CLINICAL PRACTICE

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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 32-year-old woman who emigrated from Eastern Europe is evaluated for persistent epigastric pain and bloating. Previous assessments showed a normal complete blood count and comprehensive metabolic panel and a negative result on serologic testing for celiac disease. Serum testing for *Helicobacter pylori* IgG was positive. She was treated with 20 mg of omeprazole, 1 g of amoxicillin, and 500 mg of clarithromycin, each taken twice daily for 10 days, but her symptoms persisted. How would you further evaluate and treat this patient?

THE CLINICAL PROBLEM

Helicobacter pylori infection is a common, usually lifelong, infection that is found worldwide.[1] Studies suggest that infection rates vary according to geographic region, but the number of infected people has persisted or even increased over the past three decades because of population growth and because of reinfection and recrudescence due to unsuccessful eradication.[2] A less advantaged socioeconomic status is a risk factor for *H. pylori* infection[2] because it is associated with more crowded living conditions that favor intrafamilial transmission.[3] Iatrogenic infection by means of endoscopes also occurs.[4]

Although the majority of infected persons remain asymptomatic, infection has been directly linked to several conditions — in particular, peptic ulcer disease and nonulcer dyspepsia. Evidence (reviewed below) has shown that treatment to eradicate *H. pylori* can reduce the risks of both conditions,[5-7] although the data are less consistent regarding nonulcer dyspepsia.

Gastric cancer has also been closely associated with the presence of *H. pylori*. In a study conducted in Japan, gastric cancer developed (over a mean follow-up of 7.8 years) in 2.9% of patients with peptic ulcer, dyspepsia, or gastric hyperplasia who had *H. pylori* infection, whereas no cases were detected in uninfected patients with these conditions.[8] On the basis of compelling evidence, the World Health Organization (WHO) has classified *H. pylori* as a group 1 carcinogen leading to gastric adenocarcinoma.[9,10] In addition to Japan, areas with an increased incidence of gastric carcinoma attributable to this infection include the Middle East, Southeast Asia, the Mediterranean, Eastern Europe, Central America, and South America. Immigrants who grew up in regions of the world with a high incidence of *H. pylori* infection (e.g., Eastern Europe and East Asia) and who now reside in the United States or Western Europe are also at increased risk for gastric cancer. Another neoplastic disease that is caused by chronic *H. pylori* infection is gastric mucosa–

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This article was updated on March 21, 2019, at NEJM.org.

N Engl J Med 2019;380:1158-65.
DOI: 10.1056/NEJMcp1710945

An audio version of this article is available at NEJM.org

KEY CLINICAL POINTS

***HELICOBACTER PYLORI* INFECTION**

- Testing for *H. pylori* is recommended in patients with peptic ulcer disease, gastric cancer, or gastric mucosa–associated lymphoid tissue lymphoma (MALToma). Other recommended indications for testing include dyspepsia, prolonged use of nonsteroidal antiinflammatory drugs or aspirin, unexplained iron-deficiency anemia, and immune thrombocytopenia.
- Testing for *H. pylori* can be performed directly on biopsy specimens obtained during endoscopy or performed by means of the stool antigen test or urea breath test. Proton-pump inhibitors (PPIs) interfere with the detection of bacteria and must be discontinued before any testing is performed.
- Several regimens are considered to be acceptable for initial treatment. The presence of an allergy to penicillin, previous exposure to macrolides, and high levels of macrolide resistance where the patient lives or has lived (if information is known) are relevant in choosing a regimen.
- After treatment, it is essential to document clearance of the infection, typically by means of a stool antigen test or urea breath test performed 1 month after the completion of antibiotic therapy (again, while the patient is not taking a PPI).
- Should retreatment be indicated, a different regimen that avoids repetitive use of the same antibiotic agents is recommended.

associated lymphoid tissue lymphoma (MALToma) — a condition that is much less common than peptic ulcer disease or gastric adenocarcinoma.[11]

Conditions outside the gastrointestinal tract have also been associated with *H. pylori* infection. An observed association with coronary artery disease probably reflects shared risk factors, such as poverty and suboptimal nutrition. Unexplained iron-deficiency anemia[12] and immune thrombocytopenia[13] have been associated with *H. pylori* infection; although the pathogenesis is not well understood, reports of successful treatment of *H. pylori* infection leading to an increased hemoglobin level or higher platelet count suggest causal relationships (see below).

STRATEGIES AND EVIDENCE

SCREENING AND DIAGNOSIS

Indications for screening for *H. pylori* (and for treatment if screening is positive) are reviewed in Table 1.[14-16] Direct (invasive) histologic testing of gastric mucosal biopsy samples is used for the diagnosis of *H. pylori* infection in patients with indications for endoscopy, such as epigastric pain, weight loss, iron-deficiency anemia, and dyspepsia with alarm symptoms (e.g., weight loss, severe abdominal pain, dysphagia, vomiting, gastrointestinal bleeding, and others), or in patients 60 years of age or older.[14] If a person is from a region with a greater incidence of infection and gastric cancer, this testing should be done at a younger age as guided by local recommendations (e.g., <35 years of age in China).[18] Direct testing is also recommended in patients with long-term use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs) for whom endoscopy is indicated; this ensures that the management of NSAID-induced peptic ulcer disease is not complicated by the infection.

Histologic detection of *H. pylori* in gastric tissues has a sensitivity and specificity that can exceed 95%; however, proper sampling and interpretation are required. Endoscopy is also used to determine eradication of infection but is usually repeated only in the context of persistent ulcers, to confirm healing of a gastric ulcer, or after the removal of early gastric cancer or MALToma.

Noninvasive testing is recommended in patients for whom endoscopy is not indicated but who have conditions associated with the infection (e.g., history of peptic ulcer disease, unexplained iron-deficiency anemia, or immune thrombocytopenia) or who are considered to be at increased risk for infection or complications of infection (e.g., patients with long-term use of NSAIDs or aspirin) (Table 1).[19,20] In the United States, prevalence varies regionally and according to ethnic group or socioeconomic status.[16]

Noninvasive tests for active infection include the stool antigen test and urea breath test. Stool antigen testing, which involves a mixture of monoclonal antibodies against *H. pylori*, is used for initial diagnosis and for confirming eradication of the infection[21]; the sensitivity and specificity of stool antigen tests typically exceed 92%.[22,23] Urea breath tests involve the ingestion of either ^{14}C-labeled or ^{13}C-labeled urea; if *H. pylori*

Table 1. Indications for Testing for *Helicobacter pylori* Infection, According to Guidelines.*

Active peptic ulcer disease or a history of peptic ulcer disease, unless *H. pylori* has been eradicated
Low-grade gastric mucosa–associated lymphoid tissue lymphoma (MALToma) or a history of endoscopic resection of early gastric cancer
Uninvestigated dyspepsia, with noninvasive testing in patients <60 yr of age who do not have alarm symptoms (e.g., weight loss, severe abdominal pain, dysphagia, vomiting, gastrointestinal bleeding, and others), but esophagogastroduodenoscopy is recommended in patients ≥60 yr of age or if alarm symptoms are present
Long-term aspirin use
Long-term NSAID use
Unexplained iron-deficiency anemia after thorough evaluation for other causes
Immune thrombocytopenia in adults
Completion of treatment for documented *H. pylori* infection in order to confirm eradication; testing should be performed ≥30 days after the completion of treatment and while the patient is not taking a PPI

* Guidelines are from the American College of Gastroenterology (ACG)[14] and the Maastricht V–Florence Consensus.[15] Other indications for testing have been suggested, including various demographic features that have been associated with increased risk — such as a family history of gastric cancer, status of being a first-generation immigrant from an area with high prevalence of *H. pylori* infection, and black race or Hispanic ethnic group[16] — and long-term use of a proton-pump inhibitor (PPI).[15,16] The indication regarding PPIs is based on observational studies that have shown an increased risk of atrophic gastritis, a precursor of gastric cancer, in association with long-term use of PPIs.[17] Anyone with the indications for testing who has a positive test result should be treated; after the completion of treatment, eradication should be confirmed, according to the adage "Test. Treat. Test." NSAID denotes nonsteroidal anti-inflammatory drug.

is present, bacterial urease releases the label, which is measured and compared with a baseline value. This test has a sensitivity and specificity typically exceeding 95%.[23] In addition, the ^{14}C-labeled substrate involves an unstable isotope that undergoes radioactive decay, but such isotopes are used diagnostically for several conditions and carry no restrictions for use in adults other than pregnancy.[24] The 2017 guidelines of the American College of Gastroenterology (ACG)[14] and the Houston Consensus[16] do not recommend either test preferentially, but both note the substantially lower cost of stool antigen testing. In contrast, the Maastricht V–Florence guidelines[15] recommend the urea breath test over stool antigen testing because of its somewhat greater accuracy for detecting infection. All strongly recommend confirming eradication by means of the stool antigen test or urea breath test (Table 1).

Although proton-pump inhibitors (PPIs) are not effective antimicrobial agents, they have suppressive effects on *H. pylori* and therefore should be discontinued before testing for infection and before confirming eradication by means of any testing method. Recommendations in the United States advise that patients discontinue PPIs and antibiotic agents for 30 days[25,26] before testing, whereas the Maastricht V–Florence guidelines recommend that these agents should be discontinued for only 2 weeks. The use of histamine H_2-receptor blockers does not need to be restricted and is recommended for the management of heartburn or dyspepsia during the testing window.

Serologic testing for *H. pylori* IgG is no longer recommended for the diagnosis of infection in areas in which the prevalence is 30% or less[27]; the current prevalence in the United States is estimated to be 30%. Because antibodies persist for several years, serologic testing for *H. pylori* IgG has a specificity of less than 80% for active *H. pylori* infection,[23] and repeat serum IgG testing is not useful for assessing eradication. Tests for antigen-specific IgA, IgG, and IgM in blood, urine, and saliva are no longer recommended because they lack meaningful predictive value.

TREATMENT

BENEFITS REGARDING ASSOCIATED DISEASES

Evidence to support benefits of treatment of *H. pylori* infection for the conditions for which screening is recommended derives from randomized trials and observational studies. A Cochrane review of randomized trials showed that the addition of a therapy designed to eradicate *H. pylori* in patients who tested positive for this infection led to a lower incidence of duodenal ulceration (in 34 trials) or gastric ulceration (in 12 trials) than no treatment.[28] The numbers of patients who would need to be treated for *H. pylori* infection in order to prevent a recurrent duodenal or gastric ulcer were 2 and 3, respectively. In another meta-analysis of clinical trials, the number of patients with *H. pylori* infection who would need to be treated for dyspepsia (number needed to treat, 13) was greater than that for peptic ulcer disease.[6]

Studies have compared the prevalence of infection and deaths from gastric cancer before and after the Japanese government began a program to test for and treat *H. pylori* infection in 2013.[29,30] After the initiation of the program, the number of treated patients in Japan more than

doubled, to approximately 1.5 million per year, while the number of deaths from gastric cancer steadily declined from 50,000 to 45,000 per year.[30] An observational study in Hong Kong showed a significantly lower incidence of gastric cancer among patients older than 60 years of age who had received treatment to eradicate *H. pylori* infection than the expected number of cases in the general population.[31] In a randomized, double-blind, placebo-controlled trial in South Korea, patients with early gastric cancer who received treatment for *H. pylori* infection had lower rates of metachronous gastric cancer after a median of 5.9 years than those who received placebo.[32]

Early-stage MALToma (type I or II) is effectively treated with antibiotics to eradicate *H. pylori* infection. However, the treatment of more advanced stages of MALToma typically also involves surgery, radiation, chemotherapy, or a combination of these interventions.[33]

Randomized trials have shown that screening and treatment for *H. pylori* infection in persons who are starting or taking long-term NSAID therapy reduces the risk of peptic ulcer disease.[34] Although data from randomized trials have not confirmed similar benefits in persons taking low-dose aspirin, observational data showing a higher risk of bleeding in the upper gastrointestinal tract among aspirin users who have *H. pylori* infection than among those who do not have the infection underlie recommendations for a similar strategy in this group.

Data from randomized trials have shown increases in the hemoglobin level after eradication of *H. pylori* infection.[35] However, a recent retrospective, single-center study showed no association between unexplained iron-deficiency anemia and *H. pylori* infection in populations of older patients who did not have peptic ulcer or clinically meaningful upper gastrointestinal bleeding.[36] Regarding immune thrombocytopenia, evidence to support screening for and treatment of *H. pylori* infection is largely limited to observational studies that have shown increased platelet counts with treatment; one small, randomized trial also suggested benefit.[13]

TREATMENT REGIMENS

The ACG guidelines support the use of any of the seven antimicrobial regimens listed in Table 2 as a first-line treatment.[14] Guidelines recommend that decisions regarding therapy routinely take into account whether the patient has had any previous exposure to macrolide antibiotics (e.g., clarithromycin, azithromycin, and erythromycin) and whether the patient has an allergy to penicillin. Because most patients with self-described beta-lactam "allergy" do not have a true allergy,[14] skin testing should be performed so that amoxicillin-containing regimens can be a treatment option if testing is negative. Other factors in decision making include other allergies, potential adverse reactions (e.g., gut symptoms and also tendinitis with fluoroquinolones, which is a particular concern in older men), costs, insurance coverage, and availability.

Treatment with clarithromycin combined with amoxicillin and a PPI is listed first among the ACG recommendations for patients with no history of antibiotic treatment for the infection. This regimen is also recommended by the Maastricht V–Florence Consensus, assuming that the level of clarithromycin resistance where a patient lives (or has lived) is less than 15%.[15]

Another commonly used regimen includes bismuth, tetracycline, metronidazole, and a PPI (i.e., bismuth-based quadruple therapy).[39] This regimen was the standard treatment in the early 1980s but was then largely replaced by the simplified clarithromycin-based triple-therapy regimen. Guidelines recommend the use of bismuth-based quadruple therapy for 10 to 14 days.[15,37] A randomized trial comparing bismuth-based quadruple therapy with clarithromycin-based triple therapy showed no significant difference in the percentages of patients in whom *H. pylori* was eradicated (87.7% and 83.2%, respectively)[40]; the percentages of patients who adhered to treatment and who had adverse events also appear to be similar in the two groups. Doxycycline is not considered to be as effective as tetracycline in the treatment of *H. pylori* infection.[41]

Because resistance to clarithromycin has increased in many parts of the world, the bismuth-based regimen is commonly used. Appropriate candidates for this regimen include persons who have been exposed to a macrolide, have allergy to penicillin, or both; clarithromycin-based triple therapy can also be used in such patients if amoxicillin is replaced with metronidazole. In patients with macrolide exposure and penicillin allergy, the bismuth-based regimen is essentially the only option. If the first two regimens fail, testing for antimicrobial resistance could be

Table 2. Evidence-based Treatment Regimens for *H. pylori* Infection in North America, Listed in Recommended Order.*

Treatment Type	Components	Duration	Comments†
		days	
Clarithromycin-based triple therapy‡	PPI, clarithromycin, and amoxicillin (twice daily for all antibiotics)	14	Recommended unless patient has documented allergy to ampicillin or high level of clarithromycin resistance
Bismuth-based quadruple therapy (Pylera‡)	PPI, bismuth, tetracycline, and nitroimidazole (four times daily for all antibiotics)	10–14	Recommended if patient has high level of clarithromycin resistance or history of macrolide use
Concomitant therapy	PPI, clarithromycin, amoxicillin, and nitroimidazole (twice daily for all antibiotics)	10–14	Not appropriate in patient with high level of clarithromycin resistance or documented allergy to ampicillin
Sequential therapy	PPI and amoxicillin; then PPI, clarithromycin, and nitroimidazole (twice daily for all antibiotics)	7, then 7	Not appropriate in patient with high level of clarithromycin resistance or documented allergy to ampicillin
Hybrid therapy	PPI and amoxicillin; then PPI, amoxicillin, clarithromycin, and nitroimidazole (twice daily for all antibiotics)	7, then 7	Not appropriate in patient with high level of clarithromycin resistance or documented allergy to ampicillin
Levofloxacin-based triple therapy	PPI, levofloxacin (once daily), and amoxicillin (twice daily)	10–14	Not appropriate in patient with documented allergy to ampicillin
Fluoroquinolone-based sequential therapy	PPI and amoxicillin; then PPI, levofloxacin, and nitroimidazole (twice daily for all antibiotics)	5–7, then 5–7	Complicated with regard to treatment adherence; not appropriate in patient with documented allergy to ampicillin

* The evidence-based treatment regimens for *H. pylori* infection in North America (according to the Toronto Consensus[37]) are listed in the order of recommendation that appears in the ACG 2017 guidelines.[14] PPIs are to be administered twice daily in all seven first-line treatment recommendations, and the recommended doses are as follows: omeprazole, 20 mg; esomeprazole, 20 mg or 40 mg; lansoprazole, 30 mg; dexlansoprazole, 30 mg or 60 mg; pantoprazole, 40 mg; and rabeprazole, 20 mg.[14,37] The recommended doses of the other agents are as follows: clarithromycin, 500 mg; amoxicillin, 1 g; bismuth, 120 to 300 mg (available in various formulations); tetracycline, 500 mg; nitroimidazole, 500 mg; metronidazole (a nitromidazole drug), 500 mg; and levofloxacin, 500 mg.[37,38]

† Adverse effects of all antibiotic agents include candidiasis, *Clostridium difficile* infection, and allergic reaction. Adverse effects that are particular to specific components of the regimens include the following: for clarithromycin, abnormal taste in the mouth; for metronidazole, gastrointestinal symptoms, metallic taste, rare neurologic side effects (particularly at high doses), possible disulfiram-like reaction in patients drinking alcohol (if used repeatedly or for prolonged courses), and accumulation in fetal bones and teeth when administered to pregnant women; for levofloxacin, gastrointestinal symptoms, central nervous system toxic effects (Food and Drug Administration [FDA] black-box warning about risks of delirium, memory impairment, disorientation, agitation, and disturbances in attention), tendinitis and tendon rupture, and QT prolongation (and this drug should be avoided in persons with myasthenia gravis); and for rifabutin (which is not a first-line treatment and is not typically prescribed by primary care physicians and many gastroenterologists), reversible myelotoxic effects and potential for increased prevalence of rifabutin-resistant mycobacteria. Adverse effects of long-term PPI use include an increased risk of *C. difficile* infection, microscopic colitis, kidney disease, pneumonia, dementia, atrophic gastritis, and malabsorption of iron, magnesium, calcium, and vitamin B_{12}.

‡ This therapy has been approved by the FDA.[14]

considered (although such testing is not readily available in the United States) or one of the other five recommended treatment regimens could be used (Table 2).

STRATEGIES TO ADDRESS ANTIMICROBIAL RESISTANCE

Guidelines in the United States have suggested that clarithromycin-containing regimens not be used when the level of clarithromycin resistance is more than 25%, but in the United States, there is a lack of broadly applicable data to inform local resistance patterns. A recent meta-analysis of 178 studies, which involved more than 66,000 isolates from all WHO regions, assessed the prevalence and trends in *H. pylori* resistance to commonly prescribed antibiotics.[42] Rates of primary and secondary resistance to clarithromycin, metronidazole, and levofloxacin were 15% or more in all regions, except for primary clarithromycin resistance in the Americas (10%) and Southeast Asia (10%) and primary levofloxacin resistance in Europe (11%). The prevalence of primary combined resistance to both clarithromycin and metronidazole was 19% in the Eastern Mediterranean region but less than 10% in

other regions. Primary resistance to amoxicillin and tetracycline was below 15% in all regions. Antibiotic resistance rates were heterogeneous across countries within the various regions and were generally lower among children and higher among adults; in most regions, there appeared to be increases in resistance over time (from the 2006–2008 period to the 2012–2016 period). For all the antibiotics, there were significant associations between eradication treatment failure and resistance detected before treatment.

A recent observational study showed that only 35% of patients who had been treated for *H. pylori* infection underwent follow-up testing to confirm eradication and that many patients who had treatment failure were retreated with the same regimen.[43] It is critical to test for eradication after treatment is completed and to use a different regimen when eradication failure is documented.[42] One randomized trial showed that regimens with rifabutin were effective rescue therapies in patients with treatment failure who had *H. pylori* infection that was resistant to both metronidazole and clarithromycin.[44]

AREAS OF UNCERTAINTY

Data are needed to inform strategies to improve adherence to the multidrug regimens needed for eradication. Some data, including results of a small, randomized, placebo-controlled trial, suggest that probiotics can reduce the incidence and severity of side effects of antibiotic regimens.[45,46]

More data are needed from observational trials of treatment for *H. pylori* infection in regions in which there is a high prevalence of infection and an increased incidence of gastric cancer. Such findings would help us to better assess the effects of eradication therapy on the risk of gastric cancer.

Strategies are needed to assess *H. pylori* antibiotic resistance effectively in practice in various areas of the United States. Efforts to develop a vaccine against *H. pylori* could facilitate eradication worldwide, but thus far such efforts have been unsuccessful.[47]

In Japan, vonoprazan, an oral potassium-competitive acid blocker, has been used in place of a PPI in treatment regimens for *H. pylori* infection. This agent has shown effectiveness that is similar to or greater than that with a PPI when it was used with antibiotics for the eradication of *H. pylori*.[48,49] Further study is needed to assess whether this approach will be as effective against heterogeneous strains in different regions.

GUIDELINES

All the recommendations discussed above are consistent with the ACG guidelines for the evaluation and treatment of *H. pylori* infection. An important recommendation in the 2017 ACG guidelines,[14] which represented a considerable change from the 2007 guidelines,[23] was that all infected persons should be treated and then retested to assess for successful eradication.[14] Although the recommendations of other guidelines are generally similar, they vary somewhat in view of regional differences in drug availability, antimicrobial resistance, and rates of gastric cancer.[14-16,37,50] For example, in regions that have a higher incidence of infection and earlier onset of gastric cancer, testing is suggested at a younger age, before preneoplastic changes arise.[50] The Toronto Consensus recommended that all treatment regimens be administered for 10 to 14 days,[37] and the ACG[14] and Maastricht V–Florence Consensus[15] guidelines followed this recommendation. The Houston Consensus Conference on testing for *H. pylori* infection in the United States proposed additional groups to be tested, including persons with a family history of gastric cancer, first-generation immigrants who had lived in areas with high prevalence of *H. pylori* infection, and black or Hispanic patients.[16]

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette received a diagnosis of *H. pylori* infection that was made on the basis of IgG serologic testing. More-specific testing, with the use of stool antigen or urea breath testing, would have been preferred to determine whether she had active infection. She initially received a clarithromycin-based treatment, which did not ameliorate her symptoms.

Because of cost and ease, I would recommend a stool antigen test to confirm the presence of active infection and the failure of the clarithromycin-based treatment. If the test results are positive, a different treatment regimen would be indicated. Failure of the initial clarithromycin-based regimen would not be surprising because

the patient is from Eastern Europe, an area that has a clarithromycin resistance level of 15 to 40%.[42] I would recommend treatment with bismuth-based quadruple therapy for 10 to 14 days, with a subsequent test performed 4 weeks after the completion of treatment (including the use of a PPI) to confirm eradication.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I am indebted to Drs. Guido Tytgat, David Y. Graham, and Richard H. Hunt and to many others for their pioneering work in the field of *Helicobacter pylori* and for providing inspiration to many of us who follow their guidance; and to Dr. Peter Ernst for editing assistance on an earlier version of the manuscript.

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