal of treatment of peptic ulcer disease is eradication of *H.pylori* which will decrease the recurrence rate of ulcers. Although there is as yet no consensus agreement with regards starting treatment, which antibiotics to use and the treatment routines to be followed, the current recommendation is to establish the diagnosis, give a combination of antibiotic and antisecretory drugs, and confirm that the infection has been eradicated 4-6 weeks later.[60] Currently the gold standard treatment is the one-week proton pump inhibitor-based triple regimen. This consists of proton pump inhibitors in combination with 2 antibiotics out of amoxicillin, clarithromycin, tetracycline and metronidazole.[34] Quadruple therapy is used as 2nd line therapy,[57] this

was found to be effective, regardless of the resistance to metronidazole. If *H.pylori* was found to be resistant to clarithromycin, then replacing clarithromycin with either metronidazole or other agents chosen according to the susceptibility test is recommended.[61] Ranitidine bismuth citrate with 2 antibiotic regimens is still used and may achieve an 80% eradication rate.[39] The clinical relevance of *H.pylori* infection in asymptomatic individuals and in non-ulcer dyspepsia remains to be determined and requires further studies.

Despite the fact that *H.pylori* infection is very prevalent in developing countries, only limited data exists on the susceptibility of *H.pylori* to antimicrobials commonly used in eradication regimens in these countries. Mendonca et al[62] suggested that there is a need for culture and susceptibility testing to define *H.pylori* resistance patterns in particular geographical areas before the general use of an eradication schedule. The possibility of resistance to antimicrobials agents in certain geographical areas with a high prevalence of *H.pylori* infection should be fully evaluated.

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