

Helicobacter pylori Diagnosis and Treatment Guidelines

Overview of *Helicobacter pylori*

HELICOBACTER PYLORI is one of the most common infections in humans and is associated with the development of gastritis, noncardia gastric cancer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and peptic ulcer disease.¹⁻³ The World Health Organization (WHO) has classified *H pylori* as a top carcinogen since 1994,⁴ and it is a common cause for morbidity and mortality. According to one estimate, *H pylori* affected approximately 4.4 billion people in 2015.⁵ Given that such a large portion of the global population is affected and because of the potential of *H pylori* to lead to gastrointestinal disorders, eradication is recommended for many scenarios.⁶

Cause and transmission

Although the route of *H pylori* transmission is not entirely understood, the bacterium appears to travel to its host through direct contact with another human or by way of a contaminated environment.⁴ *H pylori* infects the epithelial lining of the stomach and is most commonly acquired through interpersonal contact during childhood.^{4,5} Human-to-human transfer can be classified as vertical or horizontal. Many studies focus on vertical transmission, where *H pylori* is transferred between family members. Studies suggest that *H pylori* transfer between family members is common because family members are in close contact and can share a genetic makeup that predisposes them to *H pylori* infection. In addition, families are often exposed to a common source of infection and are often of the same socioeconomic status. In developed countries where the incidence of *H pylori* infections is low, maternal transfer to children is thought to be the primary source of infection. In countries where *H pylori* infection is common, however, maternal transfer is less likely to be the primary mode of transmission. Instead, a high prevalence of transfer appears to occur between siblings and from horizontal transmission; that is, human-to-human contact outside the household.⁴ Though all direct human-to-human transmission is thought to occur through gastro-oral, oral-oral, or fecal-oral routes, the predominant mode of transmission is unknown.⁴ *H pylori* is often present in high quantities in vomit and seems to survive in gastric juice outside the body, which suggests the prevalence of gastro-oral transmission, especially during childhood and in conjunction with poor hygienic conditions.⁴ However, *H pylori* can also colonize the mouth after vomiting or regurgitation, making saliva a possible vehicle and oral-to-oral contact a possible mode of transmission. Oral-to-oral transmission often occurs between mother and child, but it is not the main mode of transmission in adults.⁴ Furthermore, though attempts to culture *H pylori* from feces have been met with limited success, *H pylori* DNA has been found in human feces, indicating that fecal-oral transmission could be a mode of *H pylori* transfer.⁴ A final potential mode of transmission is environmental; in this, contaminated food and water are likely vehicles.⁴ Children living in homes that have an external water supply or those who consume the same raw vegetables that are often irrigated with untreated sewage water show high rates of *H pylori* infection.⁴ Effective eradication treatments can defend against these many transmission modes and prevent the long-term risks that infection presents.

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Incidence and prevalence

A systematic review and meta-analysis summarized the comprehensive global prevalence of *H pylori* infections and estimated that more than half the world's population is infected.⁵ The incidence of *H pylori* has changed over time with improvements in sanitation, but its prevalence is still high in certain areas.⁵ Africa, South America, and Western Asia are the regions where *H pylori* prevalence is highest, with rates of 70.1%, 69.4%, and 66.6%, respectively.⁵ In North America, prevalence is lower among non-Hispanic White individuals than in African Americans, Hispanics, Native Americans, Alaska Natives, and Americans of Korean or Chinese descent.⁶ *H pylori* prevalence varies depending on socioeconomic status, levels of hygiene, and race/ethnicity.⁵ High-risk groups include the elderly population, those living in poor hygienic conditions, migrants from high-prevalence areas, institutionalized individuals, and possibly people who live in rural areas.⁴ Despite advances in some regions, *H pylori* continues to present a large burden to much of the world.

Diagnosis

It is critical to establish which patients should be tested for *H pylori* because all patients with a positive test of active infection should be offered treatment.⁷ The 2017 American College of Gastroenterology (ACG) Clinical Guideline recommends that patients with active peptic ulcer disease (PUD), a history of PUD (unless previous cure of *H pylori* infection has been documented), low-grade MALT lymphoma, or a history of endoscopic resection of early gastric cancer (EGC) be tested for *H pylori* infection.⁷ A test that identifies active infection should be used for patients with a new diagnosis or a history of PUD. Such tests include urea breath tests, fecal antigen tests, or, if endoscopy is performed, mucosal biopsy-based tests. The guideline recommends that patients with a history of PUD who have been treated for *H pylori* undergo eradication testing with a urea breath test or fecal antigen test.⁷ Studies suggest that eradication of *H pylori* does not effectively prevent MALT lymphoma tumor regression, but no systematic reviews or randomized controlled trials have been performed to confirm this. Nevertheless, identifying the MALT lymphoma neoplasm remains a key indication to test for and eradicate *H pylori*.⁷ For patients under 60 years of age with uninvestigated dyspepsia and without alarm features, nonendoscopic testing should be considered; for patients who have dyspepsia and undergo upper endoscopy, testing should be conducted on gastric biopsy tissue.⁷ In a randomized study conducted in the UK, 90% of *H pylori*-positive adults who were treated for the infection achieved eradication, and a statistically significant reduction in subsequent consultations for dyspeptic complaints was also reported.⁷ No causal

relationship between *H pylori* and gastroesophageal reflux disease (GERD) has been proved; indeed, a negative association between them exists on a geographical basis, and treatment of *H pylori* infection does not improve GERD symptoms.⁷ Hence, patients with standard symptoms of GERD and no history of PUD do not need to be tested for *H pylori*. However, if patients are found to be infected, treatment should be offered.⁷ Testing should also be considered in patients taking long-term low-dose aspirin, as *H pylori* infection can cause ulcers and ulcer bleeding in this population. Eradication therapy for those who test positive could reduce ulcer bleeding.⁷ Patients beginning long-term nonsteroidal anti-inflammatory drug (NSAID) treatment, who have unexplained iron deficiency (ID) anemia, or who have idiopathic thrombocytopenic purpura (ITP) should also be tested and, if positive, offered treatment.⁷ Similar to patients taking aspirin, patients taking NSAIDs and who are positive for *H pylori* have a higher risk for developing ulcer complications.⁷ Studies report that patients with an *H pylori* infection are more likely to have ID anemia.⁷ Platelet counts may also improve after eradication of *H pylori* infection for some adults with ITP.⁷ The ACG guideline does not support routine testing and treatment of *H pylori* in asymptomatic individuals who have a family history of gastric cancer or in patients who have lymphocytic gastritis, hyperplastic gastric polyps, or hyperemesis gravidarum.⁷ The current guideline extends the list of potential patients to test for *H pylori* from the 2007 guideline, but gives no justification for universal or population-based screening in North America.⁷

Diagnostic testing methods available for *H pylori* include noninvasive and invasive techniques. Noninvasive techniques, which allow physicians to easily detect *H pylori*, include serology, urea breath testing, and stool antigen detection.⁸ Invasive techniques involve the use of endoscopy to gather gastric biopsies and include histology, culture, and rapid urease test.⁸ Serology testing is the least sensitive noninvasive technique. It has 75% to 85% sensitivity compared with greater than 95% for fecal antigen and urea breath testing. Because of this and the high rate of false positives, it is no longer recommended in the United States.⁸ Urea breath and fecal tests detect active infection, have high negative and positive predictive values, are excellent for pretreatment or posttreatment testing, and are highly specific. Disadvantages of these tests are the need for the patient to be off proton pump inhibitors (PPIs), bismuth, and antibiotics because these may inhibit *H pylori* viability.⁸ Invasive histology testing is 60% to 86% sensitive and is the costliest technique. It provides additional information on the gastric mucosa but requires immunochemistry, which increases the cost. Culture testing can also test for antibiotic sensitivity, but it has limited availability and a sensitivity of only 60%.

Finally, the rapid urease test is 80% to 95% sensitive and offers rapid testing and accurate results for patients not on PPIs. However, the test can give ambiguous results and is subject to high inter-observer bias.⁸ On account of the limitations of culturing and rapid urease testing, most invasive testing for *H pylori* is performed with routine histology and additional immunohistochemistry.⁸

The ACG Clinical Guideline recommends that patients be tested after treatment to ensure eradication of the infection. Testing should be performed using a urea breath test, fecal antigen test, or biopsy-based test at least 4 weeks after antibiotic therapy has completed and after PPI therapy has not been given for 1 to 2 weeks.⁷ Although circumstances may make additional testing impractical and providers or patients may decide that retesting is unnecessary,⁷ confirming eradication with a posttreatment test allows success rates to be defined and facilitates early detection of emerging resistance patterns. Such confirmation can prompt changes for future therapy and prevent the spread of resistance.⁸

ACG treatment guideline

The ACG treatment guideline for first-line and salvage therapies was last updated in 2017. Typically, *H pylori* is treated with 2 to 3 antibiotics and a PPI.⁷

First-line therapies

The 2017 ACG guideline outlines evidence-based, frontline treatment strategies for providers in North America. These include clarithromycin triple therapy, bismuth quadruple therapy, concomitant therapy, sequential therapy, hybrid therapy, levofloxacin triple therapy, and fluoroquinolone sequential therapy.⁷ Clarithromycin triple therapy includes treatment with a PPI, clarithromycin, and amoxicillin (metronidazole if the patient is allergic to amoxicillin). The guideline notes that, when used in North America, the treatment should last for 14 days.⁷ The success of clarithromycin triple therapy depends on the rate of clarithromycin resistance. Indeed, a 2010 meta-analysis reported an eradication rate of 22% for clarithromycin-resistant *H pylori* strains compared with 90% for clarithromycin-sensitive strains.⁷ The Maastricht/Florence consensus document published in 2012 recommended against triple therapy when the clarithromycin resistance rate exceeds 15% to 20%.⁷ At the time the ACG guidance was released in 2017, data suggested that North American resistance rates may fall within that range.⁷ The guideline noted that, should clarithromycin resistance indeed exceed 15%, clarithromycin triple therapy should be avoided.⁷

Bismuth quadruple therapy is composed of a PPI or histamine-2 receptor antagonist, bismuth, metronidazole, and tetracycline.⁷ The ACG guideline recommends giving this treatment for 10 to 14 days.⁷ Limited data exist for the

efficacy or comparative efficacy of bismuth quadruple treatment in North America, but data from around the world suggest that bismuth quadruple therapy and clarithromycin triple therapy have similar efficacy, adherence, and tolerability.⁷ Thus, in areas where clarithromycin resistance is an issue, bismuth quadruple therapy should be considered the initial treatment choice because it is not affected by clarithromycin resistance.⁷

Concomitant therapy is a first-line option for patients intolerant of bismuth⁸ and includes a PPI, amoxicillin, clarithromycin, and a nitroimidazole (tinidazole or metronidazole) given together for 3 to 10 days.⁷ Acknowledging that the efficacy of concomitant therapy had not been well studied in North America, the ACG guideline authors looked to trials from Europe, Asia, and Latin America that show that concomitant therapy has a higher intention-to-treat cure rate than clarithromycin triple therapy, with a cure rate of 90% compared with 78%, respectively.⁷ Thus, the ACG guideline recommends considering concomitant therapy as a promising treatment option with high cure rates for North America.⁷

Sequential therapy consists of a PPI plus amoxicillin for 5 days, followed a PPI, clarithromycin, and a nitroimidazole for an additional 5 days. In deciding upon the viability of sequential therapy as a first-line treatment for *H pylori* infection, the 2017 ACG guideline looked to a recent review and meta-analysis, which found the overall success rate of sequential therapy to be 84.3%. The guideline acknowledged that sequential therapy is more successful than 7 days of clarithromycin-based triple therapy, but only slightly better than 10 days of clarithromycin-based triple therapy, and not superior to 14 days of clarithromycin-based triple therapy or 10 to 14 days of bismuth quadruple therapy.⁷ Although the guideline recognized the viability of sequential therapy, it noted that sequential therapy was not superior to 14-day clarithromycin triple therapy in the North American context and that the complexity of sequential treatment makes it a less desirable first-line option on this continent.⁷

Hybrid therapy consists of 7 days of a PPI and amoxicillin followed by another 7 days of PPI, amoxicillin, clarithromycin, and a nitroimidazole.⁷ Because no randomized controlled trials had been performed in North America to evaluate the efficacy of hybrid therapy, the ACG guideline authors looked to studies from other countries to determine that its efficacy, tolerability, or adherence did not differ from that of sequential or concomitant therapies.⁷ Because of this, the ACG guideline suggests hybrid therapy as an alternative to clarithromycin triple therapy.⁷

Levofloxacin-based therapies in the first-line context include triple therapy with a PPI and amoxicillin; modified sequential therapy consisting of 5 to 7 days of a PPI, levofloxacin, and a nitroimidazole; and quadruple

therapy consisting of levofloxacin, omeprazole (a PPI), nitazoxanide, and doxycycline (LOAD therapy) given for 7 or 10 days.⁷ As with other *H pylori* therapies, the ACG guideline notes the lack of North American data regarding levofloxacin-based frontline treatments and looks to international data.⁷ Noting that levofloxacin triple therapy for 10 to 14 days may be an alternative to clarithromycin triple therapy and that fluoroquinolone-containing sequential therapy for 10 to 14 days and LOAD therapy for 7 to 10 days provide the most promising results, the ACG guideline authors nevertheless caution that fluoroquinolone resistance in North America may be even higher than clarithromycin resistance.⁷

Salvage therapies

Because 10% to 30% of first-line *H pylori* treatments fail, salvage therapy options must be considered.⁸ In its 2017 guideline, the ACG recommends that if a patient has a persistent *H pylori* infection and has been previously treated with antibiotics, the physician should avoid using the same antibiotics in future therapies.⁷ The guideline authors advise selecting the best salvage treatment from the following options based on local antimicrobial resistance data and the patient's recent exposure to antibiotics: bismuth quadruple therapy for 14 days (recommended), levofloxacin triple regimen for 14 days (recommended), concomitant therapy for 10 to 14 days (suggested), rifabutin triple regimen consisting of a PPI, amoxicillin, and rifabutin for 10 days (suggested), and high-dose dual therapy consisting of a PPI and amoxicillin for 14 days (suggested). The ACG guideline recommends against using clarithromycin triple therapy as a salvage regimen. If a patient received a first-line treatment containing clarithromycin, bismuth quadruple therapy or levofloxacin is the recommended salvage treatment option. If the patient was given bismuth quadruple therapy as the first-line treatment, they should receive clarithromycin- or levofloxacin-containing treatment regimens as salvage treatment options.⁷

Unmet Needs

Treatment guidelines discuss antibiotic resistance as it relates to *H pylori* but also could be considered to be inadvertently promoting misuse.⁹ *H pylori* is a high-priority antibiotic-resistant bacterium as defined by the World Health Organization⁹ and is included on the FDA's list of qualifying pathogens that have the potential to pose a serious threat to public health.¹⁰ In a retrospective study of patients in China, investigators evaluated the prevalence of antibiotic resistance to *H pylori* in adults with or without prior treatment for the infection, treatment-naïve children, and a general population.¹¹ Results showed high rates of resistance for metronidazole, clarithromycin,

and levofloxacin. These rates were highest for adults previously treated with antibiotics, especially metronidazole.¹¹ Portuguese investigators reviewed the resistance mechanisms of *H pylori* to clarithromycin and found many mutations in the 23S rRNA region of the isolates.¹² Because clarithromycin inhibits protein synthesis by binding to the peptidyl transferase loop of the V domain of 23S rRNA, any mutation in that RNA sequence will inhibit binding and render clarithromycin inactive.¹² Between 2006 and 2016, resistance rates were 21% to 30% for clarithromycin and levofloxacin in the United States and 10% to 20% for metronidazole in the United States and Canada.¹³ Antibiotic sensitivity is the single most important predictor of success in clinical trials for *H pylori* eradication, but antibiotic resistance to clarithromycin, metronidazole, and levofloxacin limits the success of common regimens used today.⁷

Antimicrobial sensitivity testing

Antimicrobial sensitivity testing is invaluable when deciding on the most appropriate treatment regimen for infected individuals.⁷ However, this is not a widespread practice in North America.⁶ Culture and sensitivity testing require upper gastrointestinal endoscopy, which is costly, to obtain isolates.¹⁴ In addition, *H pylori* is a microaerophile, so it requires specific conditions to grow, which makes it difficult to culture and transport.¹⁵ Nevertheless, surveillance of antibiotic resistance should be monitored over time to guide treatment.¹⁵

Costs of *H pylori*

H pylori infection is associated with the risk of peptic ulcer, gastritis, and noncardia gastric cancer.¹² It is responsible for 90% of duodenal ulcers and 70% to 90% of gastric ulcers.¹⁶ In the United States, the annual estimated health care costs associated with gastroduodenal ulcers were \$777 million in 2015. Prescription medicines accounted for \$189.6 million (24.4%) of those expenses.¹⁷ In 2014, gastritis and dyspepsia accounted for an estimated 2.8 million ambulatory care visits¹⁷ and gastritis/duodenitis resulted in more than 58,000 hospital admissions from emergency departments.¹⁷ In 2015, gastritis had a 30-day all-cause readmission rate of 14%, with a median charge of \$28,349 per index stay and \$31,111 per readmission.¹⁷ Total health care expenses related to gastritis and duodenitis were almost \$1.2 billion in 2015, including \$267 million (22.5%) for prescription medicines.¹⁷ The enormous total health care expenditures for gastrointestinal diseases contribute substantially to health care use in the United States, and costs are likely to continue to increase.¹⁷ ♦

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