

Helicobacter pylori: Review and Update

Frederick J. Hardin, MD

Richard A. Wright, MD

Since its introduction to the scientific community by Marshall and Warren almost 2 decades ago,¹ *Helicobacter pylori* has been the focus of basic biochemical and clinical research and debate. Its relevance to human disease, specifically to peptic ulcer disease, gastritis, and gastric malignancy, is indisputable. Many questions, however, still remain concerning the optimal diagnostic and therapeutic regimens with which to approach the organism. Current work is focusing on the implications of the mapping of the *H. pylori* genome and the possibility of developing an effective vaccine against the organism.

This article presents a brief overview of the epidemiology and pathogenesis of *H. pylori* infection. Typical clinical manifestations of *H. pylori* infection are discussed, as are relevant diagnostic and therapeutic strategies. The article concludes by examining emerging therapies, including development of a vaccine that may enable the future eradication of the organism as a significant human pathogen.

EPIDEMIOLOGY

Numerous studies have tried to assess the incidence and prevalence of *H. pylori* infection, its mode of transmission, and any risk factors contributing to development of the infection. The annual incidence reported in 3 adult studies in developed countries was between 0.3% and 0.5% per year.²⁻⁴ Prevalence estimates vary greatly, depending on the location of the study group and the characteristics of the population studied. In general, prevalence increases with age⁵ and correlates positively with a low socioeconomic status during childhood.⁶ Worldwide, but especially in developed nations, infection with *H. pylori* is declining.⁷

The acquisition of *H. pylori* occurs during childhood, most often by a fecal-oral or oral-oral route. Some studies have also indicated a role for a gastro-oral route of transmission.⁸ The role played by other factors, including ABO blood type, alcohol and tobacco use, dietary and nutritional influences, and genetic predisposition to infection, has also been studied, but results have been inconsistent.⁹ Interestingly, a recent

study of 655 subjects from a teaching hospital in Rome found an overall prevalence of infection of 40%, with a higher prevalence among nurses and auxiliary employees than among physicians.¹⁰

PATHOGENESIS

Pathogenicity and Virulence Factors

The earliest descriptions of the organism classified it as predominately extracellular, gram-negative, flagellated, and motile (Figure 1). With the advancement of biochemical techniques, new information about the pathogenicity and virulence factors of *H. pylori* has emerged, indicating that infection by *H. pylori* requires a complex interaction of both bacterial and host factors.

Investigators have identified several bacterial proteins necessary for colonization of the gastric mucosa by *H. pylori*, including proteins active in the transport of the organism to the surface of the mucosa (eg, flagellin, which is encoded on genes *flaA* and *flaB*).¹¹ Once in the presence of the gastric mucosa, bacteria induce a transient hypochlorhydria by an unknown mechanism. The urease enzyme produced by the bacteria alters the microenvironment of the organism to facilitate colonization.¹² Adherence then occurs via interaction between cell-surface glycolipids and adhesins specific to *H. pylori*.¹³ There also appears to be a role played by proteins called *cecropins*, which are produced by *H. pylori* and inhibit the growth of competing organisms,¹⁴ as well as by a P-type adenosinetriphosphatase, which helps prevent excessive alkalization of the microenvironment by urease.¹⁵

Once attached to gastric mucosa, *H. pylori* causes tissue injury by a complex cascade of events that depends on both the organism and the host. *H. pylori*, like all gram-negative bacteria, has in its cell wall lipopolysaccharide, which acts to disrupt mucosal integrity.¹⁶ Furthermore,

Dr. Hardin is a Fellow and Dr. Wright is a Professor and Chief, Division of Gastroenterology/Hepatology, Department of Medicine, University of Louisville, Louisville, KY.

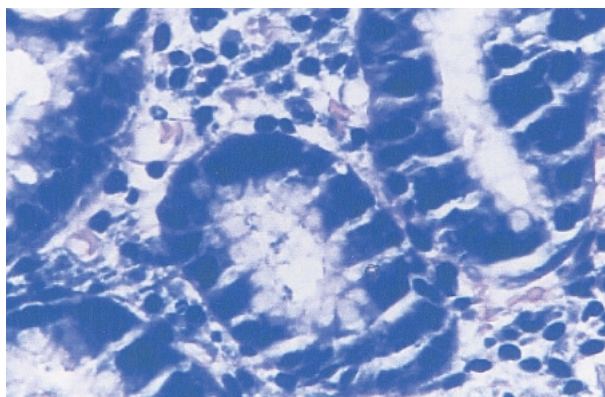


Figure 1. Photomicrograph of *Helicobacter pylori* (Giemsa, original magnification $\times 500$). Photomicrograph used courtesy of Mukunda Ray, MD, PhD.

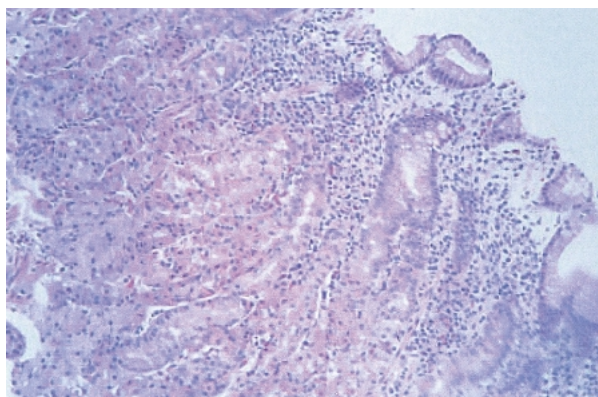


Figure 2. Photomicrograph showing type B neutrophilic gastritis (hematoxylin-eosin, original magnification $\times 125$). Photomicrograph used courtesy of Mukunda Ray, MD, PhD.

H. pylori releases several pathogenic proteins that induce cell injury. For example, the CagA protein, produced by cytotoxic-associated gene A (*cagA*), is a highly immunogenic protein that may be associated with more severe clinical syndromes, such as duodenal ulcer and gastric adenocarcinoma (although this question is far from settled).^{17,18} There is increasing evidence that CagA positivity is associated with an increased risk for distal, but not proximal, gastric adenocarcinoma.¹⁹ In addition, protein products of the vacuolating cytotoxin A gene²⁰ (*vacA*) and the A gene induced by contact with epithelium (*iceA*) are known to be associated with mucosal injury.²¹

Once colonization of the gastric mucosa has taken place, the immunogenic properties of *H. pylori* induce an inflammatory reaction with neutrophilic gastritis that ultimately results in the clinical manifestations of the infection (**Figure 2**). This process is mediated by host factors, including interleukins 1, 2, 6, 8, and 12; interferon gamma; tumor necrosis factor- α ; T and B lymphocytes; and phagocytic cells. These factors mediate injury through release of reactive oxygen species and inflammatory cytokines.²² *H. pylori* additionally appears to increase the rate of mucosal programmed cell death (also known as *apoptosis*).²³

Effects on Gastric Physiology

In addition to producing local injury of gastric mucosa, *H. pylori* alters normal gastric secretion. Interestingly, the location and severity of the infection seem closely associated with the ultimate clinical outcome, most likely because of effects on gastric physiology. Many studies have shown that patients with a duodenal ulcer who are infected with *H. pylori* have an increased serum level of gastrin, which—in turn—leads to in-

creased acid output.²⁴ These patients tend to have a milder phenotypic expression of their gastritis, with inflammation mostly in the antrum or distal part of the stomach.²⁵ In contrast, patients with gastric adenocarcinoma, a known complication of *H. pylori* infection, tend to have pangastritis, with involvement of the acid-secreting body of the stomach as well as the antrum. This condition leads to atrophy of parietal cells (which are responsible for producing acid) and gastrin-producing cells of the antrum (which stimulate acid secretion) and eventually produces achlorhydria. Patients with gastric adenocarcinoma also have impaired acid secretion in response to stimulation with gastrin.²⁶

Pathologic Findings

Although extensive work has been performed to classify histopathologic changes seen with *H. pylori* infection, there is no consensus on classification; the Sydney system²⁷ and the Houston Gastritis Workshop system²⁸ have, however, been recognized as models. After colonization, there appears to be an intense neutrophilic infiltrate in the necks of the mucosal glands. Epithelial changes are common when there is irregularity of the surface architecture, and atrophy of the glands is typical of longstanding infection. Moreover, there is usually lymphocytic infiltration of the stroma and impaired mucus secretion. Finally, areas of patchy intestinal metaplasia may be seen, which are central to the development of neoplasia.²⁹

CLINICAL MANIFESTATIONS

Gastritis and Gastric Cancer

Once infected with *H. pylori*, most persons remain asymptomatic. Some infected persons may even clear the

infection, with seroreversion rates commonly reported to be in the range of 5% to 10%; it is not known if this seroreversion is spontaneous or results from elimination of the organism by antibiotic agents used to treat other conditions.⁹ However, the typical course of disease in infected patients begins with chronic superficial gastritis, eventually progressing to atrophic gastritis. This progression appears to be a key event in the cellular cascade that results in the development of gastric carcinoma. Existing data indicate a 90-fold increase in rates of gastric carcinoma in patients with severe, multifocal atrophic gastritis, compared with normal controls.³⁰ The mechanism of tumorigenesis appears to involve DNA damage induced by different cytokines and free radicals released in the setting of chronic inflammation in susceptible persons.³¹

Although *H. pylori* is associated with the development of adenocarcinoma of the antrum and body of the stomach, it is also clearly linked with gastric mucosa-associated lymphoid tissue (MALT) lymphomas.³² *H. pylori* stimulates lymphocytic infiltration of the mucosal stroma; this infiltration may act as a focus for cellular alteration and proliferation, ultimately resulting in neoplastic transformation to lymphoma.³³ It appears that *H. pylori* also produces proteins that stimulate growth of lymphocytes in the early stages of neoplasia. Most tellingly, it has been reported that regression of low-grade gastric MALT lymphoma can be achieved in 70% to 90% of patients with eradication of *H. pylori* infection.³⁴ Recent work has shown endoscopic ultrasound examination to be invaluable in identifying the grade of MALT lymphoma and in predicting the efficacy of treating the *H. pylori* infection to obtain regression of the lymphoma.³⁵

Peptic Ulcer Disease

The relationship between *H. pylori* infection and peptic ulcer disease has been studied exhaustively, and it is now accepted that the organism is the major cause, but not the only cause, of peptic ulcer disease worldwide. Eradicating the infection can alter the natural course of peptic ulcer disease by dramatically reducing its recurrence rate in treated patients, compared with untreated patients.³⁶ This reduction occurs in patients with duodenal and gastric ulcers who have no history of nonsteroidal anti-inflammatory drug use.

The mechanism by which *H. pylori* induces peptic ulcer disease is incompletely understood but most likely involves a combination of genetic predisposition of the host, virulence factors of the organism (eg, VacA and CagA proteins), mechanical damage to the mucosa, and alterations of gastric and duodenal secretions.³⁷

Nonulcer Dyspepsia

Nonulcer dyspepsia comprises a constellation of varied symptoms, including dysmotility-like, ulcer-like, and reflux-like symptoms. Many possible causes have been suggested for nonulcer dyspepsia, including lifestyle factors, stress, altered visceral sensation, increased serotonin sensitivity, alterations in gastric acid secretion and gastric emptying, and *H. pylori* infection. A recent review also highlighted the role played by psychosocial impairment (eg, depression, somatization, anxiety) in patients with nonulcer dyspepsia.³⁸

In a study linking *H. pylori* infection to nonulcer dyspepsia, patients with the latter condition were twice as likely to be positive for the organism.³⁹ However, despite such epidemiologic evidence, treatment studies have failed to consistently show that eradication of *H. pylori* results in improvement of nonulcer dyspepsia symptoms.⁴⁰ Consequently, eradication of the organism cannot be considered the standard of care in all patients with nonulcer dyspepsia, because *H. pylori* infection is only a single part of the multifactorial etiology of the disease.

Gastroesophageal Reflux Disease

Much attention has been focused on the possible relationship between infection with *H. pylori* and gastroesophageal reflux disease (GERD) in its various manifestations (eg, esophagitis, Barrett's esophagus). Some investigators have suggested a link between the presence of *H. pylori* and a decreased risk for developing esophagitis and Barrett's esophagus⁴¹; although this inverse association is supported by many prevalence studies, others fail to show it.⁴² Studies have also indicated that certain strains of *H. pylori*, notably the CagA-positive strain, may be protective against the development of Barrett's esophagus.⁴³ Moreover, Labenz and colleagues have shown that the incidence of esophagitis may, in fact, increase after eradication of the organism.⁴⁴ Treatment of *H. pylori* infection can lead to exacerbation of GERD in many patients, prompting many gastroenterologists to defer endoscopic antral biopsies in patients with significant GERD and absent ulcer.⁴⁴

Conversely, other studies using endoscopic findings, pH probe measurements, and histology to determine the presence of *H. pylori* did not find any association between GERD (in any of its manifestations) and infection with *H. pylori*.^{45,46} Clearly, more definitive studies are necessary to define the relationship, if any, between these 2 entities.

Other Disease Associations

Investigators have further postulated a relationship between *H. pylori* infection and cardiovascular disease⁴⁷

Table 1. *Helicobacter pylori*–Associated Conditions**Association is accepted**

Gastric adenocarcinoma
 Gastric mucosa-associated lymphoid tissue lymphoma
 Gastritis
 Peptic ulcer disease

Association is controversial

Cardiovascular disease
 Gastroesophageal reflux disease
 Iron deficiency anemia
 Nonulcer dyspepsia

and iron-deficiency anemia.⁴⁸ These associations, however, require much more study before a causal relationship is established. **Table 1** summarizes the disorders that have been associated with *H. pylori* infection.

DIAGNOSTIC TESTING

Currently, there are several popular methods for detecting the presence of *H. pylori* infection, each having its own advantages, disadvantages, and limitations. Basically, the tests available for diagnosis can be separated according to whether or not endoscopic biopsy is necessary. Histologic evaluation, culture, polymerase chain reaction (PCR), and rapid urease tests are typically performed on tissue obtained at endoscopy. Alternatively, simple breath tests, serology, and stool assays are sometimes used, and trials investigating PCR amplification of saliva, feces, and dental plaque to detect the presence of *H. pylori* are ongoing.⁴⁹

Histology

Histologic evaluation has traditionally been the gold-standard method for diagnosing *H. pylori* infection. The disadvantage of this technique is the need for endoscopy to obtain tissue. Limitations also arise at times because of an inadequate number of biopsy specimens obtained or failure to obtain specimens from different areas of the stomach.⁵⁰ In some cases, different staining techniques may be necessary, which can involve longer processing times and higher costs. However, histologic sampling does allow for definitive diagnosis of infection, as well as of the degree of inflammation or metaplasia and the presence/absence of MALT lymphoma or other gastric cancers in high-risk patients.

Culture

Because *H. pylori* is difficult to grow on culture

media, the role of culture in diagnosis of the infection is limited mostly to research and epidemiologic considerations. Although costly, time-consuming, and labor intensive, culture does have a role in antibiotic susceptibility studies and studies of growth factors and metabolism. However, in the United States, culture should not be considered a routine, first-line means of diagnosis.⁵¹

Polymerase Chain Reaction

With the advent of PCR, many exciting possibilities emerged for diagnosing and classifying *H. pylori* infection. PCR allows identification of the organism in small samples with few bacteria present and entails no special requirements in processing and transport. Moreover, PCR can be performed rapidly and cost-effectively, and it can be used to identify different strains of bacteria for pathogenic and epidemiologic studies. As suggested earlier, PCR also is being evaluated for its utility in identifying *H. pylori* in samples of dental plaque, saliva, and other easily sampled tissues.⁴⁹

The major limitation of PCR is that relatively few laboratories currently have the capability to run the assay. In addition, because PCR can detect segments of *H. pylori* DNA in the gastric mucosa of previously treated patients, false-positive results can occur, and errors in human interpretation of bands on electrophoretic gels can likewise lead to false-negative results.

Rapid Urease Testing

Rapid urease testing takes advantage of the fact that *H. pylori* is a urease-producing organism.⁵² Samples obtained on endoscopy are placed in urea-containing medium; if urease is present, the urea will be broken down to carbon dioxide and ammonia, with a resultant increase in the pH of the medium and a subsequent color change in the pH-dependent indicator. This test has the advantages of being inexpensive, fast, and widely available. It is limited, however, by the possibility of false positive results; decreased urease activity, caused either by recent ingestion of antibiotic agents, bismuth compounds, proton pump inhibitors, or sucralfate or by bile reflux, can contribute to these false-positive results.⁵³

Urea Breath Test

A urea breath test similarly relies on the urease activity of *H. pylori* to detect the presence of active infection. In this test, a patient with suspected infection ingests either ¹⁴C-labeled or ¹³C-labeled urea; ¹³C-labeled urea has the advantage of being nonradioactive and thus safer (theoretically) for children and women of childbearing age. Urease, if present, splits the urea into ammonia and isotope-labeled carbon dioxide; the carbon dioxide is

absorbed and eventually expired in the breath, where it is detected.

Besides being excellent for documenting active infection, this test is also valuable for establishing absence of infection after treatment, an important consideration in patients with a history of complicated ulcer disease with bleeding or perforation.⁵⁴ In addition, a urea breath test is relatively inexpensive (whichever isotope is used), is easy to perform, and does not require endoscopy. However, if the patient has recently ingested proton pump inhibitors, antibiotic agents, or bismuth compounds, a urea breath test can be of limited value. Therefore, at least 1 week should separate the discontinuing of antisecretory medications and testing for active infection,⁵⁵ and 4 weeks should separate treatment of *H. pylori* infection and testing for eradication of the organism. Moreover, except for major medical centers or tertiary referral centers where results are usually available in fewer than 24 hours, a urea breath test may be further limited by a turnaround time of several days (or longer) required for transport of samples and analysis by specialized laboratories not present in many community settings.

Serologic Tests

In response to *H. pylori* infection, the immune system typically mounts a response through production of immunoglobulins to organism-specific antigens. These antibodies can be detected in serum or whole-blood samples easily obtained in a physician's office. The presence of IgG antibodies to *H. pylori* can be detected by use of a biochemical assay, and many different ones are available.

Serologic tests offer a fast, easy, and relatively inexpensive means of identifying patients who have been infected with the organism. However, this method is not a useful means of confirming eradication of *H. pylori*; several different samples and changes in titers of specified amounts over time would be needed.⁵⁶ In addition, few patients become truly seronegative, even after eradication of the organism.⁵⁷

In low-prevalence populations, serologic tests should be a second-line methodology because of low positive predictive value and a tendency toward false-positive results. Serologic tests may be useful in identifying certain strains of more virulent *H. pylori* by detecting antibodies to virulence factors associated with more severe disease and complicated ulcers, gastric cancer, and lymphoma.

Stool Antigen Testing

Stool antigen testing is a relatively new methodology that uses an enzyme immunoassay to detect the pres-

ence of *H. pylori* antigen in stool specimens. A cost-effective and reliable means of diagnosing active infection and confirming cure, such testing has a sensitivity and specificity comparable to those of other noninvasive tests.⁵⁸ Questions remain regarding possible cross-reactivity with other *Helicobacter* species present in the intestines, but definitive studies are lacking.

General Diagnostic Principles

The question of which patients to test, when to test them, and what test to use is still a troubling one for many physicians. Ultimately, the answer to these questions must be based on patient preference, cost, availability of different tests, and positive and negative predictive values of different tests (which depend on the individual patient population, including the prevalence of disorders caused by *H. pylori* infection in the community). Nevertheless, certain principles of testing seem universal. First, endoscopic methods of diagnosis should be used only if the procedure is necessary to detect some other condition besides *H. pylori* infection. Second, only those patients in whom treatment will make a difference should be tested. Conclusive evidence does not exist that eradication of the infection in patients with simple dyspepsia will relieve symptoms, and testing of asymptomatic patients without a history of documented peptic ulcer disease is not warranted.⁵⁹ Testing can be considered on a case by case basis in patients with symptoms suggestive of peptic ulcer disease.

Because treatment of *H. pylori* infection is definitely indicated in patients with active or previously documented peptic ulcer disease, gastric MALT lymphoma, or family history of gastric cancer, their *H. pylori* status must be clarified. Urea breath and stool antigen tests are the most cost-efficient tests to identify active infection, but their limitations must be considered. Although serology is an excellent, inexpensive test to ascertain if someone with a history of peptic ulcer disease and unknown *H. pylori* status warrants treatment, endoscopy with tissue sampling in patients with a history of peptic ulcer disease can provide more definitive diagnosis of *H. pylori* infection, as well as information about the activity of peptic ulcer disease and possibly other factors at play (including gastric carcinoma). Follow-up testing with urea breath or stool antigen tests (both of which have sensitivities and specificities greater than 90%⁵⁹) is necessary to document cure in patients with complicated peptic ulcer disease (eg, perforation, hemorrhage, obstruction) or recurrent symptoms and should be performed 4 weeks after completion of treatment.⁶⁰

Table 2. Proton Pump Inhibitors and Antibiotic Agents Recently Recommended for Initial Treatment of *Helicobacter pylori* Infection*

Proton Pump Inhibitors	Antibiotic Agents
Lansoprazole 30 mg bid [†]	Amoxicillin 1 g bid
Omeprazole 20 mg bid	Clarithromycin 500 mg bid
Pantoprazole 40 mg bid	Metronidazole 500 mg bid
Rabeprazole 20 mg bid	Tetracycline 500 mg bid

Adapted with permission from Cave DR. *H. pylori* update. AGA spring postgraduate course presented at: Digestive Disease Week; May 20–23, 2001; Atlanta, GA. Syllabus page 35.

*According to these recent recommendations, 1 of the listed proton pump inhibitors should be administered with 2 of the listed antibiotic agents for a duration of 10 to 14 days.

[†]bid = twice daily.

MANAGEMENT

General Treatment Principles

Determining the optimum treatment of *H. pylori* infection is difficult, because the organism lives in an environment not easily accessible to many medications and because emerging bacterial resistance presents an added challenge. Moreover, many of the recommended regimens are difficult for patients to take, leading to problems with compliance; specifically, having to take a large number of pills at least twice daily and coping with unpleasant adverse effects do little to encourage patient cooperation. Despite these obstacles, current regimens can obtain cure rates in excess of 85%⁶¹ in most patient populations.

Antibiotic Agents

Currently, antibiotic agents used to treat *H. pylori* infection are administered in combination, with no single agent ever used as monotherapy because of a lack of efficacy and the potential development of resistance. Metronidazole has activity independent of pH, but resistance to the drug is common in the United States. This problem with resistance is ameliorated somewhat, however, when the drug is used with clarithromycin. Metronidazole can have unpleasant adverse effects (eg, nausea), and a disulfiram-like reaction to alcohol ingestion is possible, although exceedingly rare. Clarithromycin has lower rates of resistance (approximately 7%–11%)⁶² but is not acid stable, may cause dysgeusia, and is more expensive than other antibiotic agents. Resistance to amoxicillin is rare, but this drug usually

requires the coadministration of a proton pump inhibitor because its activity is pH-dependent. Finally, tetracycline has the advantage of low cost and low occurrence of resistance but can cause discoloration of the teeth in children and photosensitivity reactions.

Adjunctive Agents

The most popular agents currently used in combination with antibiotic agents to eradicate *H. pylori* infection are the proton pump inhibitors, with omeprazole being the most widely studied drug. Omeprazole acts not only by directly inhibiting bacterial microsomal enzymes but also by raising intragastric pH, thus facilitating the action of antibiotic agents, reducing gastric secretions, and increasing antibiotic concentrations in the stomach. Other adjunctive agents include histamine receptor antagonists and ranitidine bismuth citrate, which has antisecretory properties in addition to the antibacterial action of bismuth (ie, interruption of the bacterial cell wall). However, ranitidine bismuth citrate is no longer available in the United States.

Current Regimens

Presently in the United States, the most efficacious regimens include 2 antibiotic agents and at least 1 adjunctive agent for 14 days.⁶³ A European study has claimed adequate cure rates with a 7-day course of quadruple therapy (2 antibiotics, 2 adjunctive agents),⁶⁴ but other studies have not confirmed this finding.⁶⁵

Most clinicians treat *H. pylori* infection with a triple-drug or even quadruple-drug approach. The 1998 guidelines from the American College of Gastroenterology⁶¹ judged the following 3 regimens to be optimal: (1) administration of a proton pump inhibitor, clarithromycin, and either metronidazole or amoxicillin for 2 weeks; (2) administration of ranitidine bismuth citrate (this guideline preceded the drug's withdrawal in the United States), clarithromycin, and either metronidazole, amoxicillin, or tetracycline for 2 weeks; (3) a proton pump inhibitor, bismuth, metronidazole, and tetracycline for 2 weeks. More recent recommendations outlined in a postgraduate course offered by the American Gastroenterology Association propose the use of newer proton pump inhibitors⁶⁰ (Table 2).

For patients who fail initial triple-drug therapy, according to follow-up testing, subsequent therapy should involve using a different combination of available antibiotic agents, increasing the duration of treatment, or incorporating a course of quadruple therapy.^{60,61} Culture with sensitivity testing should be performed after 2 treatment failures.

EMERGING THERAPIES**Antibiotics and Other Agents**

As emerging drug resistance continues to plague efforts to eradicate *H. pylori* infection, new therapeutic regimens incorporating existing antibiotic agents and newly developed compounds are essential. Nitazoxanide has promise as an effective agent when used in combination with omeprazole,⁶⁶ and further studies are ongoing. In addition, macrolides other than clarithromycin may play a role in future therapies.⁶⁷

The mapping of the complete genome of *H. pylori*⁶⁸ has opened the door for a new era in chemotherapeutic drugs. It will now be possible to develop agents that act on specific key protein products vital to survival of the bacterium.

Vaccines

Perhaps the most exciting work in the quest to eradicate *H. pylori* as a significant human pathogen is in the area of vaccine development. The fact that the organism is prevalent worldwide, is responsible for significant morbidity and mortality, and is difficult and expensive to eradicate makes it a prime target for vaccine therapy.

Pioneering work in the early 1990s provided evidence that vaccination against *H. pylori* infection was possible, based on murine models. It was later learned that the key mechanism of protective immunity against the organism occurred via stimulation of T-helper type 2 phenotype cells, which are induced by the production of interleukins 4 and 10 and not by antibody production.⁶⁹

Several issues remain in regard to a safe and effective vaccine against *H. pylori* infection. In the first place, a safe mucosal adjuvant or vector to stimulate an immune response must be identified. Different agents, including cholera toxin and an *Escherichia coli* heat-labile toxin, have been used in conjunction with specific *H. pylori* antigens (eg, urease) with varying success (and varying toxicities).^{70,71} Attenuated live vaccines, including strains of *Salmonella*, used in combination with *H. pylori* antigens have shown promise.⁷² Secondly, the optimal route of administration needs to be defined; studies in mice show promise with nasal and rectal routes, which would avoid the possible postimmunization gastritis likely with an oral route.⁶⁹ In addition, different regimens need to be developed to ensure complete sterilization of the gastric mucosa; the latter step has not generally been attempted in murine models. Clinical trials are underway to answer these and other questions, with the goal of producing an inexpensive, safe, and effective vaccine seeming to be within reach. **HP**

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. Parsonnet J, Blaser MJ, Perez-Perez GI, et al. Symptoms and risk factors of *Helicobacter pylori* infection in a cohort of epidemiologists. *Gastroenterology* 1992;102:41–6.
3. Cullen DJ, Collins BJ, Christiansen KJ, et al. When is *Helicobacter pylori* infection acquired? *Gut* 1993;34:1681–2.
4. Sipponen P, Kosunen TU, Samloff IM, et al. Rate of *Helicobacter pylori* acquisition among Finnish adults: a fifteen year follow-up. *Scand J Gastroenterol* 1996;31:229–32.
5. Malaty HM, Evans DG, Evans DJ Jr, Graham DY. *Helicobacter pylori* in Hispanics: comparison with blacks and whites of similar age and socioeconomic class. *Gastroenterology* 1992;103:813–6.
6. Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. *Gut* 1994;35:742–5.
7. Kosunen TU, Aromaa A, Knekt P, et al. *Helicobacter* antibodies in 1973 and 1994 in the adult population of Vammala, Finland. *Epidemiol Infect* 1997;119:29–34.
8. Stone MA. Transmission of *Helicobacter pylori*. *Postgrad Med J* 1999;75:198–200.
9. Everhart JE. Recent developments in the epidemiology of *Helicobacter pylori*. *Gastroenterol Clin N Amer* 2000;29:559–78.
10. Gasbarrini A, Anti M, Franceschi F, et al. Prevalence of and risk factors for *Helicobacter pylori* infection among health-care workers at a teaching hospital in Rome: the Catholic University Epidemiological Study. *Eur J Gastroenterol Hepatol* 2001;13:185–9.
11. Eaton KA, Suerbaum S, Josenhans C, Krakowka S. Colonization of gnotobiotic piglets by *Helicobacter pylori* deficient in two flagellin genes. *Infect Immun* 1996;64:2445–8.
12. Rektorschek M, Weeks D, Sachs G, Melchers K. Influence of pH on metabolism and urease activity of *Helicobacter pylori*. *Gastroenterology* 1998;115:628–41.
13. Segal ED, Falkow S, Tompkins LS. *Helicobacter pylori* attachment to gastric cells induces cytoskeletal rearrangements and tyrosine phosphorylation of host cell proteins. *Proc Natl Acad Sci USA* 1996;93:1259–64.
14. Putsep K, Branden CI, Boman HG, Nomark S. Antibacterial peptide from *H. pylori*. *Nature* 1999;398:671–2.
15. Meichers K, Weitznegger T, Steinhilber W, et al. A novel P type ATPase cloned from *Helicobacter pylori* [abstract]. *Gastroenterology* 1995;108:A165.
16. Moran AP. The role of lipopolysaccharide in *Helicobacter pylori* pathogenesis. *Aliment Pharmacol Ther* 1996;10 Suppl 1:39–50.
17. Censini S, Lange C, Xiang Z, et al. Cag, a pathogenicity island of *Helicobacter pylori*, encodes type I-specific and disease-associated virulence factors. *Proc Natl Acad Sci*

- USA 1996;93:14648–53.
18. Graham DY, Yamaoka Y. Disease-specific *Helicobacter pylori* virulence factors: the unfulfilled promise. *Helicobacter* 2000;5 Suppl 1:S3–9, discussion S27–31.
 19. Wu A, Crabtree J, Bernstein L, et al. Role of *Helicobacter pylori* Cag A+ strains and risk of adenocarcinoma of the stomach and esophagus [abstract]. *Gastroenterology* 2001;120:A14.
 20. Cover TL. The vacuolating cytotoxin of *Helicobacter pylori*. *Mol Microbiol* 1996;20:241–6.
 21. Peek RM Jr, Thompson SA, Donahue JP, et al. Adherence to gastric epithelial cells induces expression of a *Helicobacter pylori* gene, *iceA*, that is associated with clinical outcome. *Proc Assoc Amer Physicians* 1998;110:531–44.
 22. Go MF, Crowe SE. Virulence and pathogenicity of *Helicobacter pylori*. *Gastroenterol Clin N Amer* 2000;29:649–70.
 23. Vorobjova T, Maaros HI, Sipponen P, et al. Apoptosis in different compartments of antrum and corpus mucosa in chronic *Helicobacter pylori* gastritis. An 18-year follow-up study. *Scand J Gastroenterol* 2001;36:136–43.
 24. Peterson WL, Barnett CC, Evans DJ Jr, et al. Acid secretion and serum gastrin in normal subjects and patients with duodenal ulcer disease: the role of *Helicobacter pylori*. *Amer J Gastroenterol* 1993;88:2038–43.
 25. Schultze V, Hackelsberger A, Gunther T, et al. Differing patterns of *Helicobacter pylori* gastritis in patients with duodenal, prepyloric, and gastric ulcer disease. *Scand J Gastroenterol* 1998;33:137–42.
 26. El-Omar EM, Oien K, El-Nujumi A, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. *Gastroenterology* 1997;113:15–24.
 27. Price AB. The Sydney System: histological division. *J Gastroenterol Hepatol* 1991;6:209–22.
 28. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996;20:1161–81.
 29. Warren JR. Gastric pathology associated with *Helicobacter pylori*. *Gastroenterol Clin N Amer* 2000;29:705–51.
 30. Sipponen P, Kekki M, Haapakoski J, et al. Gastric cancer risk in chronic atrophic gastritis: statistical calculations of cross-sectional data. *Int J Cancer* 1985;35:173–7.
 31. Scheiman JM, Cutler AF. *Helicobacter pylori* and gastric cancer. *Amer J Med* 1999;106:222–6.
 32. Parsonnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med* 1994;330:1267–71.
 33. Zucca E, Bertoni F, Roggero E, et al. Molecular analysis of the progression from *Helicobacter pylori*-associated chronic gastritis to mucosa-associated lymphoid-tissue lymphoma of the stomach. *N Engl J Med* 1998;338:804–10.
 34. Morgner A, Bayerdorffer E, Neubauer A, Stolte M. Gastric mucosa-associated lymphoid tissue lymphoma and *Helicobacter pylori*. *Gastroenterol Clin North Am* 2000;29:593–607.
 35. Nakamura S, Matsumoto T, Suekane H, et al. Predictive value of endoscopic ultrasonography for regression of gastric low grade and high grade MALT lymphomas after eradication of *Helicobacter pylori*. *Gut* 2001;48:454–60.
 36. Van der Hulst RW, Rauws EA, Koycu B, et al. Prevention of ulcer recurrence after eradication of *Helicobacter pylori*: a prospective long-term follow-up study. *Gastroenterology* 1997;113:1082–6.
 37. Cohen H. Peptic ulcer and *Helicobacter pylori*. *Gastroenterol Clin North Am* 2000;29:775–89.
 38. Olden KW, Drossman DA. Psychologic and psychiatric aspects of gastrointestinal disease. *Med Clin North Am* 2000;84:1313–27.
 39. Armstrong D. *Helicobacter pylori* infection and dyspepsia. *Scand J Gastroenterol Suppl* 1996;215:38–47.
 40. Talley NJ, Vakil N, Ballard ED 2nd, Fennerty MB. Absence of benefit of eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *N Engl J Med* 1999;341:1106–11.
 41. Loffeld RJ, Werdmuller BF, Kuster JG, et al. Colonization with cagA-positive *Helicobacter pylori* strains inversely associated with reflux esophagitis and Barrett's esophagus. *Digestion* 2000;62:95–9.
 42. Newton M, Bryan R, Burnham WR, Kamm MA. Evaluation of *Helicobacter pylori* in reflux oesophagitis and Barrett's oesophagitis. *Gut* 1997;40:9–13.
 43. Vaezi MF, Falk GW, Peek RM et al. CagA-positive strains of *Helicobacter pylori* may protect against Barrett's esophagus. *Amer J Gastroenterol* 2000;95:2206–11.
 44. Labenz J, Blum AL, Bayerdorffer E, et al. Curing *Helicobacter pylori* infection in patients with duodenal ulcer may provoke reflux esophagitis. *Gastroenterology* 1997;112:1442–7.
 45. Oberg S, Peters JH, Nigro JJ, et al. *Helicobacter pylori* is not associated with the manifestations of gastroesophageal reflux disease. *Arch Surg* 1999;134:722–6.
 46. Gisbert JP, de Pedro A, Losa C, et al. *Helicobacter pylori* and gastroesophageal reflux disease: lack of influence of infection on twenty-four-hour esophageal pH monitoring and endoscopic findings. *J Clin Gastroenterol* 2001;32:210–14.
 47. Ameriso SF, Fridman EA, Leiguarda RC, Sevlever GE. Detection of *Helicobacter pylori* in human carotid atherosclerotic plaques. *Stroke* 2001;32:385–91.
 48. Annibale B, Marignani M, Monarca B, et al. Reversal of iron deficiency anemia after *Helicobacter pylori* eradication in patients with asymptomatic gastritis. *Ann Intern Med* 1999;131:668–72.
 49. Bravos ED, Gilman RH. Accurate diagnosis of *Helicobacter pylori*. Other tests. *Gastroenterol Clin North Am* 2000;29:925–9.
 50. El-Zimaity HM, Graham DY. Evaluation of gastric mucosal biopsy site and number for identification of *Helicobacter pylori* or intestinal metaplasia: role of the Sydney System. *Hum Pathol* 1999;30:72–7.

51. Perez-Perez GI. Accurate diagnosis of *Helicobacter pylori*. Culture, including transport. *Gastroenterol Clin North Am* 2000;29:879–84.
52. Mobley HL, Cortesia MJ, Rosenthal LE, Jones BD. Characterization of urease from *Campylobacter pylori*. *J Clin Microbiol* 1988;26:831–6.
53. Midolo P, Marshall RJ. Accurate diagnosis of *Helicobacter pylori*. Urease tests. *Gastroenterol Clin North Am* 2000;29:871–8.
54. Vaira D, Vakil N. Blood, urine, stool, breath, money, and *Helicobacter pylori*. *Gut* 2001;48:287–9.
55. Chey WD, Woods M, Scheiman JM, et al. Lansoprazole and ranitidine affect the accuracy of the ¹⁴C-urea breath test by a pH-dependent mechanism. *Am J Gastroenterol* 1997;92:446–50.
56. Lerang F, Haug JB, Moum B, et al. Accuracy of IgG serology and other tests in confirming *Helicobacter pylori* eradication. *Scand J Gastroenterol* 1998;33:710–5.
57. Cutler AF, Prasad VM, Santogade P. Four-year trends in *Helicobacter pylori* IgG serology following successful eradication. *Am J Med* 1998;105:18–20.
58. Monteiro L, de Mascarel A, Sarrasqueta AM, et al. Diagnosis of *Helicobacter pylori* infection: noninvasive methods compared to invasive methods and evaluation of two new tests. *Am J Gastroenterol* 2001;96:353–8.
59. Cave DR. *H. pylori* update. AGA spring postgraduate course presented at: Digestive Disease Week; May 20–23, 2001; Atlanta, GA. Syllabus pages 25–36.
60. Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol* 1998;93:2330–8.
61. Fennerty MB, Lieberman DA, Vakil N, et al. Effectiveness of *Helicobacter pylori* therapies in a clinical practice setting. *Arch Intern Med* 1999;159:1562–6.
62. Weissfeld A, Haber M, Rose P, et al. Geographic distribution in the United States of primary resistance to clarithromycin and metronidazole in patients infected with *Helicobacter pylori*. *Gastroenterology* 1997;112:A328.
63. Graham DY. Therapy of *Helicobacter pylori*: current status and issues [published erratum appears in *Gastroenterology* 2000;119:1180]. *Gastroenterology* 2000;118(2 Suppl 1):S2–8.
64. de Boer W, Driessen W, Jansz A, Tytgat G. Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. *Lancet* 1995;345:817–20.
65. Garcia N, Calvet X, Gene E, et al. Limited usefulness of a seven-day twice-a-day quadruple therapy. *Eur J Gastroenterol Hepatol* 2000;12:1315–8.
66. Megraud F, Occhialini A, Rossignol JF. Nitazoxanide, a potential drug for eradication of *Helicobacter pylori* with no cross-resistance to metronidazole. *Antimicrob Agents Chemother* 1998;42:2836–40.
67. Megraud F, Marshall BJ. How to treat *Helicobacter pylori*. First-line, second-line, and future therapies. *Gastroenterol Clin North Am* 2000;29:759–73.
68. Klenk HP, Clayton RA, Tomb JF, et al. The complete genome sequence of the hyperthermophilic, sulphate-reducing archaeon *Archaeoglobus fulgidus* [published erratum appears in *Nature* 1998;394:101]. *Nature* 1997;390:364–70.
69. Sutton P. Progress in vaccination against *Helicobacter pylori*. *Vaccine* 2001;19:2296–90.
70. Douce G, Fontana M, Pizza M, et al. Intranasal immunogenicity and adjuvanticity of site-directed mutant derivatives of cholera toxin. *Infect Immunol* 1997;65:2821–8.
71. Michetti P, Kreiss C, Kotloff KL, et al. Oral immunization with urease and *Escherichia coli* heat-labile enterotoxin is safe and immunogenic in *Helicobacter pylori*-infected adults. *Gastroenterology* 1999;116:804–12.
72. Cortesy-Theulaz I. Vaccination against *Helicobacter pylori*. *Recent Results Cancer Res* 2000;156:55–9.

Test your knowledge and comprehension of this article with Review Questions on page 50.

Copyright 2002 by Turner White Communications Inc., Wayne, PA. All rights reserved.