Helicobacter pylori Infection: Options for Testing and Treatment

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Helicobacter pylori are helical, rod-shaped, Gram-negative bacteria that penetrate the mucous layer of the stomach to colonize the luminal surface of the gastric epithelium. Several features make these bacteria particularly suited to the harsh environment of the stomach. For example, their elevated urease activity allows them to efficiently convert urea (present in the gastric juice) to alkaline ammonia and carbon dioxide. Additionally, these bacteria have prominent flagella that help them to penetrate the thick mucosa of the stomach.

Chronic infection with *H. pylori* is widespread, occurring in approximately half of the world's population, and infection is typically acquired early in life, especially among those in lower socioeconomic groups.[1] While *H. pylori* infection results in chronic inflammation of the underlying gastric mucosa, the vast majority of infected patients do not experience any clinically significant symptoms. However, *H. pylori* infection is linked with the development of certain upper gastrointestinal diseases.

For example, 1–10% of duodenal and gastric ulcers are thought to be related to *H. pylori* infection. The inflammation associated with chronic *H. pylori* infection, which is largely located within the non–acid-secreting antral region of the stomach, causes increased gastrin release, which in turn induces excess acid secretion from the fundic mucosa and damage and ulceration of the duodenal mucosa.[2,3] Treatment and eradication of *H. pylori* infection cure duodenal or gastric ulcers in over 80% of patients.

Chronic *H. pylori* infection is also strongly associated with the development of gastric cancers, especially those distal to the gastroesophageal junction.[4] This risk is highest among patients who experience *H. pylori*–related inflammation in both the antral and fundic mucosa; this inflammation can lead to mucosal atrophy and intestinal metaplasia.[5] Whether eradication of the infection reduces the risk of gastric cancer remains unclear. Additionally, several studies have demonstrated a link between *H. pylori* infection and gastric mucosa–associated lymphoid-tissue (MALT) lymphoma.[6] Localized regression of most MALT lymphomas is typically observed with eradication of the infection.[7]

Many patients diagnosed with functional dyspepsia are found on biopsy to have *H. pylori* infection and associated inflammation. However, there is little evidence that the infection itself results in upper gastrointestinal symptoms, as *H. pylori* infection and inflammation are also common among individuals with no upper gastrointestinal symptoms. Additionally, *H. pylori* eradication therapy has minimal to no effect on symptoms in these cases.

Guidelines for Clinical Practice

Several available guidelines provide recommendations for the diagnosis and management of *H. pylori* infection. In the United States, 2 of the most widely used guidelines are those from the American College of Gastroenterology (ACG) and the Maastricht III Consensus Report.[8,9] While these guidelines are largely similar, they differ regarding a few key points.

For example, the ACG guidelines list the following criteria for *H. pylori* testing: a current or prior active gastric or duodenal ulcer (that was not previously treated with *H. pylori* eradication therapy), gastric MALT lymphoma, a history of endoscopic resection of early gastric cancer, or uninvestigated dyspepsia. The Maastricht III Consensus Report lists these same criteria but augments them with the following: gastric cancer in a first-degree relative, atrophic gastritis, unexplained iron-deficiency anemia, or chronic idiopathic thrombocytopenia purpura. Finally, the Maastricht IV Consensus Report, which was published in May 2012, also recommends testing for *H. pylori* in patients with a history of peptic ulcer prior to starting nonsteroidal anti-inflammatory drug treatment, in patients with a history of gastroduodenal ulcer who are taking aspirin, and in patients with unexplained vitamin B_{12} deficiency.[10]

The age threshold for implementing a test-and-treat strategy also differs between the 2 guidelines; the ACG guidelines recommend testing in individuals younger than 55 years, while the Maastricht III guidelines recommend testing in those younger than 45 years. However, these age thresholds vary among countries, depending on the prevalence of upper gastrointestinal cancers in different regions. Clinicians should note that these age thresholds only apply to patients without alarm symptoms; patients with dysphagia, weight loss,

evidence of gastrointestinal bleeding, or persistent vomiting require endoscopic evaluation regardless of their age. Finally, these 2 guidelines differ in terms of their recommended durations of treatment: 10–14 days in the ACG guidelines compared to 7 days in the Maastricht III guidelines.

Testing for Helicobacter pylori Infection

Because most individuals with *H. pylori* infection do not experience clinical symptoms, routine screening for this infection is not recommended. However, testing is recommended if patients meet any of the previously mentioned criteria, such as confirmed duodenal or gastric ulcers, gastric MALT lymphoma, or prior resection of early gastric cancer. Both nonendoscopic and endoscopic tests are available to test for *H. pylori* infection.

Nonendoscopic strategies include serologic tests, urea breath testing, and fecal antigen tests. Serologic testing for the presence of immunoglobulin (Ig) G antibodies directed against *H. pylori* is less expensive and more widely used than other nonendoscopic tests, but the overall sensitivity and specificity of these assays are limited, and their appropriate threshold values vary among different populations.[11] Further, serologic testing is not adequate to determine if an infection has been eradicated, as anti–*H. pylori* antibodies may persist for several months following treatment.

The urea breath test measures the amount of labeled carbon (^{13}C or ^{14}C) that is converted to carbon dioxide by the *H. pylori* urease; for this test, patients drink a solution containing labeled urea, after which the amount of labeled carbon dioxide in the breath is measured. This method is associated with a sensitivity and specificity of 95%.[12] Also, unlike IgG testing, urea breath testing can effectively determine the presence of infection following *H. pylori* eradication therapy.

Similarly, fecal antigen tests are associated with high sensitivities and specificities (especially when monoclonal antibodies are used), and these tests can be used to measure the effectiveness of eradication therapy.[13] However, both urea breath testing and fecal antigen tests may yield false-negative results if patients have been recently exposed to proton pump inhibitors, antibiotics, or bismuth preparations.

Nonendoscopic testing is suggested for patients with uninvestigated and uncomplicated dyspepsia. However, this strategy is not appropriate for patients with alarm symptoms—such as weight loss, persistent vomiting, or gastrointestinal bleeding—as endoscopic examination is warranted in these individuals. Nonendoscopic testing is also not appropriate for patients with new-onset dyspepsia who are older than 45–55 years. In a randomized trial of 294 patients with uninvestigated dyspepsia who were found to be positive for *H. pylori* infection, it was shown that 7 patients would need to receive eradication therapy in order for 1 patient to experience a benefit.[14]

Finally, endoscopic tests for *H. pylori* infection—including urease-based tests, histologic assessment, and culture—all rely on biopsy of the gastric mucosa. Urease-based tests, which measure the conversion of urea to ammonia within a biopsy specimen, are rapid and inexpensive. In most patients, urease-based endoscopic tests are highly accurate, but recent exposure to proton pump inhibitors or antibiotics may trigger a false-negative result. Alternatively, both histologic staining and culture allow for direct assessment of *H. pylori* infection, but these tests require highly trained technicians and adequate facilities.

Treatment of Helicobacter pylori Infection

A number of treatment strategies are used to manage chronic *H. pylori* infection. Standard therapy consists of 1 of 3 regimens: 7–14 days of triple therapy (with a proton pump inhibitor, amoxicillin, and clarithromycin); 10–14 days of quadruple therapy (with a proton pump inhibitor, tripotassium dicitratobismuthate, tetracycline, and metronidazole); or sequential therapy (with a proton pump inhibitor and amoxicillin on Days 1–5, followed by proton pump inhibitor therapy, clarithromycin, and tinidazole on Days 6–10). In all of these regimens, the proton pump inhibitor is administered at a healing dose twice per day, and metronidazole can be used as an alternative to amoxicillin in patients who are allergic to penicillin.

Triple therapy is the most widely used first-line therapy for *H. pylori* infection. In terms of the duration of therapy, statistically significant (but not clinically meaningful) differences have been demonstrated when 10-day or 14-day regimens were compared to 7-day regimens. Quadruple therapy is generally reserved for treatment of *H. pylori* in regions with higher rates of resistance to clarithromycin or metronidazole or for treatment of patients who are at a heightened risk of resistance to these antibiotics.

It is important to confirm effective eradication of *H. pylori* infection following therapy. As discussed above, serologic testing is not useful in this setting. Follow-up testing via urea breath testing or a fecal antigen test should be performed in patients who continue to experience dyspepsia symptoms despite *H. pylori* eradication therapy; however, not all patients require second-line therapy. Second-line therapy is appropriate for patients with a confirmed complication (ie, a duodenal or gastric ulcer, gastric cancer, or gastric MALT lymphoma), but it is not necessarily indicated for patients with functional dyspepsia.

The choice of the second-line regimen depends on which regimen was used initially, as treatment failure may be due to resistance to the antibiotic(s) included in the first-line therapy (especially resistance to clarithromycin and/or metronidazole). Culturing may be helpful to determine the antibiotic resistance profiles of difficult-to-treat strains of *H. pylori*.

Commonly, second-line therapy consists of either a 7–14-day regimen of triple therapy (including a proton pump inhibitor, amoxicillin, and metronidazole) or a 10–14-day regimen of quadruple therapy (including a proton pump inhibitor, tripotassium dicitratobismuthate, tetracycline, and metronidazole). Salvage therapies may include levofloxacin or rifabutin.

Future Research

Researchers still have several important areas to explore regarding the diagnosis and management of *H. pylori* infection. Currently, there is a lack of data from randomized trials of patients with uninvestigated dyspepsia who continue to experience symptoms following *H. pylori* eradication therapy; studies are needed to determine the best management strategy in these cases. Another important point of investigation is whether eradication of *H. pylori* infection reduces the risk of gastric cancer.

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Commentary

Current Consensus and Remaining Questions Regarding the Diagnosis and Treatment of *Helicobacter pylori* Infection

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The first key point in Kenneth E. L. McColl's article in *The New England Journal of Medicine* regards the clear indications for eradicating *Helicobacter pylori* infection.[1] As McColl notes, there is general agreement in this area between the European guidelines, published in the Maastricht III Consensus Report, and the US guidelines, published by the American College of Gastroenterology.[1-3] Both guidelines recommend *H. pylori* eradication in the following groups.

Numerous studies have clearly demonstrated that eradication of *H. pylori* infection is beneficial in patients with gastric or duodenal ulcers, both in terms of facilitating ulcer healing and, more importantly, in terms of preventing ulcer recurrence. One recent study that supports this conclusion is a multicenter, collaborative, follow-up study of 1,000 patients with *H. pylori*–related peptic ulcer bleeding.[4] All of the patients in this study underwent eradication therapy for *H. pylori* infection, and eradication was confirmed by appropriate follow-up testing. Sixty-nine percent of these patients had a duodenal ulcer, 27% had a gastric ulcer, and 4% had a pyloric ulcer. Over 2 years of follow-up, only 5 patients experienced ulcer rebleeding following *H. pylori* eradication, for a rebleeding incidence of only 0.15% per patient-year of follow-up. This study shows that *H. pylori* eradication alters the natural history of peptic ulcer disease and peptic ulcer–related complications such as bleeding.

Another group of patients who clearly benefit from eradication of *H. pylori* infection are those with mucosa-associated lymphoid tissue (MALT) lymphomas of the stomach. *H. pylori* infection has been closely linked to the pathogenesis of this type of neoplasm, and eradication of *H. pylori* has

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revolutionized the treatment of these lesions. In the past, MALT lymphomas were treated with radiation or chemotherapy, but treatment now focuses primarily on eradicating *H. pylori* infection. Among patients with low-grade MALT lymphomas, a substantial proportion of patients—upward of 70–80%—will achieve complete remission following eradication of *H. pylori* infection, and some preliminary data suggest that a subset of patients with high-grade MALT lymphomas might also benefit from eradication of *H. pylori* infection.

A third group that should receive *H. pylori* eradication therapy includes patients who have undergone endoscopic resection of early gastric cancer. Several studies from the Far East have shown that eradication of *H. pylori* infection in this population markedly diminishes the likelihood of gastric cancer recurrence.

Functional dyspepsia is perhaps the most common indication for *H. pylori* eradication in developed countries and possibly worldwide. This term describes patients who have unexplained upper abdominal pain or discomfort and normal findings on upper endoscopy. Data suggest that eradicating *H. pylori* in patients with functional dyspepsia offers a small but statistically significant benefit compared to either a short course of proton pump inhibitor (PPI) therapy or placebo. One possible explanation for the benefits of *H. pylori* eradication is that some patients with functional dyspepsia actually have peptic ulcer disease that was missed or inactive at the time of their upper endoscopy. Alternatively, it is possible that the improvements in gastritis that accompany eradication of *H. pylori* infection might lead to symptom-related benefits even in the absence of peptic ulcer disease.

While the benefits of *H. pylori* eradication in the aforementioned groups are well recognized, treatment of other groups remains controversial. For example, some interesting data suggest that idiopathic thrombocytopenic purpura may resolve in some individuals after eradication of *H. pylori* infection, but more data are needed to confirm this benefit. Another very controversial area is the potential role of *H. pylori* infection as a cause of unexplained iron-deficiency anemia, but the data in this area are inconclusive. Finally, the McColl article states that *H. pylori* infection does not play a role in gastroesophageal reflux disease (GERD), but this remains a confusing topic.[1] Some data suggest that a subset of patients with GERD symptoms may improve after eradication of *H. pylori* infection, while other studies suggest that some individuals with GERD symptoms may actually worsen after eradication of *H. pylori* infection. Most often, *H. pylori* eradication leads to no significant change in GERD symptoms. Whether patients with GERD symptoms improve, worsen, or stay the same following eradication of *H. pylori* infection probably depends to a large extent on the type of gastritis caused by the infection and its attendant effects on gastric acid secretion.

Diagnosis of Helicobacter pylori Infection

As reviewed by McColl, several tests are available that can aid in the diagnosis of *H. pylori* infection.[1] Nonendoscopic tests include serology tests, urea breath testing, and fecal antigen tests; endoscopic tests include urease-based tests, histologic assessment, and culture of biopsy samples.

Serology testing has a very good negative predictive value, but its positive predictive value is poor when used in populations with a low prevalence of *H. pylori* infection. In such areas—including most of the United States—the positive predictive value of serology testing is around 50%. Thus, physicians who use serology testing can feel fairly confident that a negative result is accurate, but a positive result is not very helpful, as there is only a 50% chance that it represents a true positive result.

Because of this limitation, physicians may want to consider using either a urea breath test or a fecal antigen test in populations with a low prevalence of *H. pylori* infection, as both of these tests have excellent positive and negative predictive values. For clinicians who choose to start with a serology test, a negative result is accurate and requires no additional testing, but a positive result should be confirmed by either a urea breath test or a fecal antigen test before offering the patient antibiotic therapy.

A final point to remember is that serologic testing is not a reliable means of proving *H. pylori* eradication. If a patient initially tests positive but later tests negative, then the latter result can be helpful. However, serologic tests can remain positive for months, even years, following successful eradication of *H. pylori* infection. For this reason, either a urea breath test or a fecal antigen test should be used when clinicians want to prove that the infection has been eradicated after a course of antibiotics. As McColl notes, testing should be done at least 4 weeks after the completion of antibiotic therapy.[1]

When to Treat Patients for Helicobacter pylori Infection

When deciding which patients to test and treat for *H. pylori* infection, clinicians need to have a clear idea as to why they are testing a particular patient and whether they are committed to treatment. If a patient has one of the aforementioned indications for *H. pylori* eradication, testing should be pursued. However, testing should not be pursued unless the clinician is prepared to offer treatment for a positive result. Once clinicians commit to testing for *H. pylori*, they are obligated to discuss the potential consequences of the infection with the patient. After hearing how *H. pylori* infection is associated with peptic ulcer disease, gastric malignancy, and dyspeptic symptoms, nearly all patients will elect to pursue treatment.

The reason I emphasize this point is that gastroenterologists are increasingly being confronted with patients who have failed an initial course of antibiotic therapy. Sometimes, patients have been given 2 or even 3 courses of antibiotic therapy in an effort to eradicate *H. pylori* infection. When dealing with such a patient, the first question to critically ask is whether the indication for eradication therapy is appropriate. For example, patients with GERD symptoms or irritable bowel syndrome symptoms are unlikely to experience benefit from *H. pylori* eradication and thus do not warrant an initial attempt at antibiotic therapy, let alone repeated attempts at treatment. A simple way to think about this situation is that the benefits of treating should always outweigh the potential risks.

Further Research

While guidelines, including the recently published Maastricht IV Consensus Report, are available to aid in the management of patients with *H. pylori* infection, further research is needed in several areas.[5] First, there is a need for large-scale, randomized, controlled trials conducted in the United States to determine the most appropriate treatment regimen for US patients with *H. pylori* infection. Concern has been growing that the first-line therapy most commonly used in the United States—standard triple therapy consisting of a PPI, clarithromycin, and amoxicillin—appears to have lost some of its effectiveness over time. One possible explanation for this trend is the growing prevalence of clarithromycin resistance among *H. pylori* strains in the United States.

Taking these trends into consideration, there has been much discussion about the potential role of sequential therapy for the treatment of *H. pylori* infection. Sequential therapy typically consists of a 5-day course of a PPI plus amoxicillin, followed by a 5-day course of a PPI, clarithromycin, and an imidazole antibiotic. Data from southern Europe and parts of Asia have suggested that sequential therapy yields significantly better eradication rates than triple therapy: Meta-analyses of randomized, controlled trials report over 90% eradication with sequential therapy compared to less than 80% with standard triple therapy.[6] In small numbers of patients for whom antimicrobial sensitivity data are available, sequential therapy appears to be particularly beneficial for patients infected with clarithromycin-resistant strains of *H. pylori*.

While studies from Italy and Taiwan have touted the benefits of sequential therapy, other recent studies have not replicated these results.[7-10] For example, a recent, very large, randomized, controlled trial conducted in 7 Latin American countries yielded different results.[7,11] The Latin American study found that a 14-day course of triple therapy performed better than a 10-day course of sequential therapy or a 5-day course of concomitant therapy (giving all 4 drugs together rather than sequentially).[7] Thus, we currently have data from Europe and the Far East suggesting that sequential therapy is more effective than triple therapy, while data from Latin America suggest that triple therapy is at least as effective, and perhaps more effective, than sequential therapy. In addition, although the recent study from Latin America found a short course of concomitant therapy to be the least effective of the 3 regimens evaluated, others have found longer courses of concomitant therapy to be highly effective for eradicating *H. pylori* infection. As the data emerge, it is growing increasingly clear that a variety of factors influence the efficacy of *H. pylori* treatment regimens, including compliance, tolerability, levels of antimicrobial resistance, and duration of therapy.

The disparity among recently published studies raises important questions as to the validity of making treatment recommendations for US patients based on data generated in other countries. Until additional treatment studies—or, at a minimum, data on antimicrobial resistance—are collected in the United States, controversy and confusion will likely remain as to which regimen is the most appropriate first-line treatment for *H. pylori* infection.

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