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HELICOBACTER AND DISEASE: STILL MORE QUESTIONS THAN ANSWERS

Gabor Kandel, MD

Since the causative role of *Helicobacter pylori* in peptic ulcer and gastritis was established, a number of advances have been made. *Helicobacter* virulence factors have been identified, the changes it causes in gastric acid secretion has been elucidated, and the entire genome of *H. pylori* has been mapped. Multiple lines of evidence indicate a strong link between the bacterium and noncardia gastric cancer. The infection can be confidently diagnosed by noninvasive serologic tests and the urea breath test. Triple therapy is almost always curative, and the infection almost never recurs in Canadian adults, but eradicating the bacteria in the absence of peptic ulcer only rarely leads to resolution of dyspepsia. New studies suggest that treating *Helicobacter* may increase the risk of peptic esophagitis and adenocarcinoma of the esophagus and cardia.

Depuis qu'on a établi le lien de cause à effet entre *Helicobacter pylori* et l'ulcère gastro-duodénal et la gastrite, de nombreux progrès ont été réalisés. On a défini des facteurs de virulence d'*Helicobacter*, les changements qu'il provoque dans la sécrétion de l'acide gastrique ont été expliqués, et l'on a cartographié le génome complet de *H. pylori*. De multiples sources de données indiquent l'existence d'un lien solide entre la bactérie et le cancer de l'estomac qui ne touche pas le cardia. On peut diagnostiquer avec confiance l'infection au moyen d'épreuves sérologiques non effractives et de l'épreuve de l'urée respiratoire. La triple thérapie est presque toujours curative et l'infection ne revient presque jamais chez les adultes du Canada, mais l'éradication de la bactérie en l'absence d'ulcère gastroduodénal entraîne rarement la disparition de la dyspepsie. De nouvelles études indiquent que le traitement d'*Helicobacter* peut accroître le risque d'œsophagite peptique et de cancer de l'œsophage et du cardia.

Only 16 years ago, Marshall, a clinician, collaborating with Warren, a pathologist, made the seemingly simple observation that "curved bacilli" (now named *Helicobacter pylori*) are more common in the stomach of patients with "chronic active gastritis" than in control patients.[1] This observation led to a cure for peptic ulcers and increased understanding of gastric malignant disease. The discovery of *Helicobacter* provides a number of lessons worth emulating: the seminal link between bacterial infection and disease was made by clinically oriented physicians; simple laboratory and statistical techniques established the association; the initial connection made was between *Helicobacter* and a condition that is clinically insignificant (nonerosive gastritis), yet the discovery evolved to dramatically improve the diagnosis and treatment of a common disease with significant mortality and morbidity (peptic ulcer), and the time between the first reported isolation of *Helicobacter* and translation of the discovery to provide practical benefit for patients, was less than 1 decade. It is now understood that *Helicobacter* infects the stomach of about 90% of patients with duodenal ulcers, and that eradicating *Helicobacter* cures these ulcers with a recurrence rate of less than 10% compared with gastric-acid reducing treatments, which lead to an ulcer recurrence rate of over 70%.[2] *Helicobacter* is also associated with gastric cancer by an odds ratio of about 3, and is appreciated to be a major contributor to the cause of a

From the Division of Gastroenterology, University of Toronto, St. Michael's Hospital, Toronto, Ont.

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Correspondence to: *Dr. Gabor Kandel, Division of Gastroenterology, St. Michael's Hospital, Wellesley Central Site, 160 Wellesley St. W, Toronto ON M4Y 1Y3*

rare malignant lesion, mucosal associated lymphoid tissue (MALT) lymphoma.[3] Yet *Helicobacter* causes clinically significant disease in only a minority of people it infects.[2,4] The goal of this review of to discuss these findings, emphasizing their clinical implications.

THE BACTERIUM

H. pylori is a gram negative, urease-producing, spiral shaped, motile, microaerophilic bacterium rod, which is trophic to gastric epithelium. Attachment of the organism to the stomach is mediated by a glycoconjugate receptor on the epithelial cell surface, the Lewis b blood group antigen,[5] and a group of adhesins on the bacterium, one of which was recently purified.[6] Bacterial factors necessary for colonization include urease and flagella.[7] It is still unclear how bacteria can withstand the low pH of the human stomach. In this regard, it is intriguing to speculate that the urease of *Helicobacter* promotes colonization by neutralizing acid (by converting urea in the stomach to ammonium) to maintain a neutral pH in the local "microenvironment" of the gastric epithelial cell to which the *Helicobacter* is attached.[8] Similarly, the role of flagella may be to propel the organism from the acidic gastric lumen through the mucus layer to the less hostile pH neutral cell surface.[7] All *Helicobacter*s have both flagella and urease, so this cannot be used to explain differences in the ability of strains to cause disease.

Much of the microbiologic research on *Helicobacter* has concentrated on searching for virulence factors to explain why disease develops in only a minority of infected people (although all have gastritis histologically). At least 2 factors have been described, although neither totally explains why only selected people become ill. First, about 50% of strains induce vacuolization in cultured eukaryotic cells.[9] This phenomenon is due to the production of a 90 000 MW protein cytotoxin (vacA) produced by the *vacA* gene. Although all strains of *Helicobacter* have the *vacA* gene, only about 40% produce the vacA cytotoxin, and, in at least some studies, these strains are more commonly found in patients with peptic ulcer than patients with only gastritis.[9] Second, the 60% of *Helicobacter* strains producing the 120 000 to 140 000 CagA protein encoded by *CagA* gene have been associated with duodenal ulcer and gastric malignant disease. Genes linked to *CagA* on a gene segment termed the "*CagA* pathogenicity island" may also contribute to disease pathogenesis since these gene products seem to be involved in bacterial stimulation of host epithelial cell production of the cytokines that recruit neutrophils to the stomach lamina propria.[10]

VacA and CagA protein production are linked but map to distinctly separate genes.

The complete genome sequence of *H. pylori* was published in 1997.[11] Compared with other bacteria, most of which can thrive in multiple environments, the *Helicobacter* gene is small and has fewer of the regulatory "on-off" genes commonly used by microbes to adapt to habitat changes. This suggests that *H. pylori* has for centuries occupied only 1 niche, presumably the human stomach. Another intriguing finding was the presence of an unexpectedly larger number of genes responsible for iron scavenging pathways, pointing researchers to a unique bacterial target for pharmacologic therapy. Two-thirds of the 1 667 867 base pairs found in the circular *Helicobacter* genome are believed to have originated from other bacteria, so that *Helicobacter* may have used a form of adaptation different from the slow evolution of other organisms.

EPIDEMIOLOGY

The chief risk factor for infection by *Helicobacter* is socioeconomic status, presumably because crowding, poor sanitation and absence of a hot water supply facilitate transmission of the infection.[12,13] This explains why in the United States the infection is more common in black and Hispanic people than white people, and why the infection is more frequent in developing countries than in North America and Western Europe. There is also an increase in the prevalence of infection with age.[13] However, this observation is unlikely to be caused by an age-related predisposition to infection, because prospective studies of adults have indicated that infection is most commonly acquired in childhood, usually before the age of 5 years. Accordingly, the age-related pattern of infection is most likely due to a "cohort effect," whereby each successive generation has a lower likelihood of acquiring infection because of improved economic standards over time[13] This hypothesis is in keeping with a high prevalence of infection in adults reared during the Depression (all of whom are now are now 65 years of age or older) and a very high prevalence without an age-related association in poor countries which have not enjoyed improving economic standards.[13] On the other hand, the infection can be acquired at any age, since adults have been demonstrated to become infected in chronic care institutions and as soldiers in Operation Desert Storm.[14] A study in twins showed a genetic susceptibility.[15] This was initially related to blood type when in vitro studies indicated that the bacterium adheres only to the gastric epithelium of individuals with the Lewis b blood group antigen,[5] although a more recent prospective clinical study did not demonstrate such an association.[16]

Despite extensive work, the mode

of transmission is unclear beyond the intuitive understanding that the human stomach must acquire the organism through the mouth since the bacterium is noninvasive and therefore unlikely to reach the gastric epithelium by any other route. Most studies point to the oral–oral path as the most common route of infection since humans are the only proven reservoir, and since families are more likely to be infected when either 1 child or 1 parent is found to have the infection.[17] On the other hand, it has recently been suggested that cats harbour the bacterium,[18] pointing to fecal–oral transmission, and the isolation of *Helicobacter* from flies[19] indicates the possible role of vectors. Epidemiologic studies in Central America have indicated waterborne transmission. Gastric–oral spread has been described to occur by endoscopes and other stomach probes (such as pH catheters and pressure recorders).[20]

Acute infection

Two retrospective analyses[20,21] of iatrogenic miniepidemics of hypochlorhydria developing during research trials studying human gastric pH and 2 "volunteer" experiments[22,23] have shown that acute infection leads to neutrophilic gastritis, decreased gastric acid secretion and, in some people, transient nausea with vomiting and epigastric pain. Without treatment, *Helicobacter* persists in the stomach indefinitely, leading to permanent gastritis (as defined histologically) in virtually all infected individuals.

Diagnosis

A number of methods, invasive and noninvasive, are now available to reliably diagnose *Helicobacter* infection. The most commonly used test currently is a serologic one whereby serum immunoglobulin G antibodies to the bacterium are quantitated using an ELISA assay. A modification of this test can be done at the bedside using whole blood obtained by fingerprick. Antibody tests have a high sensitivity and specificity — more than 90% — but the false-positive rate increases with age. Moreover, antibody levels fall slowly after eradication of *Helicobacter*, so serologic testing cannot be used for follow-up after treatment. Another diagnostic technique — the urea breath test — overcomes these disadvantages while maintaining a high sensitivity and specificity, but the cost and time required for this technique are higher than the serologic test. The urea breath test is carried out by asking the patient to ingest urea labelled with a carbon isotope, and measuring the concentration of the carbon label in the breath. The labelled carbon concentration will be high only if urease is present in the stomach, and the only known gastric source of urease is *Helicobacter*. Either of 2 carbon labels can be used: carbon-14, a radioactive isotope, or carbon-13, a nonradioactive isotope. Antibiotics, proton pump inhibitors and sucralfate should be stopped for at least 14 days before the urease breath test is done, since these drugs cause false-negative readings. Histologic examination of the gastric mucosa is still considered the standard for diagnosis, but this of course depends on (invasive) endoscopic biopsy of the stomach. Ideally, 2 biopsy specimens are obtained from the gastric antrum with a large cup biopsy forceps and stained with Giemsa, Warthin–Starry or Genta stain. Hematoxylin and eosin staining is also reliable if a sufficient number of organisms are present in the stomach. Biopsy specimens can also be tested for *Helicobacter* using a rapid urease test available from various manufacturers, although this test has a false-negative rate of about 10%. Culture of *Helicobacter* is difficult, since specific transport and growth media are required with microaerobic conditions. Therefore, culture should be requested by clinicians only if antibiotic susceptibility is being sought. Saliva methods of diagnosis are not recommended since in most studies they have a lower accuracy than serologic tests.[24,25] Physicians often claim to be able to recognize *Helicobacter*-induced gastritis endoscopically, but systematic studies show that the only reliable endoscopic sign of *Helicobacter* is peptic ulceration of the duodenum or stomach. Endoscopic erythema of the stomach is neither sensitive nor specific for gastritis.[26]

Mechanism of mucosal inflammation

Helicobacter invariably causes a striking mucosal infiltrate of neutrophils, plasma cells and lymphocytes in the stomach wall (gastritis). Nevertheless, the bacterium does not seem to invade the mucosa. In fact, there is evidence that gastric mucus provides a protective niche since, despite the exuberant inflammatory response, *Helicobacter* colonization persists indefinitely without treatment.[27] Therefore, most investigators believe that *Helicobacter* causes mucosal inflammation by 1 or more of 3 mechanisms: release of host cytokines such as interleukin-8 after the bacteria directly touch adjacent gastric epithelial cells; bacterial secretion of chemotaxic substances such as urea, which attract inflammatory cells from afar; and *Helicobacter* stimulation of autoantibodies capable of reacting with host gastric epithelium.[28] This third, immunologic-based hypothesis, may seem far-fetched, but human antibodies have been isolated that recognized both *Helicobacter* lipopolysaccharide and the gastric epithelial cell membrane, and such antibodies induce gastritis when administered to mice. The epitope to which these antibodies are directed may be the Lewis b blood group antigen,

since this is expressed by both *Helicobacter* and epithelial cells.[29]

Peptic ulcer and gastric acid secretion

It took many years for the medical community to accept the causal role of *Helicobacter* in peptic ulcer disease. This was partly because it seemed incredible that an infection that could be diagnosed by simple histologic techniques had been missed for so many years, partly because only a minority of individuals with *Helicobacter* have ulceration of the upper gastrointestinal tract and partly because so much time and money had been invested in evaluating gastric acid as a cause of mucosal ulceration. Presently, however, the evidence in favour of the "*Helicobacter* hypothesis" is incontrovertible as follows:[2,30–32]

- In prevalence studies, ulcers are more common in patients with *Helicobacter* infection than in matched controls without such infection.
- In cohort studies, patients with *Helicobacter* infection more commonly suffer from peptic ulcers than those without such infection.
- In prospective studies, eradication of *Helicobacter* heals the ulcer and greatly decreases the chance of ulcer recurrences to less than 10%, whereas healing the ulcer crater by any other means is associated with an annual ulcer recurrence rate of greater than 70%.

Currently, most authorities believe that over 90% of peptic ulcers are due to either *Helicobacter* or nonsteroidal anti-inflammatory drugs.[2] Other causes of mucosal ulceration of the upper gastrointestinal tract, such as Zollinger–Ellison syndrome, ischemia, and viruses, are rare, except in select populations.[33] On the other hand, reports published within the last 3 years suggest that at least in the United States the incidence of *Helicobacter* in peptic ulcer may have been overemphasized.[34] Moreover, for reasons that are unclear, the prevalence of *Helicobacter* seems to be lower in peptic ulcer disease, declaring itself as bleeding, perforation or obstruction, than when the ulcer presents as dyspepsia alone.[35]

A major challenge in understanding the interaction between *Helicobacter* and the stomach is to explain why only about 15% of *Helicobacter*-infected patients have peptic ulcers. Variation in the virulence of the *Helicobacter* strain only partially explains this finding. Accordingly, most of the work in this regard has centred on the relationship between gastric acid production and *Helicobacter* infection. Generally, gastric acid output tends to be high in patients with peptic ulcer and low in those with gastric cancer, but these relationships are complex, and clearcut changes in acid production do not to correlate with clinical outcome.[36] Gastric acid is secreted by parietal cells in the body of the stomach. Gastrin, produced by G cells in the gastric antrum, stimulates these parietal cells directly, and indirectly by releasing histamine from the enterochromaffin-like cells in the body of the stomach adjacent to the parietal cells. D cells release somatostatin, which inhibits all of these cells. *Helicobacter* has complex effects on this system. For example, the bacteria have been described to release factors that can stimulate , and factors that can inhibit parietal cells directly. In addition, the gastric atrophy caused by *Helicobacter* infection leads to decreased acid production since the parietal cell population is diminished. Moreover, *Helicobacter* decreases expression of gastric somatostatin.[36]

In humans, the most consistent finding has been that *Helicobacter* infection increases plasma gastrin concentrations measured in the fasting state, after meals and after the stimulation of G cells with gastrin-releasing peptide.[37] This gastrin elevation is similar in *Helicobacter*-infected patients with and without peptic ulcer, but in those with ulcers, gastrin-induced acid secretion is significantly higher than in those without ulcers. Both gastrin levels and acid output gradually fall after *Helicobacter* is eradicated.[38]

Intuitively, it would seem that *Helicobacter* should contribute to nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulceration of the upper gastrointestinal tract. However, the evidence for this hypothesis is contradictory, and in the aggregate does *not* support an important relationship between *Helicobacter* and mucosal ulcers caused by NSAIDs. The largest study to date on this topic reported that eradication of *Helicobacter* in NSAID users actually impaired healing of gastric ulcers in a group at high risk for the development of NSAID-induced ulcers.[39] On the other hand, in a trial with a different design but also done prospectively, eradication of *Helicobacter before* starting NSAID use decreased the incidence of ulcers compared with a group in which the *Helicobacter* was not treated.[40] This area is still controversial, but certainly a clinician cannot rely on eradication of *Helicobacter* to prevent or treat NSAID-induced peptic ulceration.

Gastritis and gastric malignant disease

Nonerosive gastritis is defined as inflammation of the gastric mucosa demonstrated histologically. It cannot be reliably diagnosed clinically or radiologically since it causes neither symptoms nor gross changes in the gastric mucosa. However, it may be a precursor to gastric cancer. According to one formulation,[41] the first step in the development of gastric carcinoma is chronic gastritis, which then evolves into atrophy of the mucosal glands (gastric atrophy) followed by intesti-

nal metaplasia, dysplasia and ultimately cancer. The sequence may stop at any step; the progression is slow, characteristically requiring decades, and of course is not inexorable. Intestinal metaplasia, one outcome of chronic gastritis, has long been accepted as a premalignant condition. Since *Helicobacter* is at least 1 cause of gastritis, it is logical to hypothesize that this infection predisposes to cancer. Three prospective studies,[42–44] all of them case-control comparisons using stored blood samples from cancer patients and from cancer-free individuals, have demonstrated the validity of this hypothesis.[45] In these 3 studies, the matched odds ratio associating *Helicobacter* with noncardia gastric cancer ranged from 2.8 to 6.0. Cancers of the cardia were excluded, since they are currently believed to have a different pathogenesis from cancer in the rest of the stomach. When only the "intestinal" type of gastric cancer is studied (i.e., excluding the "diffuse" type of cancers), the association with *Helicobacter* is even more marked, although even "diffuse" cancers are more common if *Helicobacter* is present. The recent description of an animal model in which *Helicobacter* causes gastric cancer (the Mongolian gerbil)[46] and the crucial role of *Helicobacter* in the familial clustering of gastric cancer[47] compellingly strengthen the argument favouring a role for *Helicobacter* in gastric malignant disease. In fact, the evidence for this hypothesis is now so overwhelming that the International Agency for Research on Cancer (IARC), an arm of the World Health Organization, has classified *Helicobacter* as a class 1 or "definite" carcinogen.[48] On the other hand, when expressed in nonepidemiologic terms, the absolute difference in *Helicobacter* infection prevalence between patients with gastric cancer and control patients is not striking — about 82% to 61% — perhaps because in the older age groups in which cancer of the stomach develops, the baseline frequency of *Helicobacter* is high. Overall, these statistics emphasize that although *Helicobacter* probably predisposes to gastric cancer, multiple other factors are necessary for its development. Note that the absolute risk for the development of gastric cancer in the presence of *Helicobacter* infection approximates only about 1 to 2 in 100 to 1000, although the attributable risk (i.e., the proportion of cancers that would not have occurred had *Helicobacter* not existed) has been calculated to be between 35% and 90%.

Gastric MALT consists of the plasma cells and lymphocytes in the stomach mucosa, which act to control *Helicobacter* infection, analogous to lymphoid follicles in the rest of the body. Low-grade MALT lymphomas confined to the gastric mucosa , presumably representing monoclonal proliferation of a *Helicobacter*-reactive B cell, have been described to be amenable to complete remission by nothing more than eradication of *Helicobacter* with antibiotics.[49] This is of great theoretical interest since it provides evidence for a pathogen pathogenesis of malignant disease, but in fact MALT lymphoma is exceedingly rare, and most such tumours present at too advanced a stage to be treated solely by antibiotics.

OTHER DISEASES

After the discovery of *Helicobacter*, a large number of diseases were associated with this infection. For example, a correlation was described between coronary artery disease and *Helicobacter* gastritis. However, more in-depth studies have shown that this association is spurious, related, at least in part, to tobacco smoking being a risk factor for both coronary artery disease and peptic ulcer.[50] The most recent linking of *Helicobacter* to an unexpected disease was a strong association with otherwise unexplained iron deficiency anemia,[51] even in the absence of peptic ulcer, but this has yet to be well studied.

The connection between *Helicobacter* and nonulcer (functional) dyspepsia is more controversial, but the bulk of evidence is also against this association.[30] This is a complicated area to study because of the imprecisions involved in defining dyspepsia and because functional disease is so difficult to diagnose (e.g., some patients with this diagnosis end up having reflux without esophagitis). Of 4 large scale prospective studies on this subject,[52–55] only 1 trial concluded that *Helicobacter* played a significant role in the pathogenesis of nonulcer dyspepsia, and even in this study the difference in symptom relief between the group in which *Helicobacter* was eradicated and the control nontreated group was small (27% versus 12%).[52]

TREATMENT

All currently advised treatment regimens (Table I) consist of multiple drugs, all have been reported to have a successful eradication rate of over 85%, all have a high incidence of nuisance side effects which have to be tolerated (e.g., nausea, anorexia and a metallic taste in the mouth) and all should be discontinued if diarrhea, vomiting or a skin rash develop. Follow-up investigations are generally not advised in patients who faithfully follow the prescription, since eradication rates are so high. On the other hand, in patients who want to be sure that the *Helicobacter* has been successfully eradicated, or if the ulcer presented with a complication such as bleeding, a urea breath test can be done 1 to 3 months after the treatment has been completed. If the urea breath test is done earlier, it is impossible to distinguish suppression of *Helicobacter* (of no value to the patient) from complete eradication (the goal

of treatment). Serology is not useful for follow-up because the *Helicobacter* titre can remain elevated for years after successful eradication.[31,32]

A number of studies have shown that, at least in Western countries, the chance of reinfection is low, less than 2% per year, except perhaps in children.[2]

WHO TO TREAT?

There is universal agreement that *Helicobacter* should be pharmacologically eradicated in anyone with a peptic ulcer, especially if NSAIDs are not being taken. But is such treatment advisable in a patient with dyspepsia who has *Helicobacter* diagnosed by a noninvasive technique such as serologic testing? Most of these patients will have nonulcer dyspepsia, some will have a condition such as reflux, and in most populations only a minority will have a peptic ulcer. The traditional approach to medical care entails accurate diagnosis before treatment. However, in the specific example of *Helicobacter* and peptic ulcer, the ease of diagnosing and eradicating *Helicobacter* makes it tempting to simply treat this infection after it is diagnosed by a noninvasive test rather than recommending endoscopy or radiology to accurately determine if a peptic ulcer is present. At least some decision analyses have demonstrated the value of this "empiric approach" in selected populations, both in terms of saving money and minimizing patient discomfort, provided that patients comply with follow-up, and that investigations such as endoscopy are done within 4 to 8 weeks if *Helicobacter* eradication does not relieve symptoms.[32,56] It should also be remembered that eradicating *Helicobacter* has the added theoretical benefit of lowering the risk of a future gastric malignant disease. This "empiric treatment" management strategy is best applied to patients with a high risk of peptic ulcer and low risk of other gastric diseases (i.e., age less than 40 years, no symptoms other than dyspepsia, not taking NSAIDs and no risk factors for gastric cancer).

Arguing against the empiric "test and treat" approach are the risk of antibiotic side effects, including life-threatening pseudomembranous colitis, and the possibility that drug-resistant *Helicobacter* strains will be induced. In addition, recent clinical studies have suggested 2 long-term deleterious consequences of *Helicobacter* eradication. First, in some trials, eradication of *Helicobacter* predisposed to the development of peptic esophagitis.[57] Possible reasons for this observation include an "unmasking" of gastric hyperacidity after resolution of the *Helicobacter* infection that caused the gastric inflammation, weight gain in the treated group due to amelioration of dyspepsia after cure of the peptic ulcer, or use of antacid or gastric acid suppressants (which ameliorate esophagitis) to treat recurrent peptic ulcer in the untreated controls with persisting *Helicobacter* infection.[57] Second, there is epidemiologic evidence that at least some *Helicobacter* strains protect against cancer of the esophagus and gastric cardia, perhaps related to the bacteria's protective effect on peptic esophagitis.[58]

Although there is disagreement in the literature about who with *Helicobacter* should be treated, one consensus in this regard is that a diagnostic test for *Helicobacter* should be performed only if both the physician and the patient agree on eradication (or further investigation), since otherwise there is no logical reason to diagnose this infection. In addition, there is universal agreement that all patients with active and previous peptic ulcers (and with gastric MALT lymphoma) should be offered treatment. In other patients, the drawbacks and expected benefits of *Helicobacter* eradication should be considered before deciding upon a management strategy. However, most patients will opt for treatment when they are quoted the *Helicobacter*-associated likelihoods of 1 in 6 for the development of peptic ulcer and 1 in 100 for the development of gastric carcinoma. On the other hand, the need to treat nonulcer patients is likely to become clearer in the future, since in a field as dynamic as infectious diseases, the only thing one can be sure of is change.

Table I

Current Treatment Regimens for *Helicobacter pylori*

Possible treatment	Drug*
Treatment of choice — PAC	Proton pump inhibitor† + amoxicillin, 1 g bid, + clarithromycin, 500 mg bid
Alternative treatment — PMC	Proton pump inhibitor + metronidazole, 500 mg bid, + clarithromycin, 250 mg bid
Alternative treatment — PBMT	Proton pump inhibitor + bismuth subsalicylate, 2 tabs qid, + metronidazole, 250 mg qid, + tetracycline, 500 mg qid

*All drugs should be taken together for 7 d.
†Omeprazole, 20 mg bid, or lansporazole, 30 mg bid, or pantoprazole, 40 mg bid

References

1. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984;1:1311-5.

2. Peterson WL. *Helicobacter* and peptic ulcer disease. *N Engl J Med* 1992;324:1043-8.

3. Asaka M, Takeda H, Sugiyama T, Kato M. What role does *Helicobacter pylori* play in gastric cancer? [review]. *Gastroenterology* 1997;113(6 Suppl): S56-60.

4. Dooley CP, Fitzgibbons PL, Cohen H. Prevalence of *Helicobacter pylori* infection and histological gastritis in asymptomatic persons. *N Engl J Med* 1989;321:1562-6.

5. Boren T, Falk P, Roth KA, Larson G, Normark S. Attachment of *Helicobacter pylori* to gastric epithelium mediated by blood group antigens. *Science* 1993;262:1892-5.

6. Ilver D, Arnqvist A, Ogren J, Frick IM. *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigens revealed by retagging. *Science* 1998; 279:373-7.

7. Mobley HL. *Helicobacter pylori* factors associated with disease development [review]. *Gastroenterology* 1997;113(6 Suppl):S21-8.

8. Marshall BJ, Barrett LJ, Prakash C, McCallum RW, Guerrant RL. Urea protects *Helicobacter* (*Campylobacter*) pylori from the bactericidal effect of acid. *Gastroenterology* 1990;99(3): 697-702.

9. Peek RM, Blaser MJ. Pathophysiology of *Helicobacter pylori*-induced gastritis and peptic ulcer disease. *Am J Med* 1997;102:200-7.

10. Censini S, Lange C, Xiang J, Crabtree JE, Ghiara P, Borodovsky M, et al. cag, a pathogenicity island of *Helicobacter pylori*, encodes type I-specific and disease-associated virulence factors. *Proc Natl Acad Sci U S A* 1996;93(25): 14648-53.

11. Tomb JF, White O, Kerlavage, Clayton RA, Sutton GG, Fleischmann RD, et al. The complete genome sequence of the gastric pathogen *Helicobacter* pylori [published erratum appears in *Nature* 1997;389(6649):412]. *Nature* 1997;388(6642):539-47.

12. Graham DY, Malaty HM, Evans DG, Evans DJ, Klein PD, Adam E. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States. *Gastroenterology* 1991; 100:1495-1501.

13. Megraud F. Epidemiology of *Helicobacter pylori* infection. *Gastroenterol Clin North Am* 1993;22:73-88.

14. Whitaker CJ, Dubiel AJ, Galpin OP. Social and geographic risk factors in *Helicobacter pylori* infection. *Epidemiol Infect* 1993;111:63-70.

15. Malaty HM, Engstrand L, Pedersen NL, Graham DY. *Helicobacter pylori* infection: genetic and environmental influences. A study of twins. *Ann Intern Med* 1994;120:982-6.

16. Niv Y, Fraser G, Delpre G, Neeman A, Leiser A, Samra Z, et al. *Helicobacter pylori* and blood groups. *Am J Gastroenterol* 1996;91(1):101-4.

17. Drumm B, Perez-Perez GI, Blaser MJ, Sherman PM. Intrafamilial clustering of *Helicobacter pylori* infection. *N Engl J Med* 1990;322:359-63.

18. Handt LK, Fox JG, Stalis IH, Rufo R, Lee G, Linn J, et al. Characterization of feline *Helicobacter pylori* strains and associated gastritis in a colony of domestic cats. *J Clin Microbiol* 1995;33 (9):2280-9.

19. Grubel P, Huang L, Masubuchi N, Stutzenberger FJ, Cave DR. Detection of *Helicobacter pylori* DNA in houseflies (*Musca domestica*) on three continents. *Lancet* 1998;352:788-9.

20. Ramsey EJ, Carey KV, Peterson WL, Jackson JJ, Murphy FK, Read NW, et al. Epidemic gastritis with hypochlorhydria. *Gastroenterology* 1979;76(6): 1449-57.

21. Gledhill T, Leicester RJ, Addis B, Lightfoot N, Barnard J, Viney N, et al. Epidemic hypochlorhydria. *BMJ (Clin Res Ed)* 1985;290(6479):1383-6.

22. Marshall BJ, Armstrong JA, McGechie DB, Glancy RJ. Attempt to fulfill Koch's postulates for pyloric *Campylobacter*. *Med J Aust* 1985;142(8):436-9.

23. Morris A, Nicholson G. Ingestion of *Campylobacter pyloridis* causes gastritis and raised fasting gastric pH. *Am J Gastroenterol* 1987;82(3):192-9.

24. Cutler AF. Diagnostic tests for *Helicobacter* [review]. *Gastroenterologist* 1996;5:202-12.

25. Simor AE, Lin E, Saibil F, Cohen L, Lewis M, Pearen F, et al. Evaluation of enzyme immunoassay for detection of salivary antibody to *Helicobacter pylori*. *J Clin Microbiol* 1996;34(3):550-3.

26. Laine L, Cohen H, Sloane R, Marin-Sorensen M, Weinstein WM. Interobserver agreement and predictive value of endoscopic findings for *H. pylori* and gastritis in normal volunteers. *Gastrointest Endosc* 1995;42(5):420-3.

27. Kuipers EJ, Uyterlinde Am, Pena AS, Roosendaal R, Pals G, Nelis GF, et al. Long-term sequelae of *Helicobacter pylori* gastritis. *Lancet* 1995;345(8964): 1525-8.

28. Smoot DT. How does *Helicobacter pylori* cause mucosal damage? Direct mechanisms [review]. *Gastroenterology* 1997;113(6 Suppl):S31-4; discussion S50.

29. Appelmelk BJ, Simoons-Smit I, Negrini R, Moran AP, Aspinall GO, Forte JG, et al. Potential role of molecular mimicry between *Helicobacter pylori* lipopolysaccharide and host Lewis blood group antigens in autoimmunity. *Infect Immun* 1996;64(6):2031-40.

30. Thomson M. Commentary: *Helicobacter pylori* — the story so far. *BMJ* 1999;319(7209):541.

31. Hunt R, Thomson AB. Canadian *Helicobacter pylori* consensus conference. Canadian Association of Gastroenterology. *Can J Gastroenterol* 1998;12 (1):31-41.

32. Ofman JJ, Etchason J, Fullerton S, Kahn KL, Soll AH. Management strategies for *Helicobacter pylori*-seropositive patients with dyspepsia: clinical and economic consequences [review]. *Ann Intern Med* 1997; 126 (4):280-91.

33. Soll AH. Peptic ulcer and its complications. In: Feldman M, Scharschmidt BF, Sleisenger MH, editors. *Sleisenger and Fordtran's gastrointestinal and liver disease*. 6th ed. Philadelphia: W.B. Saunders; 1998. p. 620-78.

34. Laine L, Hopkins RJ, Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials. *Am J Gastroenterol* 1998:93;1409-15.

35. Vaira D, Menegatti M, Miglioli M. What is the role of *Helicobacter pylori* in complicated ulcer disease? [review]. *Gastroenterology* 1997;113(6 Suppl): S78-84.

36. Calam J, Gibbons A, Healey ZV, Bliss P, Arebi N. How does *Helicobacter pylori* cause mucosal damage? Its effect on acid and gastrin physiology [review]. *Gastroenterology* 1997;113(6 Suppl):S43-50.

37. el-Omar EM, Penman ID, Ardill JE, Chittajallu RS, Howie C, McColl KE. *Helicobacter pylori* infection and abnormalities of acid secretion in patients with duodenal ulcer disease. *Gastroenterology* 1995;109(3):681-91.

38. el-Omar E, Penman I, Dorrian CA, Ardill JE, McColl KE. Eradicating *Helicobacter pylori* infection lowers gastrin mediated acid secretion by two thirds in patients with duodenal ulcer. *Gut* 1993;334(8):1060-5.

39. Hawkey CJ, Tulassay Z, Szczepanski L, van Rensburg CJ, Filipowicz-Sosnowska A, Lanas A, et al. Randomised controlled trial of *Helicobacter pylori* eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDs study. Helicobacter Eradication for Lesion Prevention [published erratum appears in *Lancet* 1998;352(9140):1634]. *Lancet* 1998; 352(9133):1016-21.

40. Chan FK, Sung JJ, Chung SC, To KF, Yung MY, Leung VK, et al. Randomised trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcer. *Lancet* 1997;350 (9083):975-9.

41. Correa P. A human model for gastric carcinogenesis. *Cancer Res* 1988;48: 3554-60.

42. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 1991;325(16): 1127-31.

43. Nomura A, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N Engl J Med* 1991;325(16):1132-6.

44. The EUROGAST Study Group. An international association between *Helicobacter pylori* infection and gastric cancer [Published erratum appears in *Lancet* 1993;341(8861):1668.]. *Lancet* 1993;341(8857):1359-62.

45. Parsonett J. *Helicobacter pylori* and gastric cancer. *Gastroenterol Clin North Am* 1993;22:89-104.

46. Wantanabe T, Tada M, Nagi H, Sasaki, Nakao M. *Helicobacter pylori* infection induces gastric cancer in Mongolian gerbils. *Gastroenterology* 1998;115:628-41.

47. Parsonnett J. When hereditary is infectious. *Gastroenterology* 2000;118: 222-7.

48. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Helicobacter pylori*. In: *Schistomes, liver flukes, and* Helicobacter pylori*: views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans*. Lyon (France): International Agency for Research on Cancer; 1994. p. 177-240.

49. Isaacson PG. Gastric MALT lymphoma; from concept to cure [review]. *Ann Oncol* 1999;10(6):637-45.

50. Denesh J, Peto R. Risk factors for coronary heart disease and infection with *Helicobacter pylori*: meta-analyses of 18 studies. *BMJ* 1998;316:1130-2.

51. Annibale B, Marignani, Monarca B, Antonelli G, Marcheggiano A, Martino G, et al. Reversal of iron deficiency anemia after *Helicobacter pylori* eradication in patients with asymptomatic gastritis. *Ann Intern Med* 1999;131 (9):668-72.

52. McColl K, Murray L, El-Omar E, Dickson A, El-Nujumi A, Wirz A, et al. Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998;339(26):1869-74.

53. Blum AL, Talley NJ, O'Morain C, van Zanten SV, Labenz J, Stolte M, et al. Lack of effect of treating Helicobacter pylori infection in patients with nonulcer dyspepsia. Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment (OCAY) Study Group. *N Engl J Med* 1998;339(26): 1875-81.

54. Talley NJ, Janssens J, Lauritsen K, Racz I, Bolling-Sternevald EB. Eradication of *Helicobacter pylori* in functional dyspepsia: randomised double-blind placebo controlled trial with 12 months' follow-up. *BMJ* 1999;318: 833-7.

55. Perri F, Andriulli A. Absence of benefit of eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *N Engl J Med*. 2000;342(8):589-90.

56. Hunt RH, Fallone CA, Thomson AB. Canadian Helicobacter pylori Consensus Conference update: infections in adults. Canadian Helicobacter Study Group. *Can J Gastroenterol* 1999;13 (3):213-7.

57. Labenz J. Does *Helicobacter pylori* affect the management of gastroesophageal reflux disease? *Am J Gastroenterol* 1999;94(4):867-9.

58. Blaser MJ. Not all *Helicobacter* strains are created equal: Should all be eliminated? *Lancet* 1997;349:1020-2.