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***Helicobacter pylori* Infection**

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Since the first culture of *Helicobacter pylori* 20 years ago, the diagnosis and treatment of upper gastrointestinal disease have changed dramatically. Peptic ulcer disease is now approached as an infectious disease, in which elimination of the causative agent cures the condition. The role of *H. pylori* infection in gastric cancers is increasingly recognized, and its role in other diseases of the upper gastrointestinal tract is being evaluated. Enormous progress has been achieved in determining the pathogenesis of this infection. Effective antimicrobial therapy is available, although there is still no ideal treatment, and indications for therapy continue to evolve. This review surveys scientific knowledge concerning *H. pylori* and focuses on the many aspects of this infection that are relevant to the clinician.

Epidemiology and Transmission

Infection with *H. pylori* occurs worldwide, but the prevalence varies greatly among countries and among population groups within the same country.¹ The overall prevalence of *H. pylori* infection is strongly correlated with socioeconomic conditions.² The prevalence among middle-aged adults is over 80 percent in many developing countries, as compared with 20 to 50 percent in industrialized countries. The infection is acquired by oral ingestion of the bacterium and is mainly transmitted within families in early childhood.^{1,3} It seems likely that in industrialized countries direct transmission from person to person by vomitus, saliva, or feces predominates; additional transmission routes, such as water, may be important in developing countries.^{4,5} There is currently no evidence for zoonotic transmission, although *H. pylori* is found in some nonhuman primates and occasionally in other animals.^{6,7} *H. pylori* infection in adults is usually chronic and will not heal without specific therapy; on the other hand, spontaneous elimination of the bacterium in childhood is probably relatively common,⁸ aided by the administration of antibiotics for other reasons.

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In industrialized countries, the rate of acquisition of *H. pylori* has decreased substantially over recent decades. Therefore, the continuous increase in the prevalence of *H. pylori* with age is due mostly to a cohort effect, reflecting more intense transmission at the time when members of earlier birth cohorts were children.⁹ Mathematical modeling of prevalence trends in the United States has indicated that markedly improved sanitation in the second half of the 19th century greatly reduced *H. pylori* transmission, initiating a decline in *H. pylori* infection that will ultimately lead to its elimination from the U.S. population.¹⁰ However, without intervention, *H. pylori* is predicted to remain endemic in the United States for at least another century.¹⁰

Humans can also become infected with *Helicobacter heilmannii*, a spiral bacterium found in dogs, cats, pigs, and nonhuman primates.¹¹ The prevalence in humans is approximately 0.5 percent. *H. heilmannii* causes only mild gastritis in most cases, but it has been found in association with mucosa-associated lymphoid-tissue (MALT) lymphoma.¹²

Pathogenesis

The gastric mucosa is well protected against bacterial infections. *H. pylori* is highly adapted to this ecologic niche, with a unique array of features that permit entry into the mucus, swimming and spatial orientation in the mucus, attachment to epithelial cells, evasion of the immune response, and, as a result, persistent colonization and transmission.

The *H. pylori* genome (1.65 million bp) codes for about 1500 proteins.^{13,14} Among the most remarkable findings of two *H. pylori* genome-sequencing projects were the discovery of a large family of 32 related outer-membrane proteins (Hop proteins) that includes most known *H. pylori* adhesins and the discovery of many genes that can be switched on and off by slipped-strand mispairing-mediated mutagenesis. Proteins encoded by such phase-variable genes include enzymes that modify the antigenic structure of surface molecules, control the entry of foreign DNA into the bacteria, and influence bacterial motility. The genome of *H. pylori* changes continuously during chronic colonization of an individual host by importing small pieces of foreign DNA from other *H. pylori* strains during persistent or transient mixed infections.^{15,16}

After being ingested, the bacteria have to evade the bactericidal activity of the gastric luminal contents and enter the mucous layer. Urease production and motility are essential for this first step of infection. Urease hydrolyzes urea into carbon dioxide and ammonia, thereby permitting *H. pylori* to survive in an acidic milieu.¹⁷ The enzyme activity is regulated by a unique pH-gated urea channel, UreI, that is open at low pH and shuts down the influx of urea under neutral conditions.¹⁸ Motility is essential for colonization, and *H. pylori* flagella have adapted to the gastric niche.¹⁹

H. pylori can bind tightly to epithelial cells by multiple bacterial-surface components.²⁰ The best-characterized adhesin, BabA, is a 78-kD outer-membrane protein that binds to the fucosylated Lewis B blood-group antigen.²¹ Several other members of the Hop protein family also mediate adhesion to epithelial cells. Accumulating evidence in animal models suggests that adhesion, particularly by BabA, is relevant in *H. pylori*-associated disease²² and may influence disease severity, although the results of several studies are contradictory.

The majority of *H. pylori* strains express the 95-kD vacuolating cytotoxin VacA, a secreted exotoxin.²³ The toxin inserts itself into the epithelial-cell membrane and forms a hexameric anion-selective, voltage-dependent channel²⁴ through which bicarbonate and organic anions

can be released,²⁴ possibly providing the bacterium with nutrients. VacA is also targeted to the mitochondrial membrane, where it causes release of cytochrome *c* and induces apoptosis.²⁵ The pathogenic role of the toxin is still debated. VacA-negative mutants can colonize in animal models, and strains with inactive *vacA* genes have been isolated from patients, indicating that VacA is not essential for colonization. However, VacA-negative mutants were outcompeted by wild-type bacteria in a mouse model, indicating that VacA increases bacterial fitness in this model.²⁶ The analysis of the role of VacA in disease is complicated by extensive variability in *vacA*. In Western countries, certain *vacA* gene variants are associated with more severe disease.²⁷ However, similar associations have not been found in Asia, and the functional basis underlying these associations is unknown.

Most strains of *H. pylori* possess the *cag* pathogenicity island (*cag*-PAI), a 37-kb genomic fragment containing 29 genes (Figure 1).²⁹ Several of these encode components of a predicted type IV secretion apparatus that translocates the 120-kD protein CagA into the host cell.^{30,31} After entering the epithelial cell, CagA is phosphorylated and binds to SHP-2 tyrosine phosphatase,³² leading to a growth factor-like cellular response and cytokine production by the host cell.



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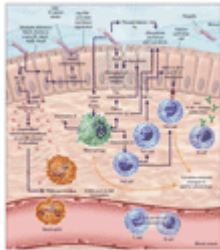
Figure 1. The *cag* Pathogenicity Island.

Most *H. pylori* strains that cause disease (so-called type I strains) contain the *cag* pathogenicity island, a chromosomal region with about 37,000 bp and 29 genes, whose location is indicated by the arrows. The figure shows the arrangement of genes in strain 26695, whose genome sequence was the first to be published.¹³ The island is split into two parts in some strains. Most of the *cag* genes are probably involved in the assembly of secretory machinery that translocates the protein CagA into the cytoplasm of gastric epithelial cells. Five genes (marked in orange) are similar to components of the type IV secretion system of the plant pathogen *Agrobacterium tumefaciens* (Vir proteins). Proteins encoded by the island are involved in two major processes, the induction of interleukin-8 production by gastric epithelial cells and the translocation of CagA from the bacterium into the host cell. All genes depicted by solid arrows are essential for the induction of interleukin-8; hatched arrows indicate genes not involved in this process. The arrows outlined in blue indicate genes required for translocation of CagA; orange lines indicate genes not essential for translocation.²⁸

Host Response to *H. pylori*

H. pylori causes continuous gastric inflammation in virtually all infected persons.³³ This inflammatory response initially consists of the recruitment of neutrophils, followed by T and B lymphocytes, plasma cells, and macrophages, along with epithelial-cell damage.³⁴ Since *H. pylori* rarely, if ever, invades the gastric mucosa, the host response is triggered primarily by the attachment of bacteria to epithelial cells. The pathogen can bind to class II major-histocompatibility-complex (MHC) molecules on the surface of gastric epithelial cells,

inducing their apoptosis.³⁵ Further changes in epithelial cells depend on proteins encoded in the *cag*-PAI and on the translocation of CagA into gastric epithelial cells.^{30,31} *H. pylori* urease and porins may contribute to extravasation and chemotaxis of neutrophils ([Figure 2](#)).^{36,37}



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Figure 2. Pathogen–Host Interactions in the Pathogenesis of *Helicobacter pylori* Infection.

The host response to *H. pylori* participates in the induction of damage to the gastric epithelium and therefore has an integral role in *H. pylori* pathogenesis. During the early phase of the infection, binding of *H. pylori* to gastric epithelial cells, in particular through BabA and by strains harboring the *cag* pathogenicity island, results in the production of interleukin-8 and other chemokines, such as epithelial-cell–derived neutrophil-activating peptide 78 (ENA-78) and growth-related oncogene α (GRO- α), by epithelial cells. Nuclear factor- κ B (NF- κ B) and the early-response transcription-factor activator protein 1 (AP-1) are the intracellular messengers involved in this process. The chemokines secreted by epithelial cells bind to the proteoglycan scaffolding, generating a gradient along which polymorphonuclear cells (PMN) are recruited. The chronic phase of *H. pylori* gastritis associates an adaptive lymphocyte response with the initial innate response. Lymphocyte recruitment is facilitated by chemokine-mediated expression of vascular addressins such as vascular-cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) that are required for lymphocyte extravasation. Macrophages that participate in interleukin-8 production produce proinflammatory cytokines involved in the activation of the recruited cells, in particular T helper cells (Th0, Th1, Th2), that respond with a biased Th1 response to *H. pylori*. In turn, Th1-type cytokines such as interferon- γ (INF- γ) induce the expression of class II major histocompatibility complexes (MHC) and accessory molecules B7-1 and B7-2 by epithelial cells, making them competent for antigen presentation. The cytotoxin VacA- and Fas-mediated apoptosis induced by tumor necrosis factor α (TNF- α) leads to disruption of the epithelial barrier, facilitating translocation of bacterial antigens and leading to further activation of macrophages. Cytokines produced by macrophages can also alter the secretion of mucus, contributing to *H. pylori*-mediated disruption of the mucous layer. Cytokines produced in the gastric mucosa induce changes in gastric-acid secretion and homeostasis (dashed lines). TNF- α , interleukin-1 β , and interferon- γ increase gastrin release, stimulating parietal and enterochromaffin cells and thus acid secretion. TNF- α also induces a decrease in the number of antral D cells, leading to decreased somatostatin production and indirectly enhancing acid production. LPS denotes lipopolysaccharide.

The gastric epithelium of *H. pylori*-infected persons has enhanced levels of interleukin-1 β ,

interleukin-2, interleukin-6, interleukin-8, and tumor necrosis factor α .^{38,39,40,41} Among these, interleukin-8, a potent neutrophil-activating chemokine expressed by gastric epithelial cells, apparently has a central role.³⁹ *H. pylori* strains carrying the *cag*-PAI induce a far stronger interleukin-8 response than *cag*-negative strains, and this response depends on activation of nuclear factor- κ B (NF- κ B) and the early-response transcription factor activator protein 1 (AP-1).^{42,43} The neutrophil-activating protein, a 150-kD surface protein of *H. pylori*, may contribute to phagocyte activation, although its relation to clinical outcome remains uncertain.⁴⁴

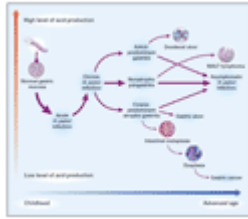
H. pylori infection induces a vigorous systemic and mucosal humoral response.⁴⁵ This antibody production does not lead to eradication of the infection but may contribute to tissue damage. Some *H. pylori*-infected patients have an autoantibody response directed against the H⁺/K⁺-ATPase of gastric parietal cells that correlates with increased atrophy of the corpus.⁴⁶

During specific immune responses, different subgroups of T cells emerge. These cells participate in mucosal protection and help distinguish pathogenic bacteria from commensals. Immature T helper (Th) 0 cells expressing CD4 can differentiate into two functional subtypes: Th1 cells, secreting interleukin-2 and interferon- γ , and Th2 cells, secreting interleukin-4, interleukin-5, and interleukin-10. Whereas Th2 cells stimulate B cells in response to extracellular pathogens, Th1 cells are induced mostly in response to intracellular pathogens. Because *H. pylori* is noninvasive and induces a strong humoral response, a Th2-cell response would be expected. Paradoxically, *H. pylori*-specific gastric mucosal T cells generally present a Th1 phenotype.⁴⁷ Studies in gene-targeted mice have further showed that Th1 cytokines promote gastritis, whereas Th2 cytokines are protective against gastric inflammation.⁴⁸ This Th1 orientation may be due to increased antral production of interleukin-18 in response to *H. pylori* infection.⁴⁹ This biased Th1 response, combined with Fas-mediated apoptosis of *H. pylori*-specific T-cell clones,⁵⁰ may favor the persistence of *H. pylori*.

In addition to the damage associated with *cag*-PAI-mediated translocation of proteins, *H. pylori* infection results in epithelial injury by several other mechanisms. Epithelial-cell damage can result from reactive oxygen or nitrogen species produced by activated neutrophils.⁵¹ Chronic inflammation also increases epithelial-cell turnover and apoptosis, which may be due to the combined effect of direct Fas-mediated contacts between epithelial and Th1 cells and interferon- γ .⁵² The expression levels of Fas, NF- κ B, and mitogen-associated protein (MAP) kinases are, in turn, regulated by interleukin-1 β . Proinflammatory polymorphisms of the interleukin-1 β gene favor the development of gastritis predominantly in the body of the stomach that is associated with hypochlorhydria, gastric atrophy, and gastric adenocarcinoma. In the absence of these proinflammatory polymorphisms, *H. pylori*-mediated gastritis develops predominantly in the antrum in association with a normal to high level of acid secretion.⁵³

Clinical Outcomes of Infection

The clinical course of *H. pylori* infection is highly variable and is influenced by both microbial and host factors (Figure 3). The pattern and distribution of gastritis correlate strongly with the risk of clinical sequelae, namely duodenal or gastric ulcers, mucosal atrophy, gastric carcinoma, or gastric lymphoma.⁵⁴ Patients with antral-predominant gastritis, the most common form of *H. pylori* gastritis, are predisposed to duodenal ulcers, whereas patients with corpus-predominant gastritis and multifocal atrophy are more likely to have gastric ulcers, gastric atrophy, intestinal metaplasia, and ultimately gastric carcinoma.



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Figure 3. Natural History of *Helicobacter pylori* Infection.

H. pylori is usually acquired in childhood. Acute *H. pylori* infection causes transient hypochlorhydria and is rarely diagnosed. Chronic gastritis will develop in virtually all persistently colonized persons, but 80 to 90 percent will never have symptoms. The further clinical course is highly variable and depends on bacterial and host factors. Patients with higher acid output are likely to have antral-predominant gastritis, which predisposes them to duodenal ulcers. Patients with lower acid output are more likely to have gastritis in the body of the stomach, which predisposes them to gastric ulcer and can initiate a sequence of events that, in rare cases, leads to gastric carcinoma. *H. pylori* infection induces the formation of mucosa-associated lymphoid tissue (MALT) in the gastric mucosa. Malignant lymphoma arising from such acquired mucosa-associated lymphoid tissue is another rare complication of *H. pylori* infection.

H. pylori is responsible for the majority of duodenal and gastric ulcers. The lifetime risk of peptic ulcer in a person infected with *H. pylori* ranges from 3 percent in the United States to 25 percent in Japan.^{1,55} Eradication of *H. pylori* drastically lowers the recurrence rate of *H. pylori*-associated peptic ulcers.⁵⁶

Gastric cancer is the second most frequent cause of cancer-related death. There is very strong evidence that *H. pylori* increases the risk of gastric cancer. *H. pylori* has been classified as a type I (definite) carcinogen since 1994, mainly on the basis of large seroepidemiologic case-control studies.^{57,58,59} Additional evidence has accumulated, including results from animal models.⁶⁰ In a recent prospective study of 1526 Japanese subjects,⁶¹ gastric cancer developed in 2.9 percent of 1246 patients with *H. pylori* infection over 7.8 years, whereas no gastric cancer was observed in 280 noninfected control subjects. Most important, no case of cancer was detected in a subgroup of 253 infected patients who received eradication therapy early in follow-up. The same investigators showed that eradication of *H. pylori* prevents relapses after endoscopic resection of early gastric cancer.⁶² The results from ongoing intervention trials of the effect of *H. pylori* eradication on the incidence of gastric cancer may have major implications for global policies concerning the treatment and prevention of *H. pylori* infection.

H. pylori infection significantly increases the risk of gastric MALT lymphoma, and 72 to 98 percent of patients with gastric MALT lymphoma are infected with *H. pylori*.^{63,64} Furthermore, eradication of *H. pylori* alone induces regression of gastric MALT lymphoma in 70 to 80 percent of cases.⁶⁵ Resistance of lymphoma to eradication therapy is strongly associated with certain genetic abnormalities in the host, such as the translocation t(11;18)(q21;q21), and is often associated with progression to high-grade tumors.⁶⁶ Most of the patients whose lymphomas respond to eradication therapy stay in remission for several years.⁶⁷ However, the long-term experience with patients in whom the lymphoma has been treated with antibiotics alone is still limited.

The role of *H. pylori* infection in dyspepsia not associated with ulcers remains controversial. An increased prevalence of *H. pylori* has been reported in this condition, but inconsistent long-term symptom relief has been observed with bacterial eradication in large, randomized trials.^{68,69} The reason for these discrepant results is not entirely clear. The studies showing benefit were conducted in geographic areas with a higher background of peptic ulcer disease. Subtle differences in dyspepsia-scoring systems may also have contributed to the outcome of these studies. A Cochrane review suggests that eradication of *H. pylori* improves symptoms in only about 9 percent of patients with dyspepsia without ulcers, but this end point may miss the other potential benefits of *H. pylori* eradication.⁷⁰

Eradication has become an issue in patients with gastroesophageal reflux disease, since long-term acid-suppressive therapy may aggravate *H. pylori*-mediated corpus gastritis and increase the risk of gastric carcinoma.⁷¹ Conversely, some case-control and cohort studies have suggested that *H. pylori* infection may protect against gastroesophageal reflux disease. Two recent, fully controlled trials showed, however, that *H. pylori* eradication did not negatively influence relapse rates in patients with gastroesophageal reflux disease,^{72,73} but additional prospective studies are needed. Eradication of *H. pylori* infection in these patients makes sense in view of the risks of peptic ulcer and gastric cancer.⁷⁴

H. pylori has also been implicated in the pathogenesis of many extragastric diseases, ranging from atherosclerosis to skin diseases, but documentation is poor and the associations are controversial.⁷⁵

Diagnostic Tests

H. pylori infection can be diagnosed by noninvasive methods or by endoscopic biopsy of the gastric mucosa; the selection of the appropriate test depends on the clinical setting.⁷⁶ Noninvasive methods include the urea breath test, serologic tests, and stool antigen assays. The urea breath test relies on the abundant, *H. pylori*-derived urease activity in the stomach; it qualitatively detects active infection with a sensitivity and specificity of more than 90 percent. The test is indicated for the initial diagnosis of the infection and for follow-up of eradication therapy. In the latter case, the urea breath test should not be performed before an interval of four weeks has elapsed, in order to avoid false negative results. The urea breath test is reliable in children over the age of six years but needs further validation in younger children.⁷⁷

H. pylori serologic testing is cheap and widely used for the diagnosis of *H. pylori* infection in patients before treatment. Although approved laboratory-based tests have sensitivity and specificity similar to those of the urea breath test, inconsistent results have been reported with some office-based tests. Because *H. pylori* strains differ among geographic locations, local validation is necessary. Serologic testing is of limited use in determining the success of therapy and is not reliable in young children. Stool antigen tests for *H. pylori* provide an alternative to the urea breath test, with a sensitivity of 89 to 98 percent and a specificity of over 90 percent.⁷⁸ Stool tests are suitable for follow-up of infection, provided that an eight-week interval is allowed after therapy. Stool tests perform well in children of all ages and may become the noninvasive method of choice for this group of patients.

Patients with alarming symptoms, such as anemia, gastrointestinal bleeding, or weight loss, as well as patients more than 50 years of age, should undergo endoscopy for the diagnosis of *H. pylori* infection. When endoscopy is clinically indicated, the test of first choice is a urease test on an antral-biopsy specimen.⁷⁶ It permits cheap and rapid detection of urease activity in the biopsy material, with a sensitivity of 79 to 100 percent and a specificity of 92 to 100 percent.⁷⁸

Sensitivity can be improved by additional biopsies, but false negative results are observed in patients with active or recent bleeding and in patients taking antibiotics or antisecretory compounds. If the urease test is negative, additional biopsy specimens stored in fixative can be sent for histologic examination. Culture of *H. pylori* with antibiotic-sensitivity testing is not routinely performed for the initial diagnosis of *H. pylori* infection, but it is recommended after the failure of second-line therapy.⁷⁹ Guidelines for performing antibiotic-susceptibility tests of *H. pylori* have been developed by the National Committee for Clinical Laboratory Standards.⁸⁰

Treatment of *H. pylori* Infection

The goal of *H. pylori* treatment is the complete elimination of the organism. Once this has been achieved, reinfection rates are low; thus, the benefit of treatment is durable. Clinically relevant *H. pylori*-eradication regimens must have cure rates of at least 80 percent (according to intention-to-treat analysis) without major side effects and with minimal induction of bacterial resistance. Such goals have not been achieved with antibiotics alone. Because luminal acidity influences the effectiveness of some antimicrobial agents that are active against *H. pylori*, antibiotics are combined with proton-pump inhibitors or ranitidine bismuth citrate. So-called triple therapies, combinations of one antisecretory agent with two antimicrobial agents for 7 to 14 days, have been extensively evaluated, and several regimens have been approved by the Food and Drug Administration (FDA) ([Table 1](#)).

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Table 1. FDA-Approved Treatment Options for *H. pylori* Eradication.

The combination of two or more antimicrobial agents increases rates of cure and reduces the risk of selecting for resistant *H. pylori*. The chief antimicrobial agents used in these regimens are amoxicillin, clarithromycin, metronidazole, tetracycline, and bismuth. Primary resistance to amoxicillin and tetracycline remains uncommon, but the frequency of clarithromycin resistance is now around 10 percent in most European countries and the United States and even higher in Japan.⁸¹ Metronidazole resistance ranges between 20 percent and 30 percent and is more frequent among women and among both men and women in developing countries, because of the frequent use of nitroimidazoles to treat other diseases.⁸¹ Resistance of *H. pylori* to macrolides is caused by point mutations in the 23S ribosomal RNA genes. Resistance to metronidazole is caused primarily by mutations in nitroreductase genes (*rdxA* and *frxA*) that interfere with the intracellular activation of nitroimidazoles.⁸²

First-Line Therapies

Proton-Pump-Inhibitor–Based Triple Therapies

Following the success of initial trials of proton-pump-inhibitor–based triple therapy in Italy and France, large, randomized trials confirmed the effectiveness of treatment twice daily for seven days with 20 mg of omeprazole, given either with 1 g of amoxicillin and 500 mg of

clarithromycin, or with 400 mg of metronidazole and 250 mg of clarithromycin.^{83,84,85,86} Several comparative trials have demonstrated the equivalence of 30 mg of lansoprazole twice daily, 40 mg of pantoprazole twice daily, 20 mg of rabeprazole daily, and 20 mg of esomeprazole twice daily with omeprazole in these triple therapies.^{87,88,89,90}

In a meta-analysis of 666 studies that included 53,228 patients, combinations of a proton-pump inhibitor, clarithromycin, and a nitroimidazole; a proton-pump inhibitor, clarithromycin, and amoxicillin; and a proton-pump inhibitor, amoxicillin, and a nitroimidazole were judged to be similar, with rates of cure of 78.9 to 82.8 percent according to intention-to-treat analyses.⁹¹ Increasing the dose of clarithromycin to 1.5 g per day improved rates of cure, but increasing the doses of the other antibiotics did not. In another pooled analysis, no effect of larger doses of proton-pump inhibitors was observed among the triple therapies.⁹² The duration of therapy remains controversial. In Europe, 7-day treatment is recommended,⁷⁹ whereas in the United States, 14-day courses have been found to be better than shorter courses and are approved by the FDA. In a recent meta-analysis, 14-day treatment achieved rates of cure 7 to 9 percentage points better than 7-day treatment.⁹³ Primary resistance to clarithromycin and metronidazole decreases rates of cure by 50 percent and 37 percent, respectively.⁹⁴ The indication for therapy, bacterial factors, patient compliance, and geographic differences can further affect rates of cure.⁹⁵

Ranitidine Bismuth Citrate–Based Therapies

Ranitidine bismuth citrate in dual therapy with clarithromycin for two weeks has been approved by the FDA.⁹⁶ Meta-analyses suggest that ranitidine bismuth citrate with clarithromycin and amoxicillin, or with clarithromycin and a nitroimidazole, performs as well as corresponding proton-pump-inhibitor–based therapies.^{91,97} Ranitidine bismuth citrate–based regimens may be less influenced by antibiotic resistance than their proton-pump-inhibitor–based counterparts.^{98,99} No ranitidine bismuth citrate–based triple therapy has been approved by the FDA.

Bismuth-Based Triple Therapies

Bismuth in association with metronidazole and tetracycline compares well in meta-analyses with therapies based on proton-pump inhibitors or ranitidine bismuth citrate, even if the duration of treatment is reduced to seven days.^{91,98} This inexpensive regimen remains an important option. Efficacy is negatively affected by metronidazole resistance.⁹⁸ Furazolidone, a nitrofurantoin derivative, has also been proposed for use in bismuth-based triple therapies. Triple therapy for two weeks, consisting of 100 mg of furazolidone four times daily, amoxicillin, and bismuth, was successful in 86 percent of cases. However, furazolidone, particularly when combined with bismuth for two weeks, is associated with substantial side effects. Standard bismuth-based therapy and its furazolidone-containing alternatives were recommended at the 1999 Latin American Consensus Conference.¹⁰⁰

Three regimens were recommended by the 1998 U.S. Consensus Conference⁷⁶: a proton-pump inhibitor, clarithromycin, and either amoxicillin or metronidazole for two weeks; ranitidine bismuth citrate, clarithromycin, and amoxicillin, metronidazole, or tetracycline for two weeks; and a proton-pump inhibitor, bismuth, metronidazole, and tetracycline for one to two weeks. The regimens recommended by the European Maastricht 2–2000⁷⁹ conference are a proton-pump inhibitor (or ranitidine bismuth citrate), clarithromycin, and amoxicillin or metronidazole for seven days. Because there are insufficient data for the pediatric age group,

no treatment regimen for children infected with *H. pylori* was recommended by the European Paediatric Task Force.⁷⁷ FDA-approved regimens are listed in [Table 1](#).

Second-Line Therapies

Eradication is more difficult when a first treatment attempt has failed, usually because of either poor patient compliance or the development of antibiotic resistance. Therefore, a 10-to-14-day treatment course is advocated for second-line therapies. However, the optimal strategy for retreatment after the failure of eradication has not yet been established.

Because the failure of therapy is often associated with secondary antibiotic resistance, retreatment should ideally be guided by data on susceptibility. However, such information is often unavailable, so quadruple therapies, in which a proton-pump inhibitor or an H₂-receptor antagonist is added to a bismuth-based triple regimen with high-dose metronidazole, have been suggested as optimal second-line therapy. According to a recent meta-analysis, the pooled eradication rate in 30 trials in which this strategy was tested was 76 percent.¹⁰¹ This second-line therapy was recommended at major consensus conferences,^{79,102} although it may prove disappointing, given the failure of regimens containing metronidazole.¹⁰¹

Another approach to retreatment without susceptibility testing is to prescribe a second course of proton-pump-inhibitor–based triple therapy, avoiding antimicrobial agents against which prior therapy may have induced resistance and avoiding less effective combinations, such as amoxicillin and tetracycline. If a clarithromycin-based regimen is used first, a metronidazole-based regimen should be used afterward, or vice versa. This concept is supported by pooled analysis,¹⁰¹ but prospective studies of consecutive combinations of triple therapies are needed. Alternative approaches to second-line proton-pump-inhibitor–based therapies have been reported recently, but mostly in abstract form. Rifabutin, given in association with amoxicillin and pantoprazole for 10 days, achieved an 86 percent rate of cure, even in patients with resistant strains.¹⁰³

In a pooled analysis of nine studies, retreatment with ranitidine bismuth citrate–based triple therapy yielded an 80 percent rate of cure,¹⁰¹ similar to the rates with quadruple therapies; and in a recent randomized trial, ranitidine bismuth citrate, clarithromycin, and tinidazole achieved an 81 percent rate of cure after the failure of triple therapies based on proton-pump inhibitors.¹⁰⁴ In locations where ranitidine bismuth citrate is available, triple therapies based on this compound can be used for second-line treatment.

Indications for Therapy

The National Institutes of Health Consensus Development Conference in 1994 was the first to propose generalized guidelines for the management of *H. pylori* infection. These guidelines were updated in 1997, but the most recent U.S. guidelines were prepared in 1998 by the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology.⁷⁶ Testing for *H. pylori* is recommended only if treatment is intended. Primary indications for such testing and subsequent treatment include active peptic ulcer disease, a history of documented peptic ulcer, or gastric MALT lymphoma. Testing of patients with nonulcer dyspepsia may be performed on a case-by-case basis, but it is not indicated in asymptomatic patients or in patients receiving long-term treatment with a proton-pump inhibitor for gastroesophageal reflux disease. No recommendations were issued for patients receiving only nonsteroidal antiinflammatory drugs (NSAIDs).

The recommendations issued by the more recent European Maastricht 2–2000 panel are organized in two levels and are presented in [Table 2](#).⁷⁹ Canadian and Asia–Pacific guidelines correspond largely to the Maastricht 2–2000 guidelines. The European Paediatric Task Force identified gastric and duodenal ulcer disease as indications for therapy in children. This panel agreed that there is no specific clinical picture associated with *H. pylori* in children, and that the benefit of *H. pylori* eradication in children with dyspepsia has not been established. Therefore, in children, testing for *H. pylori* is recommended only if the symptoms are severe enough to justify therapy. In populations with a high prevalence of *H. pylori*, routine screening would lead to the treatment of large numbers of children, with no demonstration of benefits as compared with risks and costs, because *H. pylori*–related ulcer disease is much less frequent in children than in adults and because therapy for the prevention of other consequences of the infection can be postponed.

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Table 2. Current Guidelines for the Treatment of *H. pylori* Infection, According to the Maastricht 2–2000 Consensus Report.

Several issues regarding indications for therapy remain unresolved. The available results suggest that subgroups of patients with nonulcer dyspepsia may benefit from the eradication of *H. pylori* infection, but clear criteria for the identification of these subgroups are lacking.⁷⁰ In dyspeptic patients who have not been evaluated by endoscopy, however, testing for *H. pylori* and treating patients with positive findings may be as effective as endoscopy-based management and may reduce costs.¹⁰⁵ The precise contribution of *H. pylori* to ulcerogenesis and to upper intestinal bleeding in users of NSAIDs remains unclear. Finally, the risk of cancer may be high in patients with nonulcer dyspepsia.⁶¹ Although more studies are needed to confirm these results, it can be argued that *H. pylori* infection should be treated in these patients on the basis of the risk of cancer alone.

Perspective

H. pylori continues to be one of the most common bacterial infections in humans. Functional genomics may fill many of the gaps in our understanding of the pathogenesis of *H. pylori* infection and accelerate the development of novel therapies, including *H. pylori*–specific antimicrobial agents. Although enormous progress has been made in studying the virulence factors of *H. pylori* and their variation, this information has not yet been used in clinical practice. Associations between bacterial characteristics and disease risks have not yet been defined sufficiently well to guide the clinician in treatment decisions. Prophylactic and therapeutic vaccination have been successful in animal models, but the translation to a human vaccine remains difficult, in part because the immunology of the stomach is still poorly understood.^{106,107} All of these developments will probably be needed to prevent and treat this infection in areas of the world where there is a high prevalence of chronic infection.

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