FRI FOOD SAFETY REVIEWS

Helicobacter spp. — Food- or Waterborne Pathogens?

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INTRODUCTION

Helicobacter spp. are Gram-negative, curved or spiral-shaped bacteria that live in the stomach, intestine, and liver of mammals, birds, and reptiles. Helicobacters are fastidious, difficult to cultivate, and are notorious for entering a viable but non-culturable state when exposed to adverse environmental conditions (*9*). These characteristics make it difficult to determine the species of different isolates. Numerous species have been described, but the taxonomy of this genus is still in flux because many isolates have not been completely characterized (*24*).

Most *Helicobacter* isolates from humans are classified as *H. pylori*, but this species is rarely detected in other animals. *H. pylori* has been associated with humans for at least 50,000 years and during that time has evolved to adapt to conditions in the human gut as humans have also adapted to the presence of these bacteria. *H. pylori* was first described in 1984 from the stomach of patients with gastritis and peptic ulcers (*35*). Approximately 70–90% of persons in developing countries and 25–50% of those in developed countries are colonized by *H. pylori*. Some strains are more virulent than others and are more often associated with more severe gastric diseases, including ulcers and cancer. Most people colonized with *H. pylori*, perhaps as many as 90%, experience only a mild inflammatory response and are asymptomatic.

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In fact, it has been suggested that colonization with *H. pylori* is the "normal" condition for humans and that the recent "loss" of *H. pylori* in people in more developed societies (living in more hygienic conditions) may be one factor causing increases in some "modern" diseases (*6*).

Some *Helicobacter* species usually associated with animals have also been detected in humans. These are sometimes referred to as "*H. heilmannii*," but this group probably includes several distinct species. Estimates of the prevalence of human infection with non-*H. pylori* helicobacters (NHPH) range from 0.2–6.0% (*7;57*). *H. suis* is the most common NHPH isolated from humans, accounting for up to 31% of human NHPH infections (*65*). Genetic analyses of some NHPH reveal that they do not produce some of the major virulence factors of *H. pylori* but they do have wide metabolic flexibility, react to a range of environmental signals, and produce other enzymes that may act as virulence factors (*52*).

Helicobacters have been detected in 142 vertebrate species, including livestock, companion animals, horses, ferrets, geese, tortoises, possums, whales, and dolphins. Several reviews discuss important veterinary *Helicobacter* spp. (*24;26;57*). Strains associated with livestock and companion animals include *H. suis* (pigs, monkeys), *H. felis* (cats, dogs, rabbit), *H. bizzozeronii* (dogs, cats), *H. pullorum* (chickens, turkeys), and *H. bovis* (cattle). Prevalence of *H. suis* in pigs is usually reported as 60% or more and is sometimes associated with gastritis and stomach ulcers. *Helicobacter* spp. have been detected in 67–86% of healthy dogs and in 41–100% of healthy cats. Higher prevalences have been reported in animals with chronic vomiting (*7*). As in humans, many animals colonized with *Helicobacter* spp. are asymptomatic. However, these bacteria can induce a chronic inflammatory response that results in lesions in the stomach, intestine, or liver.

VIRULENCE FACTORS

Two important virulence factors in *H. pylori* are the vacuolating cytotoxin (VacA) and the CagA protein encoded by a cytotoxin-associated gene pathogenicity island (*cag*PAI). VacA interacts with receptors on the surfaces of cells lining the gastrointestinal tract, modifying some cell functions and causing vacuolation and apoptosis. CagA protein is injected into cells by a type IV secretion system also encoded by *cag*PAI. Once internalized, CagA is phosphorylated by host cell kinases and then acts as a signaling molecule disrupting cellular activities. These toxins not only adversely impact intracellular metabolism but can also attack tight junctions between cells, causing tissue damage and allowing *H. pylori* cells to penetrate the intestinal epithelial layer (*59*).

Numerous other proteins associated with pathogenicity have been identified, including adhesins that facilitate binding to intestinal epithelial cells and enzymes. For example, in order to survive stomach acidity, helicobacters synthesize urease enzymes to degrade urea. The ammonia produced by these reactions neutralizes hydrochloric acid around the cells, thereby providing a safe microniche for bacterial growth. Some mucoid strains of *H. pylori* have been isolated from gastric biopsies. The exopolysaccharide produced by these strains may protect cells from acid, antibiotics, and high oxygen levels (*55*).

ASSOCIATED DISEASES

Infection with *H. pylori* irritates the stomach lining, causing gastritis. Some individuals may mount an effective defense clearing the infection, although this is considered uncommon. Most infections progress to chronic active gastritis. However, in 80–90% of people, these inflammatory reactions are mild and there are no obvious symptoms of infection. In other people, depending on the extent and location of the gastritis, either duodenal ulcers or gastric ulcers and gastric cancer may develop. It has been estimated that about 10% of all infected persons develop peptic ulcers, another 1–3% develop gastric cancer, and <0.1% develop another type of gastric tumor, mucosa-associated lymphoid tissue (MALT) lymphoma (*66*). There are reports that infection with *H. pylori* is associated with other human diseases, but in many cases evidence is not compelling.

Several factors, such as smoking, diet, and use of non-steroidal anti-inflammatory drugs, influence the development of gastrointestinal illnesses. Genetic characteristics of infecting strains of *Helicobacter* and of the human host also determine the nature and severity of illness. Certain genotypes of *H. pylori* were found to be more often associated with esophagitis or with peptic ulcer disease in 286 symptomatic, *H. pylori*-positive Alaskan adults (*37*). A study of low income African-Americans found that those with the greatest percentage of genetic markers indicating African ancestry had a higher prevalence of antibodies to *H. pylori* and to CagA. Some genotypic characteristic or lifestyle variations associated with African ancestry may explain the higher prevalence of virulent *H. pylori* in this population (*14*).

Gastrointestinal Disease

Ulcers. *H. pylori* infection is the most prominent risk factor associated with gastroduodenal ulcers. Infections are reported in 60% to 80% of those with gastric ulcers and in 95% of those with duodenal ulcers (*2*). When *H. pylori* gastritis occurs primarily in the antrum area of the stomach, acid secretion is increased and this is associated with ulcer formation (*5*).

Cancer. In 1994, an IARC monograph reviewed 4 cohort and 9 case–control studies and concluded that *H. pylori* was a cause of gastric cancer in humans. A more recent analysis of a substantial number of prospective cohort and nested case–control studies revealed a significant association between *H. pylori* infection and non-cardia gastric cancer (*28*). Studies examining cardia gastric cancer have not confirmed *H. pylori* as a significant risk factor. (The cardia region of the stomach is at the top, near the attachment to the esophagus.) A greater cancer risk is associated with CagA-positive *H. pylori* strains as compared to CagA-negative strains. The exact mechanism by which *H. pylori* exerts carcinogenic effects is not understood but infection with this bacterium can cause DNA damage as well as affecting the immune system and causing chronic inflammation. These effects may initiate or promote development of cancer cells (*62*).

MALT lymphoma is also caused by *H. pylori*. Strong evidence for this comes from studies in which eradication of *H. pylori* results in high rates (62–100%) of complete regression of the tumors. IARC has concluded that *H. pylori* is carcinogenic to humans, causing non-cardia gastric carcinoma and low-grade B-cell MALT gastric lymphoma (*28*).

Significant geographic differences in gastric cancer incidence have been reported, with high rates occurring in Japan and Korea. Countries in south Asia and sub-Saharan Africa have relatively low rates of gastric cancer, even though the prevalence of *H. pylori* infection in those regions is high. *H. pylori* strains circulating in high cancer incidence areas contain more virulent forms of the CagA and VacA virulence factors (*67*). Atrophic gastritis, usually caused by *H. pylori*, is an important risk factor for gastric cancer that can be detected by depressed serum levels of pepsinogen I (*1*). It has been suggested that all older Japanese (>50 years) be screened for antibodies to *H. pylori* and serum pepsinogen levels to identify persons who should be treated to eradicate *H. pylori*. This strategy is predicted to significantly reduce the burden of gastric cancer within several years (*4*).

Within the U.S., incidence of gastric cancer in African-Americans is twice that of white Americans. It is not clear whether lifestyle variations or genetic susceptibility cause this difference but some evidence indicates that both factors may be important (*14*). Several recent reviews discuss the roles of *H. pylori* virulence factors, host physiology, dietary factors, and smoking in modulating gastric cancer risk (*2;11;30;66*).

Other gastrointestinal effects. Ten randomized controlled trials investigating the association between *H. pylori* infection and gastroesophageal reflux disease (GERD) were analyzed in a recent meta-analysis (*47*). Although there was no statistically significant relationship between *H. pylori* status and symptomatic GERD or endoscopic evidence of reflux esophagitis, there was a significantly lower incidence of GERD symptoms after *H. pylori* was eradicated from patients.

Inflammatory bowel diseases (IBD), Crohn's disease, and ulcerative colitis (UC) are characterized by chronic inflammation, suggesting the possible involvement of a chronic bacterial infection. Some NHPH are known to initiate IBD in laboratory rodents. Although there is some molecular evidence of NHPH in human cases of UC, there is no firm evidence of their involvement in human disease. In fact, some studies indicate that *H. pylori* has a protective effect against IBD in humans (*25;61*).

Eradication of *H. pylori* in symptomatic individuals is sometimes recommended to prevent ulcers and gastric cancer. However eradication may have unintended adverse consequences. Ghrelin is a hormone produced in the gastric mucosa that partially regulates appetite and energy expenditure. Results from some studies indicate that *H. pylori* colonization of the stomach suppresses ghrelin production and that eradication of these bacteria elevates ghrelin levels and increases appetite, potentially leading to overeating (*15;29*). In some other experiments, ghrelin levels following *H. pylori* eradication did not change significantly (*40*).

Neurological Disease

Some epidemiological studies have demonstrated that *H. pylori* infections are more common in people with Parkinson's disease (PD) than in the general population, and it has been suggested that the presence of *H. pylori* interferes with the absorption of levodopa, which is used to treat PD. A recent systematic review summarized available data on the prevalence of *H. pylori* infection in PD patients and whether antibiotic treatment to eradicate *H. pylori* infections improved symptoms in patients. Four surveys reported that PD patients were not more likely to harbor *H. pylori* than the general population. A small study of 34 people found that eradication of *H. pylori* improved levodopa absorption and motor function. A larger study with 100 PD patients is underway (*45*).

In recent experiments, older mice who were infected with *H. pylori* or were fed *H. pylori* extracts were found to decline in locomotor activity and have reduced dopamine levels in the brain—symptoms similar to those observed in humans with Parkinson's disease. *H. pylori* produces a cholesterol-sugar derivative that resembles one of the toxins in cycad seeds that has been associated with amyotrophic lateral sclerosis/Parkinson's disease in residents of Guam. The compound produced by *H. pylori* may be transported to the brain, causing some of the neuronal damage observed in Parkinson's patients (*60*).

Other Diseases

Cardiovascular Disease. It has been proposed that *H. pylori* contributes to development of cardiovascular disease (CVD) by inducing a chronic inflammatory response and increasing insulin resistance leading to obesity (*31;41*). However, some studies demonstrated no significant correlation between *H. pylori* infection and CVD and concluded that *H. pylori* plays at most a minor role in development of CVD (*10;46;53*).

Autoimmune Diseases. Since *H. pylori* has evolved strategies to evade the host immune response and has been implicated in some diseases involving immune dysregulation, some researchers have suggested that infection with this bacterium may precipitate some autoimmune diseases. A recent review concluded that available data do not support this theory because of the conflicting and inconclusive results of currently published studies (*27*).

Respiratory Diseases. Since both *H. pylori* infections and some respiratory diseases are characterized by the release of proinflammatory cytokines and B and T cell responses, it has been suggested that *H. pylori* may be responsible for development of some respiratory disorders. A recent systematic review of the literature concluded that current data do not support a causal relationship between *H. pylori* infection and respiratory disorders (*33*).

EPIDEMIOLOGY

Prevalence

Over half the world's population is colonized by *H. pylori*. In developing countries, prevalence is approximately 70–90% and most people are infected as infants or young children and remain infected for life. In more developed countries, about 25–50% of people harbor these bacteria and prevalence appears to increase with age. Within countries, persons at lower socioeconomic levels generally have higher rates of infection. This indicates that environmental factors, including crowded living conditions and lack of access to clean water and sufficient food, may facilitate spread of these bacteria (*28*).

Data from NHANES surveys in 1999–2000 and 1988–1991 on *H. pylori* prevalence in different racial/ethnic groups in the U.S. revealed significantly higher age-standardized rates in Mexican-Americans (64%) and non-Hispanic Blacks (52%) than in non-Hispanic Whites (21.2%). Seroprevalence increased with age in all subgroups in both surveys, but there was a smaller increase for non-Hispanic Whites in the 1999–2000 survey compared to the earlier survey (*22*).

Humans are the only known reservoir of *H. pylori*, and most of these bacteria reside in the stomach. This bacterium, like many other human pathogens, can enter a viable but nonculturable (VBNC) state when exposed to environmental stresses. VBNC cells remain metabolically active but cannot be grown on commonly used culture media. One recent study found that *H. pylori* cells deposited on spinach leaves became VBNC within 24 hours. However, the cells remained metabolically active, producing mRNA and *vac*A for up to 6 days. Exposure to white light appeared to be a major factor in inducing the VBNC state (*9*). In another study, VBNC *H. pylori* cells persisted in biofilms exposed to low concentrations of chlorine (0.2–2.0 mg/L) for up to 26 days (*18*).

Transmission

H. pylori is believed to be transmitted primarily by fecal–oral or oral–oral routes, with water and food as possible vehicles of infection. However, exact modes of transmission are not easily determined because *H. pylori* is difficult to culture from environmental samples. There is some evidence for iatrogenic transmission through inadequately sterilized endoscopes. *H. pylori* has been detected in vomitus, indicating the potential for gastro–oral transmission (*58*).

Oral–oral transmission. Several studies have reported the presence of *H. pylori* genes in the oral cavity, usually in dental plaque. Presence of these bacteria in the oral cavity is significantly associated with their presence in the stomach and with symptomatic gastric disease (*32;38;39;56*). *H. pylori* genes have also been detected within yeasts (*Candida* spp.) from the oral cavity and upper gastrointestinal tract. Fluorescence microscopy revealed bacteria in yeast vacuoles, where they are protected from environmental stresses (*49;50*).

Water as a vector. Numerous epidemiological studies have reported positive associations between untreated or fecally contaminated drinking water and incidence of *H. pylori* infection. However, viable cells have not been cultured from water samples. When suspended in water, *H. pylori* cells change morphologically from mostly spiral shapes to mostly coccoid or U-shapes and enter a viable but nonculturable state. Some experiments with animals, but not all, indicate that these coccoid forms are still infective. It appears that the morphological change is a response to stress, and coccoid cells die after some time, depending on environmental conditions (*8*).

Genes specific to *H. pylori* have been detected by molecular methods in drinking water and surface waters, including sea water, and experiments indicate that *H. pylori* can survive up to several weeks in water, depending on temperature, salt content, and nutrient

levels (*19;51;63*). Biofilms formed in drinking water protect *H. pylori* cells, allowing them to persist without a noticeable decrease in numbers for more than 25 days even in the presence of chlorine (*17;18*).

Food as a vector. Food is a plausible source of *H. pylori* infections. Possible routes of foodborne transmission were discussed in a recent review (*64*). The fastidious growth requirements of these bacteria along with their ability to enter a viable but nonculturable state when exposed to stress have made it very difficult to isolate them from different foods. Therefore, molecular methods relying on detection of *H. pylori*-specific DNA or RNA sequences are often used as assays for the presence of *H. pylori*. However, these may not distinguish between living and dead cells. *H. pylori* genes have been reported to be present within cells of brewers' and bakers' yeast (*Saccharomyces cerevisiae*). Yeast may protect the bacteria and aid in their dispersal (*54*).

A multiplex PCR assay detected *H. pylori* on 4 of 12 raw chickens from a grocery store and on 8 of 18 samples of ready-to-eat raw tuna from a restaurant (*36*). Other PCR assays detected *H. pylori* in raw bovine milk by detection of urease A genes (*16*) and in raw sheep, goat, and cow milk by detection of phosphoglucosamine mutase gene (*44*). Fluorescence in situ hybridization detected *H. pylori* ribosomal RNA in 4 of 20 raw bulk milk samples (*3*). Of 92 Holstein cows tested in Iran, 25 were seropositive for an *H. pylori* antibody. The urease C gene was detected in milk samples from 4 of the seropositive cows and in fecal samples from 10 cows (*48*).

In other experiments, *H. pylori* cells were inoculated on different foods and survival was monitored during subsequent storage. *H. pylori* was reported to survive:

- at 4°C, in pasteurized milk and tofu for 5 days and in lettuce and chicken for 2 days; no cells survived in yogurt (*42*)
- on raw carrots for up to 120 hours at 8°C (*20*)
- at 4°C, in pasteurized milk for 9 days and in UHT milk for 12 days (*43*)
- in a Turkish sausage mixture (sucuk) during fermentation and drying at 22°C for 7 days (*23*)
- on spinach at room temperature for up to 6 days (*9*)

Some NHPH (non-*H. pylori* helicobacters) have been detected in foods, indicating that food may occasionally be a vehicle for human infection with other *Helicobacter* species. Viable *H. suis* were reportedly detected in raw pork (*13*). *H. pullorum* has been detected in cecal contents of turkeys (*68*) and chickens (*34*) and in raw chicken (*12;21*).

SUMMARY

Helicobacter pylori resides primarily in the human stomach and has been definitely identified as a cause of atrophic gastritis, ulcers, and gastric cancer. In most cases, *H. pylori* causes a mild, asymptomatic gastritis; more serious illness is associated with certain more virulent strains of *H. pylori* and with people with certain physiological or lifestyle characteristics. *H. pylori* may be involved in development of other diseases, perhaps because of the chronic inflammatory response it induces, but conflicting results have been reported and evidence that *H. pylori* causes other disorders is not considered compelling. Some other species of *Helicobacter* have been detected in humans and may contribute to some gastrointestinal illness.

H. pylori is believed to be transmitted primarily by fecal–oral or oral–oral routes, with water and food as possible vehicles of infection. However, exact modes of transmission are not easily determined because *H. pylori* is fastidious and difficult to culture from environmental samples. When exposed to environmental stress, these bacteria assume a coccoid shape and enter a viable but nonculturable state. *H. pylori* genes have been detected in surface waters and in drinking water, in milk, and in some other foods. When *H. pylori* cells were inoculated on vegetables, milk, and meat they were found to persist from a few days to a few weeks. Some non-*H. pylori* helicobacters have been detected in foods, indicating that some foods may occasionally be vehicles for human infection with other *Helicobacter* species.

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FRI Briefings

Helicobacter pylori

first published August 1996
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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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January 1997 Update to *Helicobacter pylori* Briefing

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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Last modified: 10 June 1998

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