Helicobacter pylori: Epidemiology, diagnosis and clinical relevance

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SJO VELDTHUYZEN VAN ZANTEN, PM SHERMAN. *Helicobacter pylori*: Epidemiology, diagnosis and clinical relevance. *Can J Gastroenterol* 1993; 7(5):390-394. The following aspects of *Helicobacter pylori* infection are summarized: the epidemiology of *H pylori* infection, data on the prevalence of the organism in Canada, methods of diagnosis, and evidence for an association between *H pylori* and gastritis, duodenal ulcers, nonulcer dyspepsia and gastric cancer.

Key Words: Duodenal ulcer, Dyspepsia, Gastric cancer, Gastritis, *Helicobacter pylori*, Urease

Helicobacter pylori: Épidémiologie, diagnostic et pertinence clinique

RÉSUMÉ: Les aspects suivants de l'infection à *Helicobacter pylori* sont résumés: l'épidémiologie de l'infection à *H pylori*, les données sur la prévalence de ce pathogène au Canada, les méthodes diagnostiques, et les preuves d'association entre *H pylori* et la gastrite, les ulcères duodénaux, la dyspepsie non ulcéreuse et le cancer de l'estomac.

HELICOBACTER PYLORI HAS BEEN isolated worldwide from the antrum of individuals with chronic active (type B) gastritis. Although *H pylori*

can infect gnotobiotic piglets and non-human primates (1,2), humans are the predominant host. The prevalence of *H pylori* colonization is high even in

asymptomatic populations. Prevalence increases with age, race (ie, higher in black Americans) and lower socioeconomic status (3,4). Of these factors age is the strongest predictor of *H pylori* infection (3,5,6). In Peru the source of water supply was found to be a risk factor for *H pylori* infection (7). In developing countries the prevalence is higher than in North America and Western Europe and the infection is acquired at a younger age (5,6,8). The date of acquisition may be important, especially with regard to the possible link that exists with later development of gastric cancers. It is possible that the longer a person has chronic *H pylori* associated gastritis, the higher the subsequent risk for development of gastric cancer.

The exact mode of transmission of the organism in humans is unclear. There is familial clustering of *H pylori* suggesting either a common source of infection or that close personal contact is necessary for transmission of the organism (either oral-oral or fecal-oral) (9-11). Recently, successful culture of *H pylori* from human feces has been reported (12). In an animal model of gastritis due to helicobacter-like organ-

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isms in the ferret (*Helicobacter mustelae*), evidence for fecal-oral transmission has also been found (13). In the ferret model hypochlorhydria promotes fecal transmission of *H mustelae* (14). This raises the question whether inhibition of gastric acid may make humans more prone to colonization with *H pylori*.

Despite the high prevalence of *H pylori* in the general population we do not know the exact timing and source of acquisition in most individuals. A few isolated cases of new onset *H pylori* colonization have been described (15-17), which indicate that it can present with an acute upper-gastrointestinal syndrome accompanied by nausea, vomiting and epigastric discomfort. Spontaneous clearance of *H pylori* infection rarely occurs. Therefore most infected people harbour a lifelong bacterial infection in the gastric antrum.

H PYLORI IN CANADA

A number of studies have reported on the prevalence of *H pylori* in Canada. In children with a mean age of 11 years who underwent endoscopy in Toronto, seven of 67 (10%) were positive for *H pylori* in the antrum (18). Of these 67 patients, 49 had normal histological findings as seen on antral biopsies and in eight children histologic evidence of gastritis was explained by Crohn's disease, eosinophilic gastritis or use of medications that are known to cause gastropathy. Of the 10 cases with unexplained antral gastritis, seven children were *H pylori* positive; this specificity provides support that the organism plays an important role in antral gastritis. In a study of healthy asymptomatic adult volunteers and dyspeptic patients in Toronto, six of 54 (11%) volunteers and 36 of 65 (55%) patients were *H pylori* positive (19). In dyspeptic adults, who underwent endoscopy in Hamilton, Ontario, the prevalence was 56% (20). In both these studies *H pylori* prevalence increased with age. Two large serological studies have been performed, one in blood donors in Manitoba and one in individuals randomly selected from the general population in Nova Scotia (21,22). The results of both studies are comparable and show

Figure 1) Hydrolysis of urea by the urease enzyme to carbon dioxide and ammonia

that the prevalence of *H pylori* infection varied from approximately 20% in 18-year-olds to 50% in persons over age 70. All these results are similar to the *H pylori* prevalence rates found in cross sectional studies performed in other affluent countries (5,6).

DIAGNOSIS OF H PYLORI

Five types of diagnostic tests are currently available: histology, culture, rapid urease testing, ^{13}C - or ^{14}C -urea breath tests and serology (eg, enzyme-linked immunosorbent assay [ELISA]). Both rapid urease testing (two tests are commercially available in Canada: Campylostat; Intercon Pharma, and CLOtest; Mui Scientific) and the breath test are based upon the very high activity of the urease enzyme, a characteristic feature of the organism (23,24). As shown in Figure 1, the urease enzyme converts urea in the presence of water into carbon dioxide and ammonia. For the rapid urease test a buffered medium is used to which an indicator such as phenol red is added that gives a colour change in an alkaline pH (in this case by the production of ammonia) (25-27). For the urea breath tests urea is labelled with either ^{13}C or ^{14}C and is administered to the patient together with a test meal. If *H pylori* organisms are present in the stomach the radiolabelled urea will be converted into $^{13}\text{CO}_2$ or $^{14}\text{CO}_2$, which can be measured in expired breath samples by either mass spectrometry ($^{13}\text{CO}_2$) or in a scintillation counter ($^{14}\text{CO}_2$) (28-31).

The urease activity of *H pylori* is much higher than found in other urea-splitting organisms such as *Proteus mirabilis*, *Proteus vulgaris* and *Providencia* species (23,32). Another difference is

that the urease of *H pylori* is acid stable whereas urease from other bacterial species such as proteus is acid labile (32,33). The urease of *H pylori* may therefore offer protection to the organism against destruction by gastric acid.

H pylori is a difficult organism to grow and requires dedicated technicians in the microbiology laboratory in order to obtain reliable results (34). For histological identification several stains are useful: hematoxylin-eosin stain, modified Giemsa and Steiner or Warthin Starry silver stain. In patients not treated with anti-helicobacter therapy it is often possible to recognize *H pylori* organisms in hematoxylin-eosin stained sections. A careful search for the organism should always be undertaken if there is histological evidence of antral gastritis. After anti-helicobacter therapy the number of organisms may be low and additional stains may be required to ensure that eradication of the infection has been achieved.

Several serological assays that measure antibodies against *H pylori* have been developed (35). These assays use either complement fixation, bacterial agglutination, immunofluorescence, ELISA or flow cytometry to detect *H pylori* specific immunoglobulin (Ig) G in serum (35,36). In the initial assays crude antigens, such as whole-cell sonicates, were used but now more purified cell surface antigens, including urease, are available (37-39).

All of the diagnostic tests perform well with a sensitivity of greater than 80% and a specificity greater than 95% (20). The operating characteristics of breath tests and serology are slightly better than the other diagnostic tests. This is probably due to the fact that

these two tests are less prone to sampling error. For practical purposes reliable detection of *H pylori* can be achieved at the time of diagnostic upper gastrointestinal endoscopy by the combination of culture and histology (and rapid urease test if available) of antral biopsies. In most studies this combination is used as the accepted gold standard to diagnose *H pylori* infection (40).

The antrum is the most commonly involved portion of the stomach. However, the presence of *H pylori* may be patchy on the gastric mucosa and the organism missed if only a single biopsy is taken. Therefore, it is recommended that two gastric biopsies are taken at endoscopy for culture and two for histology. This way more than 90% of infected patients will be identified correctly (20). It is preferable that two biopsies are taken from the antrum and two from the body of the stomach. There are two reasons for this proposal. The new Sydney classification of gastritis recognizes the importance of the dynamics of gastritis that exist between the antrum and body (41). By taking biopsies from both sites the diagnosis of histological gastritis will improve. Second, there is some evidence that after treatment colonization of *H pylori* may move to the body while at the same time it is difficult to find in the antrum. This has been found, for example, following treatment with the proton pump inhibitor omeprazole (42). There is a poor correlation between the endoscopic appearance of the gastric mucosa and histological presence of gastritis (18,43). Therefore, even if the gastric mucosa looks endoscopically normal it is necessary to obtain gastric biopsies to determine whether *H pylori* is present.

CLINICAL RELEVANCE OF *H PYLORI*

We recently performed a systematic review of evidence for a causal relationship between *H pylori* infection and gastritis, duodenal ulcer, gastric cancer and nonulcer dyspepsia (44) and an evaluation by meta-analysis of treatment indications for *H pylori* infection (45). We refer the interested reader to

these publications. In this review we will briefly summarize the evidence for a causal relationship between *H pylori* infection and gastritis, duodenal ulcer, gastric cancers and nonulcer dyspepsia.

***H pylori* as a cause of gastritis:** Evidence for a causal link between the presence of the organism and gastritis is fivefold: presence of the organism is invariably associated with histological evidence of gastric inflammation (19, 46-48); eradication of *H pylori* leads to healing of gastritis (49); self inoculation experiments in human volunteers, who were initially *H pylori* negative, led to the development of gastritis in the antrum (50,51); outbreaks of epidemic hypochlorhydria are associated with histological gastritis for which *H pylori* was found to be the best explanation (52); and prevalence of the organism is low in other forms of gastritis such as eosinophilic gastritis, Crohn's disease and bile reflux (18,53-55). Taken together, these findings fulfil each of Koch's postulates and thereby establish *H pylori* as the cause of chronic active gastritis in humans.

***H pylori* and duodenal ulcer:** *H pylori* is now considered to be an important causal factor in the development of peptic ulcers not related to the concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) (56). There are five levels of evidence. First, more than 90% of adult patients with duodenal ulcers are *H pylori* positive (57). Second, eradication of *H pylori* results in a lower relapse rate of peptic ulceration (58, 59). With the current therapeutic arsenal of H₂ receptor antagonists, sucralfate and omeprazole it is easy to heal most ulcers and control them with maintenance treatment. However, discontinuation of maintenance therapy leads to an ulcer relapse rate of up to 85% at one year of follow-up (60). Bismuth compounds have a convincingly better track record for lower relapse rates of ulcers after a course of treatment (61,62). Possible explanations for this observation are either the anti-helicobacter effect of bismuth compounds or the better quality of healing of the inflamed duodenal and antral mucosa or both (63). Third, *H pylori* relapses before the ul-

cer recurs (64). Fourth, heavy colonization with *H pylori* organisms may be associated with more frequent ulcer relapse (65). Finally, the addition of anti-helicobacter treatment to an H₂ blocker accelerates the rate of healing of duodenal ulcers (66). It is important to remember that *H pylori* infection by itself is not a sufficient cause for development of duodenal ulcers, because gastric acid is needed as well (67).

Association with gastric cancer: The role of *H pylori* acting as a cofactor for the development of stomach cancers is becoming increasingly clear (68-71). The attributable risk of *H pylori* infection to gastric cancer is estimated to be as high as 60% (68,70). It is possible that the risk of gastric cancer is related to the duration of the presence of chronic inflammation in the stomach. A trend towards acquisition of the organism at an older age, as is the case in developed countries, could result in a decrease in the frequency of gastric carcinomas. In Canada the incidence and mortality rates for gastric cancer have declined steadily over the past decades (72).

Association with nonulcer dyspepsia: To date there is no convincing evidence that *H pylori* plays a role in the subgroup of nonulcer dyspepsia patients that are *H pylori* positive. The prevalence of *H pylori* is generally not higher in patients with nonulcer dyspepsia compared with asymptomatic controls (73,74). In addition, there is no difference in symptom severity in *H pylori* positive and negative patients suffering from nonulcer dyspepsia (20). Finally, currently there is no evidence that eradication of *H pylori* leads to an improvement in symptom severity that is superior to placebo (45).

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