Helicobacter pylori

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Gastrointestinal diseases

Ulcer treatment has been revolutionized by recently discovered knowledge about *Helicobacter pylori*, a bacterium commonly found in the human gastrointestinal tract. These bacteria were originally thought to be a species of *Campylobacter*, but a later, more thorough examination revealed that they were different enough to be assigned to a new genus. Current evidence indicates that *H. pylori* is associated with Type B gastritis (a persistent inflammation of the stomach involving the loss of normal gastric glands), ulcers, and gastric cancer. In most cases, eradication of these bacteria leads to a long-term improvement in symptoms of gastritis and ulcers. As yet there is very little information on actual modes of transmission of this organism, but its presence in the stomach suggests that *H. pylori* may be food- or waterborne (from fecal contamination). It may also be expelled during vomiting and then, under unhygienic conditions, be acquired by a new host. This update on *Helicobacter pylori* will summarize and discuss recent discoveries relevant to the pathogenicity and acquisition of this bacterium.

Although much research has been devoted to determining how *Helicobacter* infections are acquired, the simple answer is that, with the exception of a few patients who have been infected during gastric endoscopy, we don't know how this organism is introduced into the stomach. However, once an infection has been established, it apparently persists indefinitely. Prevalence of infection in different populations today varies greatly, with reports of 50–90% of people in developing countries of Asia, Africa, and South America carrying *H. pylori* whereas a lower prevalence exists in industrialized countries. However, within all countries, those in lower socioeconomic groups (who typically have a less nutritious diet and live in less sanitary conditions) and persons who live in institutions are more likely to be infected than their better-off compatriots (*1*). It appears that most infections are acquired during childhood. Data from a cohort of Ethiopian children demonstrated that by age 4, 60% of them already had been exposed to these bacteria, as demonstrated by the presence of antibodies to *H. pylori*. By 12 years of age, nearly 100% had seroconverted. Among Swedish children, the sharpest rise in prevalence was between the ages of 9 and 10, with 20% of children infected by age 10 (*2*). Adults in developed countries continue to acquire *H. pylori* but at a very low rate: 0.44% per year measured during a 15-year follow-up study in Finland and 0.3–1.0% yearly increases in incidence measured in populations in the Netherlands, Canada, Australia, and the USA (*3*,*4*).

This socioeconomic and age-related pattern of acquisition suggests that poor hygiene is involved in transmission. Helicobacters may leave the stomach through the esophagus and mouth by gastro-esophageal reflux and by vomiting or through the intestines and be deposited in fecal material. Attempts to culture *H. pylori* from feces of infected people have had little success, although some immunoassays and PCR (polymerase chain reaction) assays reveal the presence of *Helicobacter*-specific compounds in feces. It is not known whether these assays are detecting remnants of dead cells or whether helicobacters are present as resistant, non-culturable cells. Such non-culturable, coccoid forms have been observed to develop in in vitro cultures of *H. pylori*. Examination of 48 drinking water samples from Peru using a PCR assay for the *H. pylori* adhesin gene indicated that 11 were contaminated with this organism, possibly as a result of fecal contamination (*5*). When cultured in the laboratory, *H. pylori* grows slowly and does not compete well with other bacteria. This makes it difficult to isolate it from complex environmental samples. More research is needed to optimize conditions for the isolation and cultivation of this bacterium.

Helicobacter has been cultured from a small percentage of saliva and dental plaque samples examined. However, it is likely that these cells are transients and have not permanently colonized the mouth. Their presence does indicate that the bacteria could be dispersed by spitting, coughing, or vomiting. Since *H. pylori* probably doesn't survive long outside the human body, the presence of a suitable, nearby host is critical. This may explain the higher rate of infection in young children who are often putting fingers and other objects into the mouth (*6*). In fact, Axon (*7*) suggests that since *H. pylori* doesn't cause diarrhea, it is probably not spread by the fecal–oral route. Rather he proposes that *H. pylori* facilitates its transmission to a new host by inducing an upset stomach and vomiting in children, resulting in the spread of infection in crowded conditions where sanitation is inadequate.

To date, no significant non-human reservoirs of infection have been identified. Some Old World primates harbor this bacterium, and recent experiments have demonstrated that *H. pylori* can colonize the stomachs of cats and gnotobiotic pigs. However, neither animal normally contains *H. pylori* and it is unlikely that they are a source of human infections (*8*).

Present evidence indicates that *H. pylori* infections arise primarily by person-to-person transfer among children and there is some suggestive evidence that contaminated water, and therefore foods washed with contaminated water, can also be a vehicle for infection. Further research is needed to define modes of transmission so that effective preventive measures can be instituted.

The natural habitat of *H. pylori* is the gastric mucosa, the interior surface of the human stomach beneath a thick mucus layer. Mucus partially protects the bacteria from stomach acid. In addition, the bacteria secrete an enzyme, urease, which breaks down urea to produce ammonia, which neutralizes stomach acid. In animal models, urease is essential for colonization. Because *H. pylori* is microaerophilic, it grows well under conditions of reduced oxygen tension found in the stomach. The presence of flagella and a spiral shape makes these bacteria highly motile, while components of the bacterial cell wall, which are specific for gastric glycerolipids, enable the bacteria to adhere tightly to the stomach mucosa. Stomach tissue colonized by helicobacters is nearly always inflamed, and this inflammation may progress to more serious gastric diseases.

Within the last decade, since the discovery of *H. pylori*, an exciting revolution has occurred in ulcer treatment. Prior to this, the only identifiable external cause of duodenal ulcer disease was the use of aspirin and other non-steroidal anti-inflammatory drugs. However, epidemiological studies have demonstrated that *H. pylori* is present in an average of 94% of about 1700 duodenal ulcer patients (24 different groups of subjects) and in 84% of 1400 gastric ulcer patients (25 groups). It is now apparent that idiopathic ulcer disease is virtually non-existent: nearly all ulcers are caused by *H. pylori* and most of the remainder are the result of the use of anti-inflammatory drugs (*9*). Therefore, current ulcer treatment is directed at eradicating the bacteria using a series of drugs rather than at reducing stomach acidity.

Elimination of *H. pylori* not only abolishes ulcer symptoms in nearly all patients, but also has been found to decrease basal and peak acid outputs in the stomach (*10*). Observations on ulcer patients, before and after treatment for *H. pylori*, revealed that elimination of this bacterium restored normal physiological processes which control stomach acid secretions (*11*). Following traditional ulcer treatment with medication to control stomach acidity, ulcers typically recur in 50–75% of patients in the following year. But following eradication of *H. pylori*, ulcer recurrence is less than 5%.

Why don't all *H. pylori*–infected individuals have ulcers? A variety of external factors, such as genetic background and cigarette smoking, are known to affect ulcerogenesis, but the production of cytotoxins by *H. pylori* may also be a significant factor. When cultured in vitro, approximately 50–60% of *H. pylori* isolates produce a vacuolating toxin (a 94-kDa polypeptide) that has been shown to erode gastric epithelium in experimental animals. In addition, many pathogenic strains also produce a highly immunogenic cytotoxin-associated protein. Bacterial strains bearing CagA (cytotoxin-associated gene) have been found in 84% and 93.4% of peptic ulcer disease patients in two studies (*12,13*). Only 29% of asymptomatic, helicobacter-positive persons contain CagA-positive strains. Therefore, strains producing this toxin are apparently more pathogenic.

It is difficult to assess the importance of infection with *H. pylori* for the development of gastric cancer because the bacterial infection may be lost as the cancer develops. However, results from 10 retrospective studies demonstrated that 52–89% of cancer patients harbored these bacteria. Prospective studies, in which serum samples from cancer-free persons were collected and stored, demonstrated a higher prevalence of antibodies to *H. pylori* in those who eventually developed stomach cancer. After 14 years' follow-up, persons with *H. pylori* infections were estimated to be about 8.7 times more likely to develop stomach cancer than those who were uninfected (*14*). CagA-positive strains also predominate in patients with atrophic gastritis and with gastric cancer and have been associated with increased risk for these diseases (*15*). The chronic inflammation induced by *H. pylori*, which persists for years and even decades, may predispose the stomach to neoplastic changes later in life.
An association between coronary heart disease and *H. pylori* infection has been observed in some studies. Results of a prospective study of a cohort of British men enrolled in 1978–1980 demonstrated a high rate of *H. pylori* infection in 135 cases of myocardial infarction and in 137 cases of stroke that occurred prior to 1991. When potential confounding factors were controlled, the association between the bacterial infection and infarction was still significant while the association with stroke was not (*16*). In another study of 47 men who had suffered ischemia or infarction, 36 had antibodies to *H. pylori* (*17*). Correspondence related to this research report included brief descriptions of other studies demonstrating an association between *H. pylori* and hypertension and myocardial infarction. However, some researchers pointed out that other risk factors for cardiovascular disease may not have been adequately controlled for and that, even if they were, *H. pylori* may not be causally related to cardiovascular disease (*18*).

Urticaria

Chronic urticaria (skin rash) that is not drug-related and cannot be identified as an allergic reaction remains a puzzle, and therefore dermatologists are eager to investigate any likely causes. Of 25 German patients with chronic urticaria, 17 were found to harbor *H. pylori*. Treatment with drugs eradicated the bacteria in 14 people, and all exhibited either remission (>75% improvement) or partial remission (50–75% improvement) of urticaria. In contrast, symptoms did not subside in the 3 patients who still had *H. pylori* infections nor in the 8 uninfected patients (*19*). Other research has indicated that *H. pylori* may be involved in dermatologic diseases, but so far the evidence is inadequate to prove that this bacterium is a causative factor.

Summary

Helicobacter pylori is certainly an etiological factor in Type B gastritis and duodenal and gastric ulcer and may also be an important factor in the development of gastric cancer. *Helicobacter pylori* may also have pathogenic effects on other organs and systems besides the gastrointestinal tract but, at present, the evidence for these effects is less compelling. The mode of acquisition of *H. pylori* remains a mystery but it is associated with lower socioeconomic status and poor hygienic conditions. Therefore, we should keep in mind the possibility that these bacteria might be transmitted via contaminated water and food.

Another source of background information on *H. pylori* and discussion of recent research developments is the Helicobacter Foundation Home Page (http://www.helico.com/).

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Two recently published articles present more information on the survival of *H. pylori* in food and on possible routes of transmission. Böhmler et al. examined 177 samples of udder secretions from cows with mastitis, 199 samples of milk from healthy cows, and 100 chicken stomachs and found that none contained *H. pylori.* When milk was inoculated with this bacterium, viable cells were found after 6 days when milk was stored in a refrigerator, but after only 3–4 days if it was stored at room temperature. Survival time was much shorter in acidic milk products such as yogurt and kefir. *H. pylori* cells also survived for up to several weeks in drip water from a thawed chicken which had been frozen at –20°C. These results indicate that fresh milk and chicken are not likely to contain *H. pylori* but that if these foods were contaminated because of inadequate hygiene, the bacteria may survive long enough to cause infection.

Li et al. described the use of a newly developed PCR assay to detect *H. pylori* in gastric biopsy specimens, saliva, and feces. Of 88 biopsy specimens, *H. pylori* was detected in 71. *H. pylori* DNA was detected in saliva from 68 of those 71 cases tested. However, only 15 of 61 of the positive patients tested had detectable *H. pylori* DNA in fecal specimens.

In other research on virulence factors in *H. pylori*, Censini et al. reported on their analyses of the structure and function of the *cagA* gene which is present only in type I strains which are associated with severe gastroduodenal disease. The *cagA* region of the chromosome appears to code for several membrane-associated proteins and also contains a gene sequence similar to the toxin-secretion gene of *Bordetella pertussis* and to a gene controlling plasmid transfer in *Agrobacterium tumefaciens*. It appears that the *cag* region codes for a secretion system for the export of some virulence

factors.

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