CLINICAL PRACTICE

Helicobacter pylori Infection

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 29-year-old man presents with intermittent epigastric discomfort, without weight loss or evidence of gastrointestinal bleeding. He reports no use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs). Abdominal examination reveals epigastric tenderness. A serologic test for *Helicobacter pylori* is positive, and he receives a 10-day course of triple therapy (omeprazole, amoxicillin, and clarithromycin). Six weeks later, he returns with the same symptoms. How should his case be further evaluated and managed?

THE CLINICAL PROBLEM

Helicobacter pylori, a gram-negative bacterium found on the luminal surface of the gastric epithelium, was first isolated by Warren and Marshall in 1983[1] (Fig. 1). It induces chronic inflammation of the underlying mucosa (Fig. 2). The infection is usually contracted in the first few years of life and tends to persist indefinitely unless treated.[2] Its prevalence increases with older age and with lower socioeconomic status during childhood and thus varies markedly around the world.[3] The higher prevalence in older age groups is thought to reflect a cohort effect related to poorer living conditions of children in previous decades. At least 50% of the world's human population has *H. pylori* infection.[2] The organism can survive in the acidic environment of the stomach partly owing to its remarkably high urease activity; urease converts the urea present in gastric juice to alkaline ammonia and carbon dioxide.[4]

Infection with *H. pylori* is a cofactor in the development of three important upper gastrointestinal diseases: duodenal or gastric ulcers (reported to develop in 1 to 10% of infected patients), gastric cancer (in 0.1 to 3%), and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma (in <0.01%). The risk of these disease outcomes in infected patients varies widely among populations. The great majority of patients with *H. pylori* infection will not have any clinically significant complications.

GASTRIC AND DUODENAL ULCERS

In patients with duodenal ulcers, the inflammation of the gastric mucosa induced by the infection is most pronounced in the non–acid-secreting antral region of the stomach and stimulates the increased release of gastrin.[5] The increased gastrin levels in turn stimulate excess acid secretion from the more proximal acid-secreting fundic mucosa, which is relatively free of inflammation.[5,6] The increased duodenal acid load damages the duodenal mucosa, causing ulceration and gastric metaplasia. The metaplastic mucosa can then become colonized by *H. pylori*, which may contribute to the ulcerative process. Eradication of the infection provides a long-term cure of duodenal ulcers in more than 80% of patients whose ulcers are not associated with the use of NSAIDs.[7] NSAIDs are the main cause of *H. pylori*–negative ulcers.

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Figure 1. *Helicobacter pylori*.
H. pylori is a gram-negative bacterium with a helical rod shape. It has prominent flagellae, facilitating its penetration of the thick mucous layer in the stomach.

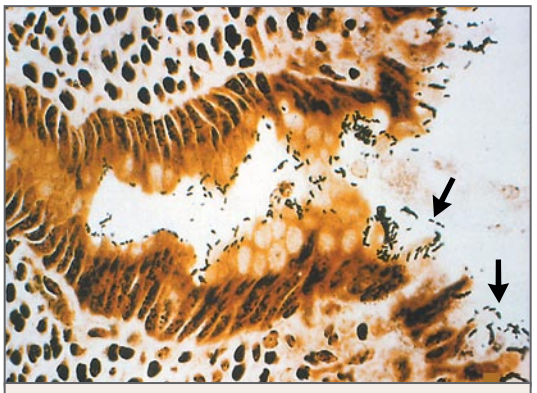

Figure 2. Gastric-Biopsy Specimen Showing *Helicobacter pylori* Adhering to Gastric Epithelium and Underlying Inflammation.
H. pylori is visible as small black rods (arrows) on the epithelial surface and within the glands. The underlying mucosa shows inflammatory-cell infiltrates.

Ulceration of the gastric mucosa is believed to be due to the damage to the mucosa caused by *H. pylori*. As with duodenal ulcers, eradicating the infection usually cures the disease, provided that the gastric ulcer is not due to NSAIDs.[8]

GASTRIC CANCER

Extensive epidemiologic data suggest strong associations between *H. pylori* infection and noncardia gastric cancers (i.e., those distal to the gastroesophageal junction).[9] The infection is classified as a human carcinogen by the World Health Organization.[10] The risk of cancer is highest among patients in whom the infection induces inflammation of both the antral and fundic mucosa and causes mucosal atrophy and intestinal metaplasia.[11] Eradication of *H. pylori* infection reduces the progression of atrophic gastritis, but there is little evidence of reversal of atrophy or intestinal metaplasia,[12] and it remains unclear whether eradication reduces the risk of gastric cancer.[13]

GASTRIC MALT LYMPHOMA

Epidemiologic studies have also shown strong associations between *H. pylori* infection and the presence of gastric MALT lymphomas.[14] Furthermore, eradication of the infection causes regression of most localized gastric MALT lymphomas.[15]

OTHER GASTROINTESTINAL CONDITIONS

At least 50% of persons who undergo endoscopy for upper gastrointestinal symptoms have no evidence of esophagitis or gastric or duodenal ulceration and are considered to have nonulcer or functional dyspepsia. In such patients, biopsy specimens of the gastric mucosa often reveal the presence of *H. pylori* and associated inflammation, although this finding is also common in persons without upper gastrointestinal symptoms. Most randomized trials of therapy for *H. pylori* eradication in patients with nonulcer dyspepsia have shown no significant benefit regarding symptoms; a few have shown a marginal benefit,[16,17] but this can be explained by the presence of unrecognized ulceration.[18] There is thus little evidence that chronic *H. pylori* infection in the absence of gastric or duodenal ulceration causes upper gastrointestinal symptoms.

The prevalence of *H. pylori* infection is lower among patients with gastroesophageal reflux disease (GERD)[19] and those with esophageal adenocarcinoma (which may arise as a complication of GERD) than among healthy controls.[20] *H. pylori*–associated atrophic gastritis, which reduces acid secretion, may provide protection against these diseases. A recent meta-analysis showed no significant association between *H. pylori* eradication and an increased risk of GERD.[21]

STRATEGIES AND EVIDENCE

CANDIDATES FOR TESTING FOR *H. PYLORI* INFECTION

Since the vast majority of patients with *H. pylori* infection do not have any related clinical disease, routine testing is not considered appropriate.[22,23] Definite indications for identifying and treating

the infection are confirmed gastric or duodenal ulcers and gastric MALT lymphoma.[22,23] Testing for infection, and subsequent eradication, also seems prudent after resection of early gastric cancers.[24] In addition, European guidelines recommend eradicating *H. pylori* infection in first-degree relatives of patients with gastric cancer and in patients with atrophic gastritis, unexplained iron-deficiency anemia, or chronic idiopathic thrombocytopenic purpura, although the data in support of these recommendations are scant.[23]

Patients with uninvestigated, uncomplicated dyspepsia may also undergo testing for *H. pylori* infection by means of a nonendoscopic (noninvasive) method[22,23,25]; eradication therapy is prescribed for patients with positive test results. The rationale for this strategy is that in some patients with dyspepsia, underlying *H. pylori*–induced ulcer disease is causing their symptoms. This nonendoscopic strategy is not appropriate for patients with accompanying alarm symptoms (e.g., weight loss, persistent vomiting, or gastrointestinal bleeding) or for older patients (≥45 or ≥55 years of age, depending on the specific set of guidelines) with new-onset dyspepsia, in whom endoscopy is warranted.[22,23,25] The nonendoscopic strategy is also not generally recommended for patients with NSAID-associated dyspepsia, since NSAIDs can cause ulcers in the absence of *H. pylori* infection.

An attraction of the test-and-treat strategy is that it avoids the discomfort and costs of endoscopy. However, because only a minority of patients with dyspepsia who have a positive *H. pylori* test have underlying ulcer disease,[26,27] most patients treated by means of the test-and-treat strategy incur the inconvenience, costs, and potential side effects of therapy without a benefit. In a placebo-controlled trial of empirical treatment involving 294 patients with uninvestigated dyspepsia and a positive *H. pylori* breath test, the 1-year rate of symptom resolution was 50% in those receiving *H. pylori*–eradication therapy, as compared with 36% of those receiving placebo ($P=0.02$)[28]; 7 patients would need to receive eradication therapy for 1 patient to have a benefit. A greater benefit would be expected if treatment were limited to patients with an increased probability of having an ulcer. However, neither the characteristics of the symptoms nor the presence of other risk factors for ulcer (e.g., male sex, smoking, and family history of ulcer disease) are particularly useful in clinical practice for identifying patients with ulcer dyspepsia and those with nonulcer dyspepsia.[29]

In randomized trials comparing a noninvasive test-and-treat strategy with early endoscopy[26,27] or with proton-pump–inhibitor therapy,[30,31] the three strategies resulted in a similar degree of symptom improvement, but early endoscopy was more expensive than the other two strategies.[32] However, the test-and-treat strategy is unlikely to be cost-effective in populations with a prevalence of *H. pylori* infection below 20%.[33] Information is lacking on the longer-term outcomes of these strategies.

TESTS FOR *H. PYLORI* INFECTION

Table 1 summarizes the various tests for *H. pylori* infection.

Nonendoscopic Tests

Serologic testing for IgG antibodies to *H. pylori* is often used to detect infection. However, a meta-analysis of studies of several commercially available quantitative serologic assays showed an overall sensitivity and specificity of only 85% and 79%, respectively.[34] The appropriate cutoff values vary among populations, and the test results are often reported as positive, negative, or equivocal. Also, this test has little value in confirming eradication of the infection, because the antibodies persist for many months, if not longer, after eradication.

The urea breath test involves drinking ^{13}C-labeled or ^{14}C-labeled urea, which is converted to labeled carbon dioxide by the urease in *H. pylori*. The labeled gas is measured in a breath sample. The test has a sensitivity and a specificity of 95%.[35] The infection can also be detected by identifying *H. pylori*–specific antigens in a stool sample with the use of polyclonal or monoclonal antibodies (the fecal antigen test).[36] The monoclonal-antibody test (which also has a specificity and a sensitivity of 95%[36]) is more accurate than the polyclonal-antibody test. For both the breath test and the fecal antigen test, the patient should stop taking proton-pump inhibitors 2 weeks before testing, should stop taking H_2 receptor antagonists for 24 hours before testing, and should avoid taking antimicrobial agents for 4 weeks before testing, since these medications may suppress the infection and reduce the sensitivity of testing.

Table 1. Tests for *Helicobacter pylori* Infection.*

Test	Advantages	Disadvantages
Nonendoscopic		
Serologic test	Widely available; the least expensive of available tests	Positive result may reflect previous rather than current infection; not recommended for confirming eradication
Urea breath test	High negative and positive predictive values; useful before and after treatment	False negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations; considerable resources and personnel required to perform test
Fecal antigen test	High negative and positive predictive values with monoclonal-antibody test; useful before and after treatment	Process of stool collection may be distasteful to patient; false negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations
Endoscopic		
Urease-based tests	Rapid, inexpensive, and accurate in selected patients	False negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations
Histologic assessment	Good sensitivity and specificity	Requires trained personnel
Culture	Excellent specificity; provides opportunity to test for antibiotic sensitivity	Variable sensitivity; requires trained staff and properly equipped facilities

* PPI denotes proton-pump inhibitor.

Endoscopic Tests

H. pylori infection can be detected on endoscopic biopsy of the gastric mucosa, by means of several techniques. The biopsy specimens are usually taken from the prepyloric region, but an additional biopsy specimen obtained from the fundic mucosa may increase the test's sensitivity, especially if the patient has recently been treated with a proton-pump inhibitor.

The urease-based method involves placement of the endoscopic biopsy specimen in a solution of urea and pH-sensitive dye. If *H. pylori* is present, its urease converts the urea to ammonia, increasing the pH and changing the color of the dye. Recommendations for avoiding proton-pump inhibitors, H_2 receptor antagonists, and antimicrobial therapy before testing apply to this test as well, to minimize the chance of false negative results.[37] The test has a sensitivity of more than 90% and a specificity of more than 95%.[35]

Another means of diagnosis involves routine histologic testing of a biopsy specimen; if there is *H. pylori* infection, the organism and associated gastritis are apparent on sections stained with hematoxylin and eosin or Giemsa. Although culturing of the organism is also possible and permits testing for sensitivity to antimicrobial agents, facilities for the culture of *H. pylori* are not widely available and the method is relatively insensitive.

TREATMENT OF *H. PYLORI* INFECTION

Various drug regimens are used to treat *H. pylori* infection (Table 2). Most include two antibiotics plus a proton-pump inhibitor or a bismuth preparation (or both). The most commonly used initial treatment is triple therapy consisting of a proton-pump inhibitor plus clarithromycin and amoxicillin, each given twice per day for 7 to 14 days. Metronidazole is used in place of amoxicillin in patients with a penicillin allergy.

The recommended duration of triple therapy is typically 10 to 14 days in the United States and 7 days in Europe.[22,23] A recent meta-analysis of 21 randomized trials showed that the rate of eradication was increased by 4 percentage points with the use of triple therapy for 10 days as compared with 7 days and by 5 percentage points with the use of triple therapy for 14 days as compared with 7 days[38] — absolute differences that are statistically significant but of marginal clinical significance.

Another possible initial therapy in areas with a high prevalence of clarithromycin-resistant *H. pylori* infection (i.e., >20%) is quadruple therapy comprising the use of a proton-pump inhibitor, tetracycline, metronidazole, and a bismuth salt for 10 to 14 days[23]; however, bismuth salts are not available in some countries. A recent meta-analysis of 93 studies showed a higher rate of eradication with quadruple therapy that included

both clarithromycin and metronidazole than with triple therapy that included both these agents in populations with either clarithromycin or metronidazole resistance.[39]

An alternative initial regimen is 10-day sequential therapy, involving a proton-pump inhibitor plus amoxicillin for 5 days followed by a proton-pump inhibitor plus clarithromycin and tinidazole for 5 more days. This regimen was reported to achieve an eradication rate of 93%, as compared with a rate of 77% with standard triple therapy, in a meta-analysis of 10 randomized trials in Italy.[40] However, in a trial in Spain, the eradication rate among patients randomly assigned to receive sequential therapy was only 84%, indicating a need to confirm its efficacy before it is used widely.[41]

CONFIRMATION OF ERADICATION

It is important to confirm the eradication of *H. pylori* infection in patients who have had an *H. pylori*–associated ulcer or gastric MALT lymphoma or who have undergone resection for early gastric cancer.[22,23] In addition, to avoid repeated treatment of patients whose symptoms are not attributable to *H. pylori*, follow-up testing is indicated in patients whose symptoms persist after *H. pylori* eradication treatment for dyspepsia. Eradication may be confirmed by means of a urea breath test or fecal antigen test; these are performed 4 weeks or longer after completion of therapy, to avoid false negative results due to suppression of *H. pylori*.[22] Eradication can also be confirmed by testing during repeat endoscopy (Table 1) for patients in whom endoscopy is required.

MANAGEMENT OF PERSISTENT INFECTION AFTER TREATMENT

Before prescribing a second course of therapy, it is important to confirm that the infection is still present and consider whether additional antimicrobial treatment is appropriate. Further attempts at eradication are indicated in patients with confirmed ulcer or gastric MALT lymphoma or after resection for early gastric cancer. However, if the initial therapy was for uninvestigated dyspepsia, which is associated with a low likelihood of underlying ulcer and symptomatic benefit from eradication, the appropriateness of further eradication therapy is unclear; data from studies designed to determine the optimal management of such cases are lacking. Options for treatment include empirical acid-inhibitory therapy, endoscopy to check for underlying ulcer or another cause of symptoms, and repeat use of the noninvasive test-and-treat strategy. The possibility that symptoms may be due to a different cause (e.g., biliary tract, pancreatic, musculoskeletal, or cardiac disease or psychosocial stress) should routinely be considered. If another course of therapy is administered to eradicate *H. pylori* infection, the importance of adherence to the treatment regimen should be

Table 2. Regimens Used to Treat *Helicobacter pylori* Infection.

Standard initial treatment (use one of the following three options)
Triple therapy for 7–14 days
PPI, healing dose twice/day*
Amoxicillin, 1 g twice/day†
Clarithromycin, 500 mg twice/day
Quadruple therapy for 10–14 days‡
PPI, healing dose twice/day*
Tripotassium dicitratobismuthate, 120 mg four times/day
Tetracycline, 500 mg four times/day
Metronidazole, 250 mg four times/day§
Sequential therapy
Days 1–5
PPI, healing dose twice/day*
Amoxicillin, 1 g twice/day
Days 6–10
PPI, healing dose twice/day*
Clarithromycin, 500 mg twice/day
Tinidazole, 500 mg twice/day§
Second-line therapy, if triple therapy involving clarithromycin was used initially (use one or the other)
Triple therapy for 7–14 days
PPI, healing dose once/day*
Amoxicillin, 1 g twice/day
Metronidazole, 500 mg (or 400 mg) twice/day§
Quadruple therapy, as recommended for initial therapy

* Examples of healing doses of proton-pump inhibitors (PPIs) include the following regimens, all twice per day: omeprazole at a dose of 20 mg, esomeprazole at a dose of 20 mg, rabeprazole at a dose of 20 mg, pantoprazole at a dose of 40 mg, and lansoprazole at a dose of 30 mg. In some studies, esomeprazole has been given at a dose of 40 mg once per day.

† If the patient has an allergy to amoxicillin, substitute metronidazole (at a dose of 500 mg or 400 mg) twice per day and (in initial triple therapy only) use clarithromycin at reduced dose of 250 mg twice per day.

‡ Quadruple therapy is appropriate as first-line treatment in areas in which the prevalence of resistance to clarithromycin or metronidazole is high (>20%) or in patients with recent or repeated exposure to clarithromycin or metronidazole.

§ Alcohol should be avoided during treatment with metronidazole or tinidazole, owing to the potential for a reaction resembling the reaction to disulfiram with alcohol use.

Table 3. Guidelines for Evaluation and Management of *Helicobacter pylori* Infection.*

American College of Gastroenterology	Maastricht III Consensus Report
Criteria for testing	
Active gastric or duodenal ulcer, history of active gastric or duodenal ulcer not previously treated for *H. pylori* infection, gastric MALT lymphoma, history of endoscopic resection of early gastric cancer, or uninvestigated dyspepsia	Same as American College of Gastroenterology criteria, with the following additional criteria: gastric cancer in first-degree relative, atrophic gastritis, unexplained iron-deficiency anemia, or chronic idiopathic thrombocytopenic purpura†
Criteria for test-and-treat strategy	
Age <55 yr and no alarm symptoms§	Age <45 yr and no alarm symptoms‡§
Duration of therapy	
10–14 Days	7 Days

* The American College of Gastroenterology guidelines are reported by Chey, Wong, and the Practice Parameters Committee of the American College of Gastroenterology[22]; the Maastricht III consensus report guidelines are reported by Malfertheiner and colleagues.[23] MALT denotes mucosa-associated lymphoid tissue.

† Eradication of *H. pylori* in patients with chronic idiopathic thrombocytopenic purpura has been reported to increase the platelet count, although the data are limited.

‡ The age cutoff varies among countries, depending on the prevalence of upper gastrointestinal cancer.

§ Alarm symptoms include dysphagia, weight loss, evidence of gastrointestinal bleeding, and persistent vomiting.

emphasized, since poor adherence may underlie the failure of initial therapy.

The choice of second-line treatment is influenced by the initial treatment (Table 2). Treatment failure is often related to *H. pylori* resistance to clarithromycin or metronidazole (or both agents). If initial therapy did not include a bismuth salt, bismuth-based quadruple therapy is commonly used as second-line therapy, with eradication rates in case series ranging from 57 to 95%.[42] Triple therapies have also been tested as second-line therapies in patients in whom initial therapy failed. A proton-pump inhibitor used in combination with metronidazole and either amoxicillin or tetracycline is recommended in patients previously treated with a proton-pump inhibitor, amoxicillin, and clarithromycin.[23,43] Clarithromycin should be avoided as part of second-line therapy unless resistance testing confirms that the *H. pylori* strain is susceptible to the drug.[44]

Patients in whom *H. pylori* infection persists after a second course of treatment and for whom eradication is considered appropriate should be referred to a specialist with access to facilities for culturing *H. pylori* and performing sensitivity testing and experience with alternative treatments for the infection. Several regimens have been reported to be effective as salvage therapy in case series. For example, retreatment after treatment failure with a triple regimen consisting of levofloxacin or rifabutin, along with a proton-pump inhibitor and amoxicillin, has been associated with high rates of eradication.[45-47] However, caution is warranted in the use of rifabutin, which may lead to resistance of mycobacteria in patients with preexisting mycobacterial infection.

AREAS OF UNCERTAINTY

Data from randomized trials are lacking to guide the care of patients whose symptoms persist after completion of *H. pylori* eradication therapy for uninvestigated dyspepsia. The effect of eradication of *H. pylori* infection on the risk of gastric cancer is unclear but is currently under study.

GUIDELINES

The American College of Gastroenterology guidelines[22] and the Maastricht guidelines[23] differ slightly in their recommendations for testing and treatment of *H. pylori* infection (Table 3).

CONCLUSIONS AND RECOMMENDATIONS

The noninvasive test-and-treat strategy for *H. pylori* infection is reasonable for younger patients who have upper gastrointestinal symptoms but not alarm symptoms, like the patient in the vignette. Noninvasive testing can be performed with the use of the urea breath test, fecal antigen test, or serologic test; the serologic test is the least accurate. Triple therapy with a proton-pump inhibitor, clarithromycin, and amoxicillin or metronidazole remains an appropriate first-line therapy, provided that there is not a high local rate of clarithromycin resistance. Recurrence or persistence of symptoms after eradication therapy for uninvestigated dyspepsia is much less likely to indicate that treatment has failed than to indicate that the symptoms are unrelated to *H. pylori* infection. Further eradication therapy should not be considered unless persistent *H. pylori* infection is confirmed. Data are lacking to inform the op-

timal management of recurrent or persistent dyspepsia after noninvasive testing and treatment of *H. pylori* infection. Options include symptomatic acid-inhibitory therapy, endoscopy to check for underlying ulcer or another cause of symptoms, and repeat of the *H. pylori* test-and-treat strategy; other potential reasons for the symptoms should also be reconsidered.

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