CME CREDIT

Current status of *Helicobacter pylori* in peptic ulcer disease

GARY W. FALK, MD

SUMMARY All patients with documented, past or present gastric or duodenal ulcers and who are infected with *Helicobacter pylori* should undergo antimicrobial therapy to eradicate it. Data do not yet support giving antimicrobial therapy to treat nonulcer dyspepsia or to prevent gastric neoplasia.

KEY POINTS *H pylori* infection is the main cause of chronic superficial gastritis and is associated with both gastric and duodenal ulcers. However, it has no proven relationship with nonulcer dyspepsia. *H pylori* infection is currently diagnosed by either endoscopic biopsy or serologic titers for a specific immunoglobulin (IgG) antibody. No noninvasive technique is available to document eradication of infection, although urea breath tests will soon simplify both the diagnosis of infection and documentation of eradication. Eradicating *H pylori* infection decreases the rate of ulcer recurrence. Treatment currently involves a 2-week, three-drug regimen of bismuth subsalicylate, tetracycline, and metronidazole, or a two-drug regimen of omeprazole and amoxicillin; other, simpler regimens are under investigation.

INDEX TERMS: *HELICOBACTER* INFECTIONS; *HELICOBACTER PYLORI*; PEPTIC ULCER CLEVE CLIN J MED 1995; 62:95–104

From the Department of Gastroenterology, The Cleveland Clinic Foundation.

Address reprint requests to G.W.F., Department of Gastroenterology, Desk S40, The Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195.

PEPTIC ULCER disease is a common clinical problem once thought to be caused by hypersecretion of acid and pepsin. However, although the injury caused by acid and pepsin is necessary for ulcers to form, acid secretion is normal in almost all patients with gastric ulcers and is increased in only approximately one third of patients with duodenal ulcers.[1] It is now clear that an ulcer is the end result of an imbalance between aggressive and defensive factors in the gastroduodenal mucosa. Part of that imbalance is related to infection with *Helicobacter pylori*, which may also be related to the development of adenocarcinoma and lymphoma of the stomach. This paper will review the role of *H pylori* in upper gastrointestinal diseases and provide strategies for detecting and eradicating it.

BIOLOGY OF *H PYLORI*

H pylori is a gram-negative, spiral-shaped bacillus with flagella at one end. It lives in the interface between the surface of gastric epithelial cells and the overlying mucus gel layer, often clustering

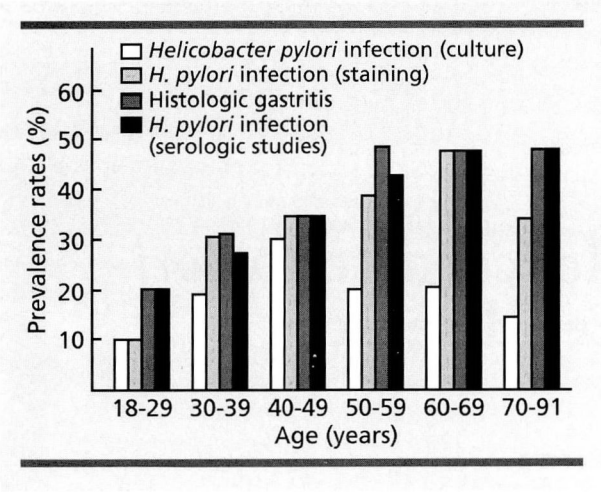

FIGURE 1. Age-specific prevalence rates for *H pylori* infection according to the results of cultures, staining, and serologic studies, and prevalence of histologic gastritis. From Dooley et al, reference 4; used with permission.

around the junction between epithelial cells. It may also be found atop metaplastic gastric epithelium in the duodenum and esophagus.[2] It is not invasive, although some organisms actually adhere to cells.

H pylori produces urease, which can increase the juxtamucosal pH[2]; this may account for its ability to survive in the hostile, acidic environment of the stomach. Other features that enable it to colonize the stomach include its inherent motility and its ability to adhere to the mucosa. However, how it escapes the bactericidal effects of gastric acid, colonizes the gastric mucosa, and damages the underlying epithelial cells is still not well understood. Once acquired, *H pylori* persists in the stomach indefinitely—apparently for life.[3]

EPIDEMIOLOGY

The only known reservoir of *H pylori* is humans. The prevalence of infection in healthy people increases with advancing age to over 50% in people older than 60 years (*Figure 1*).[4,5] The prevalence is higher in blacks than in whites and is inversely related to socioeconomic status.[6] Clusters of infections in families, custodial institutions, and nursing homes suggest that *H pylori* is spread by close personal contact.[7] However, whether transmission occurs via the oral-oral route or the fecal-oral route is unclear.

PATHOGENESIS OF *H PYLORI*-INDUCED INJURY

H pylori clearly causes histologic gastritis and is responsible for most cases of gastritis not associated with a known primary cause (eg, eosinophilic gastritis or autoimmune gastritis).[7] *H pylori* antral gastritis is found in 95% to 100% of patients with duodenal ulcers and in up to 80% of patients with gastric ulcers.[7] However, only a minority of patients with *H pylori* gastritis eventually acquire peptic ulcers. In fact, although infection typically lasts for years or even decades, most infected people have no symptoms and never acquire peptic ulcer disease. The mechanism whereby infection with *H pylori* results in peptic ulcer disease is not well understood.

Colonization results in an inflammatory response and chronic superficial gastritis of the antrum and the fundus in virtually all infected individuals. It is unclear to what extent the inflammation is a result of direct destruction by *H pylori*, as opposed to *H pylori* being an "innocent bystander" that induces an immune inflammatory response. Both processes are probably involved.

Mediators of inflammation produced by the organism include urease (which itself is damaging and which generates ammonia), cytotoxins, other toxic proteins, platelet activating factor, and a lipopolysaccharide (overproduced in its outer membrane). In a variety of studies, each of these mechanisms has caused cellular injury.[3]

In response, neutrophils, monocytes, and macrophages are activated, specific antibodies (primarily immunoglobulin G [IgG] and specific secretory immunloglobulin A [IgA]) are produced, and T cells proliferate. In essence, the host recognizes *H pylori* and responds to it, but is unable to eliminate it completely. The intensity of the response can result in one of several end points. The most common is chronic superficial gastritis, which may persist for years. This condition is characterized by an inflammation in which lymphocytes, plasma cells, eosinophils, and monocytes infiltrate the lamina propria and subsequently injure the gastric glands. The inflammatory response may actually benefit *H pylori* by releasing nutrients locally. Moreover, it may harm the host by damaging epithelial cells and impairing their function. To avoid this damage, the host may down-regulate the immune response; chronic superficial gastritis represents an equilibrium between the host's inability to remove the organism and its ability to contain damage.[3]

Other end points of infection include duodenal ulcers, gastric ulcers, atrophic gastritis, and, possibly, adenocarcinoma, lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphomas. The factors that determine these end points are unclear. Characteristics of both the host and the organism probably play a role. There is no evidence that *H pylori* is associated with nonulcer dyspepsia.

H pylori is genetically diverse, having many different strains.[8] DNA hybridization studies indicate that strains associated with duodenal ulcer disease are distinct from those associated with chronic superficial gastritis.[9] Environmental factors such as cigarette smoking also may be involved.

H pylori infection results in a number of alterations in gastrin secretion. Under normal conditions, plasma gastrin levels increase in response to a meal and then return to baseline in response to the feedback inhibition of intraluminal acid. In chronic *H pylori* infection, the basal gastrin level increases, as does the gastrin response to a meal.[10–12] This response returns to normal after *H pylori* is eradicated.[11,13,14] Interestingly, this increase in gastrin is associated with normal acid secretion.[3,11,13] Hence, there are two disruptions in the normal feedback mechanisms of gastrin release: (1) normal acid levels do not shut down gastrin secretion, and (2) elevated gastrin levels do not result in gastric acid hypersecretion in most people. The cause of these disruptions is uncertain, although the regulation of antral G cells may be altered by active antral inflammation, inducing the release of gastrin.[8] Alternatively, there may be an abnormality in the ability of the adjacent somatostatin-producing D cells to shut down gastrin release; eradication of *H pylori* increases the production of D-cell mRNA and the number of D cells.[15]

Atrophic gastritis may be a consequence of either aging or chronic inflammation without sufficient down-regulation of the immune response, thereby causing continued epithelial destruction and then atrophy.[3] Atrophy may then increase the risk for developing gastric cancer.

In summary, *H pylori* inflammation probably reflects a complex interplay between the organism (which directly damages the mucosa) and the immune response directed against it. The resulting equilibrium between the organism and the host is manifested by chronic superficial gastritis. In some people, intense inflammation may ensue as a result of inadequate down-regulation of the immune response, whereas in a subset of patients with peptic ulcer disease, abnormalities in gastrin physiology may result in G-cell hyperfunction and abnormalities in gastric acid secretion. An outline of these mechanisms, proposed by Blaser,[3] is shown in *Figure 2*.

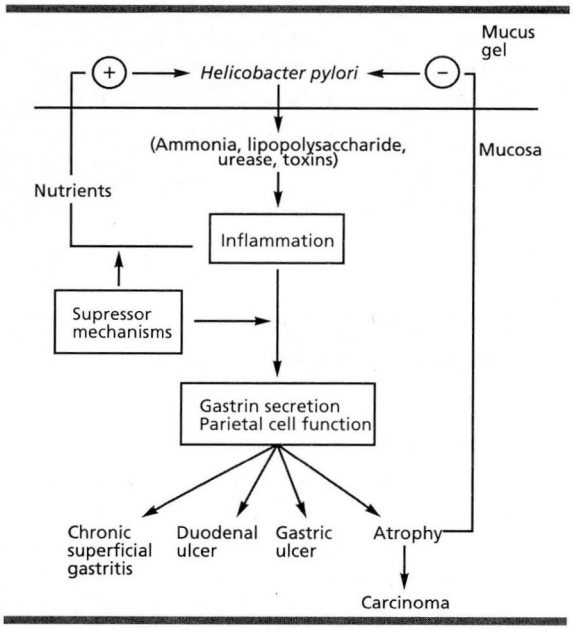

FIGURE 2. Hypothetical relationship between *H pylori* infection and gastroduodenal injury. In this model, *H pylori*, living in the mucus gel above the gastric epithelium, releases products that result in inflammation. In turn, inflammation releases host factors into the mucus gel that the organism can use for nutrition. Chronic inflammation affects both gastrin secretion and parietal cell function, but host immunologic suppressor activity inhibits this process. The ultimate outcome of infection depends on the interaction of bacterial-mediated inflammation and host immune suppression on gastric secretory physiology. Possible outcomes of infection include chronic superficial gastritis, duodenal ulcer, gastric ulcer, or atrophic gastritis, which may be a precursor lesion of adenocarcinoma of the stomach. From Blaser, reference 3; used with permission.

DIAGNOSING *H PYLORI* INFECTION

A number of diagnostic tests are available to detect *H pylori* infection (*Table 1*). These tests can be divided into invasive techniques (which require endoscopy) and noninvasive techniques (which do not). Fortunately, all of them have excellent sensitivity and specificity. Their advantages and disadvantages are outlined below.

TABLE 1
DIAGNOSTIC TESTS FOR *HELICOBACTER PYLORI**

Test	Sensitivity (%)	Specificity (%)	Endoscopy needed?	Relative cost†
Culture	77–92	100	Yes	High
Histologic study	93–99	95–99	Yes	High
Rapid urease test (*Camplyobacter*-like organism test)	89–98	93–100	Yes	Low
Serologic study	88–99	86–100	No	Low
Carbon 13 urea breath test	90–100	98–100	No	Moderate
Carbon 14 urea breath test	90–97	89–100	No	Moderate

*Modified from Brown and Peura, reference 16; used with permission
†Excluding cost of endoscopy when applicable

Invasive techniques

Culture. Under normal circumstances, demonstration of an organism by culture is the criterion of an infection. However, culturing *H pylori* is tedious and difficult, owing to the fastidious nature of the organism. Culture is no more sensitive than routine histologic analysis and also entails the cost of endoscopy. For these reasons, cultures are not indicated for diagnosis.

Histologic analysis of biopsy samples is readily available, but some caveats should be kept in mind. The organism may have a patchy distribution, especially in the body and fundus of the stomach. Because the antrum is more uniformly involved, two biopsy specimens from the prepyloric antrum generally suffice.[16] The yield may be increased further by sampling the fundus as well as the antrum. Routine hematoxylin and eosin staining may be unreliable for detecting *H pylori* by microscopy; the Giemsa and Warthin-Starry stains permit easier visualization, especially by inexperienced observers. Histologic analysis also has the advantage of visualizing the mucosa, permitting the detection of histologic gastritis as well as unsuspected lesions, such as MALT-type lymphomas. This invasive technique is expensive because it requires endoscopy, and an additional charge is incurred for interpretation. Several days are necessary to obtain the diagnosis.

The Camplyobacter-like organism (CLO) test. Mucosal biopsy specimens may be directly inoculated into a medium containing urea and phenol red, which turns pink if the pH rises above 6.0. This change occurs when urea in the gel is metabolized to ammonia by the urease of the organism. This test is commercially available and inexpensive, and can often provide a diagnosis within 1 hour of inoculation of the biopsy specimen. Its sensitivity and specificity have been reported to be up to 98% and 100%, respectively, at 24 hours.[17] The low cost and excellent reliability of this test make it the endoscopic method of choice for diagnosis.

Noninvasive techniques

Breath tests. The urease activity of *H pylori* can also be detected noninvasively. After urea labelled with carbon 13 or carbon 14 is ingested, urease produced by the organism splits off labelled carbon dioxide, which can be detected in the breath. Both breath tests are accurate, with a sensitivity and specificity of up to 100%.[16,18,19] Carbon 13 is a stable isotope that does not emit radiation. Unfortunately, detecting it requires a mass spectrometer, which is often not readily available. The carbon 14 test involves a small amount of radiation exposure, but uses a scintillation counter, which is more readily available. Neither technique is commercially available yet. The carbon 13 test is expected to become the ideal noninvasive test once it is commercially available because it does not involve radiation exposure, reflects current infection only, and can rapidly document both infection and clearance of the organism.

Serologic testing for antibodies to H pylori. The enzyme-linked immunosorbent assay (ELISA) is simple, inexpensive, and commercially available. Detection of IgG antibody has a sensitivity of up to 99% and a specificity of up to 100% for diagnosing infection.[19] Occasionally, IgA levels may be elevated without a concomitant increase in IgG levels.[20] An elevated antibody titer to *H pylori* indicates current infection, because spontaneous clearance is rare. Although the antibody titer falls after eradication, the rate of this decline is uncertain.

There are several limitations to the use of serologic analysis to document eradication. Titers must be monitored for at least 6 months to determine a decline. However, the cutoff value marking a significant decline is uncertain. Kosunen et al[20] reported that a 50% decline in IgG titer at 6 months had a sensitivity of 97% and specificity of 95%, while Cutler et al[21] reported that a 20% decline in antibody titer at 6 months had a sensitivity of 86% and a specificity of 88%. For the comparison to be accu-

rate, both the baseline and the follow-up titer must be measured at the same time to control for the inherent variability in the assay if it is run at different times.[21] These problems limit the use of serologic testing for documenting eradication. However, excellent accuracy and low cost make serologic testing the noninvasive method of choice to document infection with *H pylori*.

In practice, endoscopy is still required to diagnose ulcer disease, and the current standard requires two biopsy specimens from the antrum for CLO testing or histologic review. Alternatively, patients with a history of documented ulcer disease or who have an ulcer demonstrated by barium radiography can undergo testing for IgG antibodies to *H pylori* by ELISA. The full spectrum of noninvasive tests will probably be available soon, with IgG antibodies ideal for documenting infection and the carbon 13 urea breath test ideal for assessing the response to treatment.

TREATMENT

Several excellent treatments are available for peptic ulcers. With histamine H_2-receptor antagonists, 90% to 95% of duodenal ulcers and 88% of gastric ulcers heal within 8 weeks[22]; with omeprazole, 80% to 95% of duodenal ulcers heal within 4 weeks.[23] However, peptic ulcer disease is chronic, and both duodenal and gastric ulcers rapidly recur after successful antisecretory therapy.[1] Relapses can be prevented by long-term, low-dose (half-strength) maintenance therapy with any of the histamine H_2-blockers.[22] Now that *H pylori* infection has been recognized as an important factor in the pathogenesis of peptic ulcer disease, the 1994 National Institutes of Health (NIH) consensus conference[24] has recommended that all infected patients with duodenal and gastric ulcers undergo antimicrobial therapy.

H pylori is sensitive in vitro to a variety of antibiotics, but the in vivo activity of these same drugs is disappointing. This discrepancy may be related to where *H pylori* resides: under a mucus gel layer in the stomach, where the acidic environment decreases the activity of many antibiotics.[24] The lack of a suitable animal model of *H pylori* infection makes selecting appropriate antibiotics more difficult as well.

Triple therapy

Eradication of *H pylori* is defined as the absence of the organism at 4 or more weeks after completion of therapy. In a meta-analysis, Chiba et al[25] found that the eradication rate for single-drug therapy with agents such as bismuth or amoxicillin was 19%; for double-drug therapy, the rate was 48%, and for triple therapy the rate was 82%. The highest eradication rate was achieved with a combination of bismuth, metronidazole, and tetracycline. The organism is almost never eradicated with antisecretory therapy alone.

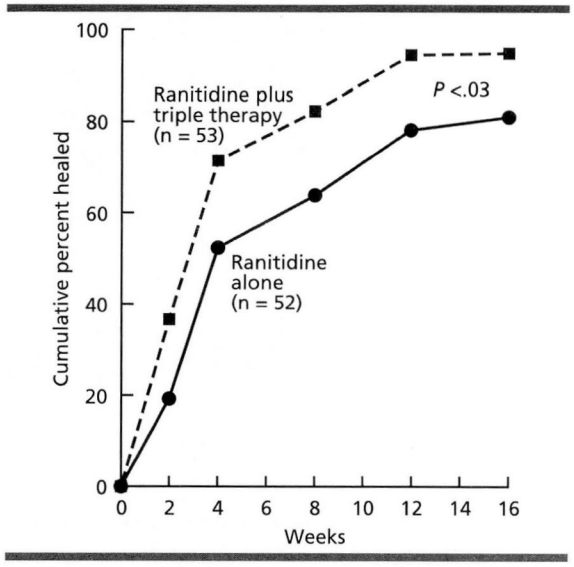

FIGURE 3. Healing rate of duodenal ulcers in two groups of patients. Healing was more rapid in patients receiving ranitidine plus triple antimicrobial therapy than in patients receiving ranitidine alone ($P < .01$). From Graham et al, reference 27; used with permission.

Multidrug therapy is inconvenient, making compliance a problem. In a trial of triple therapy, Graham et al[26] confirmed that compliance was a key factor in predicting efficacy: subjects who took less than 60% of their trial medication had an eradication rate of 69%, whereas those who took more than 60% had an eradication rate of 96%. Multidrug therapy is also complicated by adverse effects, most notably diarrhea, nausea, and vomiting, which may occur in up to 19% of patients.[26]

Eradication of *H pylori* accelerates the rate of duodenal ulcer healing. Graham et al[27] found that at 4 weeks of treatment, ulcers had healed in 74% of 53 patients who received ranitidine plus triple therapy and in 53% of 52 patients who received ranitidine alone (*Figure 3*). This effect alone is of little clinical

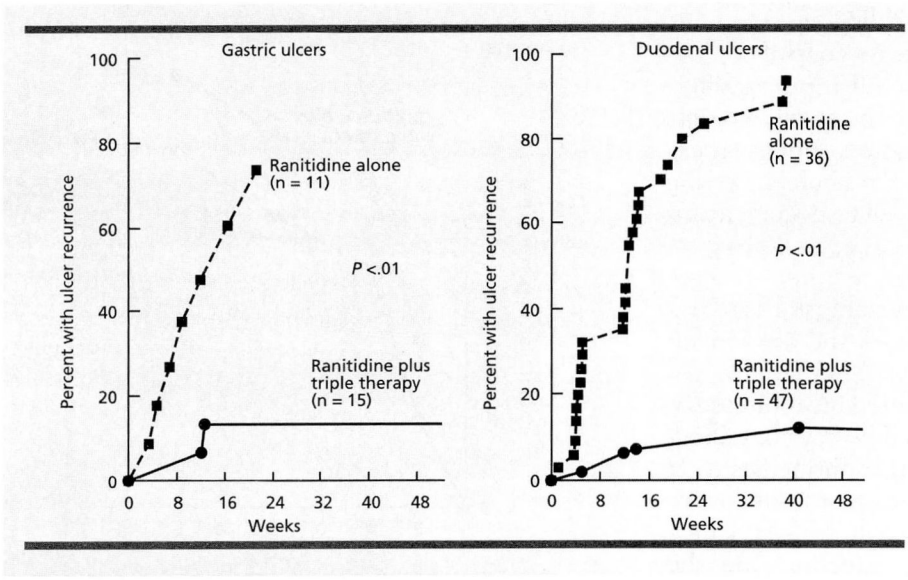

FIGURE 4. Recurrence rate of gastric ulcers (left) and duodenal ulcers (right) after successful healing with ranitidine alone or ranitidine plus triple antimicrobial therapy. No maintenance therapy was given. The recurrence rate of both types of ulcers was significantly greater ($P < .01$) in the patients treated with ranitidine alone than in those who received triple therapy plus ranitidine. From Graham et al, reference 28; used with permission.

importance, given the inconvenience, cost, and adverse effects of triple therapy plus histamine H_2-receptor antagonists when compared with the simpler and equally efficacious strategies, such as a single daily dose of omeprazole for the same period. However, interest in treating *H pylori* increased after eradication was found to markedly change the natural history of both duodenal and gastric ulcers.[28] In 26 patients with healed gastric ulcers and 83 patients with healed duodenal ulcers, the 1-year relapse rate was 13% and 12%, respectively, in those treated with ranitidine and triple therapy compared with 74% and 95% in those treated with ranitidine alone (*Figure 4*). All patients who had relapses after triple therapy either never had the organism eradicated initially or subsequently received nonsteroidal anti-inflammatory drugs (NSAIDs). Interestingly, none of the patients in whom *H pylori* was eradicated became reinfected within the 2 years of follow-up. Long-term follow-up of patients treated for *H pylori* also indicates that reinfection is uncommon. Forbes et al[29] recently reported that 32 (91%) of 35 patients given successful eradication therapy remained *H pylori*-negative after 7 years. The estimated annual reinfection rate in this group of patients was 1.2%.

Cigarette smoking has been implicated in the high recurrence rate of duodenal ulcers.[30] However, if *H pylori* is successfully eradicated, cigarette smoking does not appear to increase the risk of recurrence.[31]

Simpler regimens

Because of the inconvenience, expense, and adverse effects of triple therapy, other, simpler regimens are under investigation. Hentschel et al[32] recently found that duodenal ulcers healed in 48 (92%) of 52 of patients treated for 12 days with amoxicillin (750 mg three times a day) and metronidazole (500 mg three times a day) plus ranitidine for 6 weeks, whereas ranitidine alone was effective in only 39 (75%) of 52 patients. *H pylori* was eradicated in 89% of the antibiotic treatment group but in only 2% of the ranitidine group. The 1-year relapse rate was also lower in the antibiotic group (8%) than in the group treated with ranitidine only (86%) (*Figure 5*).

Omeprazole has a bacteriostatic effect on *H pylori*, decreases the density of *H pylori* colonization, and decreases histologic gastritis in patients with duodenal ulcers.[33] The mechanism of these effects is unclear. Omeprazole in varying dosages combined with amoxicillin has an eradication rate of greater than 80%.

Recently, 10 days of therapy with omeprazole (40 mg twice a day) combined with amoxicillin (1 g twice a day) was compared with omeprazole alone (40 mg daily) for healing duodenal ulcers. Both regimens were followed by omeprazole (20 mg daily) for an additional 4 weeks.[34] The healing rates at 6 weeks were comparable: ulcers had healed in all 27 patients receiving omeprazole plus amoxicillin and in 25 (96%) of 26 patients receiving omeprazole alone. Combination therapy resulted in an eradication rate of 82%, compared with 0% with omeprazole alone, and the relapse rate at 9 months of follow-up was 0% for the combination therapy group and 48% for

the omeprazole monotherapy group. This dual therapy regimen was well tolerated.

When omeprazole (20 mg twice a day) combined with amoxicillin (500 mg four times a day) was compared with triple therapy with tetracycline, metronidazole, and bismuth in a group of 38 patients, the healing rates were comparable, as were the eradication rates: 79% in the omeprazole group and 84% in the triple therapy group.[35]

It is unclear how omeprazole enhances the antibacterial action of amoxicillin. Amoxicillin is acid-labile, and the profound rise in intragastric pH caused by inhibition of the proton pump is hypothesized to result in less degradation of amoxicillin.[36] Pretreatment with omeprazole alone before instituting antibiotic therapy markedly attenuates the efficacy of dual therapy with amoxicillin and omeprazole and should be avoided.[37] More data are soon expected on the optimal doses of this therapy, as well as on other new proton-pump inhibitors combined with single antimicrobial agents. Clearly, dual therapy has the advantages of simplicity and better patient tolerance.

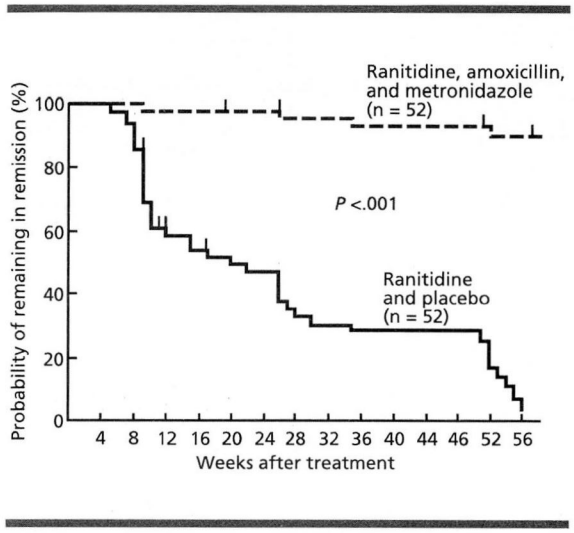

FIGURE 5. Probability that a duodenal ulcer would remain in remission after successful treatment with ranitidine plus placebo or ranitidine plus amoxicillin and metronidazole. The recurrence rate of ulcers in the patients given ranitidine plus placebo was significantly greater ($P < .001$) than in those who received ranitidine plus two antibiotics. The tick marks represent patients who, because of nonadherence to the protocol, were considered to have withdrawn from the study. From Hentschel et al, reference 32; used with permission.

Recommendations

The long-term effect of therapy on complications of ulcer disease remains incompletely understood. In a study of 31 patients who presented with major upper gastrointestinal bleeding from peptic ulcers, the rebleeding rate after ulcer healing was 29% in a group treated with ranitidine alone and 0% in the group treated with triple therapy plus ranitidine.[38] However, follow-up averaged only 9 months or less. Therefore, until more and longer follow-up data are available, maintenance doses of histamine H_2-receptor antagonists are recommended in this situation.[24]

Eradication of *H pylori* is now recommended in all infected patients with peptic ulcer disease (*Table 2*).[24] Before treatment for *H pylori* can be considered, both the organism and an ulcer need to be documented. Eradication should also be attempted in patients with chronic peptic ulcer disease severe enough to prompt consideration of long-term maintenance therapy or elective surgery, and in any patient already receiving maintenance therapy.

The recommended regimen for *H pylori* eradication is a 2-week course of a combination of bismuth subsalicylate (two tablets four times a day), tetracycline (500 mg four times a day, or amoxicillin 500 mg four times a day in patients who cannot tolerate tetracycline) and metronidazole (250 mg three times a day). Alternatively, omeprazole (20 mg twice a day) plus amoxicillin (500 mg four times a day) is a reasonable option (*Table 3*). If active disease is present at diagnosis, antisecretory therapy should be administered for the conventional time period of 8 weeks for histamine H_2-receptor antagonists (for duodenal or gastric ulcers) or 4 weeks for omeprazole (for duodenal ulcers only).

Eradication probably needs to be documented only in patients who would otherwise have been candidates for maintenance therapy because of a major complication, such as bleeding. Documentation should be by biopsy techniques at present, but by noninvasive breath tests when they become available.[39] As mentioned above, serologic methods are currently impractical for documenting eradication. If eradication fails, triple therapy should be repeated with clarithromycin (500 mg three times a day) instead of metronidazole.[39] Reinfection after eradication is uncommon and appears to occur at a rate of 1% to 3% annually.[29,32,40]

TABLE 2
WHEN TO BEGIN ANTIMICROBIAL TREATMENT OF *HELICOBACTER PYLORI* INFECTION*: GUIDELINES

Diagnosis	*H pylori*-negative	*H pylori*-positive
Asymptomatic (no ulcer)	No	No
Nonulcer dyspepsia	No	No
Gastric ulcer	No	Yes
Duodenal ulcer	No	Yes

*From the 1994 NIH consensus conference statement, reference 24

TABLE 3
CURRENT 2-WEEK ANTIMICROBIAL REGIMENS FOR THE TREATMENT OF *HELICOBACTER PYLORI* INFECTION

Triple therapy
- Bismuth subsalicylate, two tablets four times a day
- Metronidazole, 250 mg three times a day
- Tetracycline (or amoxicillin), 500 mg four times a day

Proton pump double therapy
- Omeprazole, 20 mg twice a day
- Amoxicillin, 500 mg four times a day

However, antimicrobial therapy should not yet be instituted for nonulcer dyspepsia, chronic *H pylori* gastritis, NSAID-induced ulcers without *H pylori*, or Zollinger-Ellison syndrome.[24,41] Routine therapy in these conditions would likely hasten the emergence of resistant strains and other untoward side effects of widespread antimicrobial therapy, such as pseudomembranous colitis.

H PYLORI AND NSAIDs

NSAIDs are associated with an increased risk of duodenal and gastric ulcers, regardless of enteric coating or delivery in a prodrug formulation. The frequency of *H pylori* infection and NSAID ingestion both increase with age. However, *H pylori* infection does not appear to increase the risk of duodenal or gastric ulcers in patients taking NSAIDs long-term.[42–44] Nevertheless, patients who develop peptic ulcer disease while taking NSAIDs should still be treated with antimicrobial therapy if they are infected with *H pylori*.[24] Whether eradication of *H pylori* will decrease the frequency of NSAID-induced peptic ulcers remains to be seen.

H PYLORI AND NONULCER DYSPEPSIA

Dyspepsia is persistent or recurrent abdominal pain or discomfort centered in the upper abdomen.[45] The terms "nonulcer dyspepsia" or "functional dyspepsia" apply to chronic dyspepsia without a known cause. Approximately 50% of patients with nonulcer dyspepsia are infected with *H pylori*.[46] However, the prevalence of *H pylori* is probably no higher in patients with nonulcer dyspepsia than in asymptomatic controls. Furthermore, the mechanism whereby histologic gastritis causes symptoms is not clear.

Trials assessing treatment of *H pylori* in patients with nonulcer dyspepsia all have had serious methodologic flaws.[46] A review of sixteen trials indicates that anti-*H pylori* therapy was effective in eight of these studies but ineffective in the other eight.[46] This contradiction is not surprising, given the emerging concept that functional dyspepsia is most likely the result of an abnormal sensory perception of visceral events.[47] Therefore, treatment of *H pylori* in patients with nonulcer dyspepsia is not indicated.

H PYLORI AND GASTRIC NEOPLASIA

As improbable as the association between *H pylori* and peptic ulcer disease once seemed, the organism is also hypothesized to be associated with an increased risk of gastric carcinoma. In a case-control study, Parsonnet et al[48] found that 84% of 186 patients with gastric adenocarcinoma had been previously infected with *H pylori*, compared with 61% of the control population. The mean time between documentation of infection and the diagnosis of carcinoma was 14.2 years. Similar results have been described by others.[49,50]

Possible mechanisms of carcinogenesis include injury caused by metabolic products of the organism, rapid turnover of cells caused by chronic inflammation (which may increase the risk of mutation and cellular transformation), and cellular injury, mutation, and transformation caused by inflammatory products.[48] However, most infected patients never develop cancer, and gastric carcinoma can also develop in subjects who are not infected. Therefore, other factors besides *H pylori* must play a role in the pathogenesis of gastric carcinoma.

Gastric non-Hodgkin's lymphoma is rare, although the stomach is the most common extranodal site of this tumor. Lymphoid tissue is normally absent from the stomach, probably accounting for the rarity of gastric lymphoma. Early in life, the stomach is

devoid of lymphocytes. However, in the presence of *H pylori*, chronic inflammation with lymphocytes occurs in the stomach.

Recently, Parsonnet et al[51] examined the relationship between non-Hodgkin's lymphoma of the stomach and infection with *H pylori* in a case-control study of 230 593 participants. In this study, the 33 patients with gastric non-Hodgkin's lymphoma were more likely to have evidence of previous infection with *H pylori* than did the control group (odds ratio 6.3). However, no association was seen between infection with *H pylori* and non-gastric non-Hodgkin's lymphoma. Perhaps chronic inflammation results in lymphoid proliferation, thereby increasing the chance of mutation, although diet, age, strain of bacteria, environmental cofactors, socioeconomic status, and genetic factors clearly must be involved as well.[51,52]

H pylori is also associated with MALT lymphoma, a low-grade subtype of non-Hodgkin's lymphoma of the stomach.[53] MALT lymphomas are characterized by a lymphoepithelial lesion that destroys the normal gastric architecture. Wotherspoon et al[54] eradicated *H pylori* in six patients who had MALT lymphoma, and in five of the six, eradication was accompanied by complete regression of the lesion. This regression suggests that *H pylori* eradication is a reasonable initial treatment strategy for this tumor.

SUMMARY AND FUTURE PERSPECTIVES

H pylori clearly causes chronic superficial gastritis. It also is involved in the pathogenesis of peptic ulcer disease, although the mechanism is incompletely understood. Strain variability and host factors probability account for the different outcomes of infection in different individuals. *H pylori* infection may also increase the risk of developing gastric adenocarcinoma and lymphoma. No clear relationship exists between *H pylori* infection and nonulcer dyspepsia. Infection can be diagnosed by either endoscopic biopsy or serologic tests for IgG antibodies. There is no noninvasive method to document eradication of infection, although the urea breath tests will probably soon be available for this purpose. Treatment with either a triple antimicrobial regimen or dual therapy with omeprazole is indicated in all patients infected with *H pylori* with present or past documented peptic ulcer disease, but not in nonulcer dyspepsia. Eradication greatly decreases the recurrence rate of peptic ulcer disease.

Many questions remain regarding the role of *H pylori* in peptic ulcer disease. The mechanism whereby infection results in an ulcer is still not understood. Cost-effective strategies for both diagnosis and treatment are anticipated in coming years. Most important, it will be necessary to determine what approach to take when a patient presents with dyspepsia. Should either a breath test or a serologic test be performed before considering endoscopic or radiographic studies? Should patients be treated empirically? Empiric therapy already has its advocates, but until more data are available, this approach should be avoided because of the risks of adverse effects from unnecessary antibiotic exposure, such as pseudomembranous colitis and increasing antibiotic resistance of the bacteria. Also in the coming years, the relationship between the organism and dyspepsia will undoubtedly be determined as well. The intriguing observations linking *H pylori* to gastric neoplasia will be an area for additional investigation. Finally, work is underway to develop a vaccine against *H pylori*, an approach that may obviate many of the questions outlined above.

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