Practice Guidelines

H. pylori Infection: ACG Updates Treatment Recommendations

Key Points for Practice

- Testing for *Helicobacter pylori* is indicated for certain conditions, such as peptic ulcer disease, and it should be treated in any patient who tests positive.
- Patients should be asked about previous antibiotic exposure to help guide the treatment regimen and avoid failures because of resistance.
- A urea breath test, fecal antigen testing, or biopsy-based testing should be used to determine treatment success.

From the *AFP* Editors

***Helicobacter pylori* infection** is one of the most common chronic bacterial infections. The American College of Gastroenterology (ACG) has updated its clinical guidelines in response to significant scientific advances in the management of this disease.

Because there is a lack of randomized controlled trials in North America (defined as the United States and Canada in this guideline) that assess modern treatment regimens, the ACG's treatment recommendations mostly rely on clinical trial data generated in other parts of the world. These treatment recommendations are based on a series of questions.

What Is Known About the Epidemiology of *H. pylori* Infection in North America? Which Are the High-Risk Groups?

H. pylori infection usually occurs during childhood, although the means of acquisition is unclear. Risk factors include low socioeconomic status; increased number of siblings; and having an infected parent, particularly a mother. The incidence and prevalence of the disease are generally higher among persons born outside of North America. Within North America, it is more common in immigrants and in certain racial groups. (in general, the prevalence is lower among non-Hispanic whites than among other groups such as blacks, Hispanics, Native Americans, and Alaska Natives).

What Are the Indications for *H. pylori* Testing and Treatment?

Testing for *H. pylori* is indicated in certain patients. Any patient who tests positive for *H. pylori* infection should be treated.

All patients with active or previous peptic ulcer disease should be tested for *H. pylori* infection unless there is documentation that the infection was previously cured. Patients with low-grade gastric mucosa–associated lymphoid tissue lymphoma or a history of endoscopic resection of early gastric cancer should also be tested. Testing in patients with gastroesophageal reflux disease is not recommended unless the patient has a history of peptic ulcer disease or dyspepsia. If a patient with gastroesophageal reflux disease is tested and found to have *H. pylori* infection, treatment should be offered with the acknowledgment that symptoms of gastroesophageal reflux disease are unlikely to improve.

Based on low-quality evidence, the ACG also recommends testing for those initiating long-term nonsteroidal anti-inflammatory drug therapy, those with unexplained iron deficiency anemia, and adults with idiopathic thrombocytopenic purpura.

Ideally, tests that identify active infection, such as a urea breath test, fecal antigen test, or endoscopic biopsy, should be used in the diagnosis of *H. pylori* infection. However, because the pretest probability of infection is higher in patients with documented peptic ulcer disease, immunoglobulin G antibody testing is acceptable in these patients. Nonendoscopic testing is an option in patients younger than 60 years with uninvestigated dyspepsia without red flags. If endoscopy is used in patients with dyspepsia, gastric biopsies should be performed.

There is insufficient evidence to make a recommendation about testing and treatment in asymptomatic patients with a family history of gastric cancer or in patients with lymphocytic gastritis, hyperplastic gastric polyps, or hyperemesis gravidarum.

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This series is coordinated by Sumi Sexton, MD, Associate Deputy Editor.

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Author disclosure: No relevant financial affiliations.

What Are Evidence-Based First-Line Treatment Strategies for Clinicians in North America?

H. pylori is typically treated with a combination of antibiotics plus a proton pump inhibitor (PPI). Patients should be asked about previous antibiotic exposure to help guide the treatment regimen. There is no regimen with a 100% cure rate for *H. pylori* infection, and there are few, if any, regimens with a 90% cure rate. The authors used the terms recommended and suggested to express their preferences.

RECOMMENDED

Clarithromycin triple therapy consists of a PPI, clarithromycin (Biaxin), and amoxicillin or metronidazole (Flagyl) for 14 days. The effect of *H. pylori* resistance to clarithromycin is well documented. Clarithromycin should be avoided in locations where resistance is greater than 15% and in patients with any previous macrolide exposure.

Bismuth quadruple therapy consists of a PPI, bismuth, tetracycline, and a nitroimidazole for 10 to 14 days. It may be a particularly good option in patients with macrolide exposure or who are allergic to penicillin. Although metronidazole resistance impacts the effectiveness of this regimen, it is not nearly as profound as with clarithromycin triple therapy. Bismuth quadruple therapy should be strongly considered as first-line treatment where clarithromycin resistance is high or in patients with any previous macrolide exposure.

Concomitant therapy consists of a PPI, clarithromycin, amoxicillin, and a nitroimidazole (tinidazole [Tindamax] or metronidazole) for 10 to 14 days. This regimen is a promising option that has been shown in international studies to be at least as effective as clarithromycin triple therapy with similar tolerability. Limited data show that the effects of clarithromycin resistance with this regimen are less than with clarithromycin triple therapy. A duration of 10 to 14 days seems appropriate, although studies to assess whether extending therapy to 14 days improves eradication are ongoing.

SUGGESTED

Sequential therapy consists of a PPI and amoxicillin for five to seven days followed by a PPI, clarithromycin, and a nitroimidazole for five to seven days. Although 10 days of sequential therapy appears to be a viable alternative to 14 days of clarithromycin triple therapy, 10 days of sequential therapy has not been shown to be superior to 14 days of clarithromycin triple therapy. Extending sequential therapy to 14 days may improve eradication rates, but more studies are needed. The complexity of sequential therapy may limit its use.

Hybrid therapy, a cross between sequential and concomitant therapies, consists of a PPI and amoxicillin for seven days followed by a PPI, amoxicillin, clarithromycin, and a nitroimidazole for seven days. This regimen is a promising option that has been shown in international studies to be at least as effective as clarithromycin triple therapy with similar tolerability. Although randomized controlled trials showed hybrid therapy to be similar to concomitant therapy, the complexity of hybrid therapy may limit its use.

Levofloxacin triple therapy consists of a PPI, levofloxacin (Levaquin), and amoxicillin for 10 to 14 days. Levofloxacin is a fluoroquinolone with in vitro antimicrobial activity against gram-positive and gram-negative bacteria, including *H. pylori*. The few data that exist suggest that fluoroquinolone resistance may be as high, if not higher, than clarithromycin resistance in North America. There is also a lack of data regarding the impact of fluoroquinolone resistance on treatment. Levofloxacin triple therapy for 10 to 14 days appears to be a comparable alternative to clarithromycin triple therapy. The best options appear to be fluoroquinolone-containing sequential therapy (a PPI and amoxicillin for five to seven days followed by a PPI, a fluoroquinolone, and nitroimidazole for five to seven days) or LOAD therapy (levofloxacin, omeprazole [Prilosec], nitazoxanide [Alinia], and doxycycline for seven to 10 days).

What Factors Predict Successful Eradication When Treating *H. pylori* Infection?

Determinants of success can be related to patient factors or to the infection. The main determinants are choice of regimen, patient adherence to a multidrug regimen with frequent adverse effects, and the sensitivity of the *H. pylori* strain to the combination of antibiotics used. The number of doses per day and the severity of adverse effects influence treatment adherence. It is important for physicians to discuss the benefits and challenges of therapy before beginning the regimen. Other patient factors, such as cigarette smoking, diabetes mellitus, and genetics, may also have a role in treatment failure.

Of the infection-related factors, antibiotic sensitivity was found to be the most important determinant of treatment success in clinical trials and population-based studies. Resistance to clarithromycin, metronidazole, and levofloxacin limits their effectiveness and increases the prevalence of *H. pylori* infection. Resistance to amoxicillin, tetracycline, and rifabutin (Mycobutin) is rare.

What Do We Know About *H. pylori* Antimicrobial Resistance in North America? What Methods Can Be Used to Evaluate Resistance, and When Should They Be Used?

Data on resistance are scarce. More research is needed to determine local, regional, and national patterns of *H. pylori* resistance to antibiotics to guide the choice of regimen.

Resistance can be evaluated using culture or molecular testing; however, these methods are not widely available

in the United States. Testing through culture is difficult to perform and takes several days. If successful, cultural methods include agar dilution, disk diffusion, and the E-test. Molecular tests, such as polymerase chain reaction or fluorescently labeled nucleic acid hybridization, are faster, simpler alternatives to culture. However, molecular testing for *H. pylori* resistance is not currently approved by the U.S. Food and Drug Administration.

The lack of knowledge on *H. pylori* resistance in the United States is in sharp contrast to other parts of the world, creating a barrier to evidence-based treatment recommendations.

Should We Test for Treatment Success After *H. pylori* Eradication Therapy?

Because of the declining success rate of *H. pylori* eradication therapy, persistent infection is not uncommon after treatment. A urea breath test, fecal antigen testing, or biopsy-based testing should be used to determine treatment success. Testing should be performed at least four weeks after completion of antibiotic therapy and after PPI therapy has been withheld for one to two weeks. Although the recommendation for posttesting is intuitive, the scientific evidence regarding the cost-effectiveness of such testing is lacking, except for the scenario of bleeding peptic ulcers.

When First-Line Therapy Fails, What Are the Options for Salvage Therapy?

If infection persists after treatment, the same antibiotics should be avoided when retreating the patient. Bismuth quadruple therapy or levofloxacin regimens are preferred for patients who initially received a regimen containing clarithromycin. A regimen containing clarithromycin or levofloxacin is preferred for patients who initially received bismuth quadruple therapy. Local antimicrobial resistance data and the patient's previous antibiotic exposure should be considered when choosing salvage therapy. Like first-line therapy, the ACG recommendations for salvage therapy are based on empiric selection rather than results of culture and antimicrobial sensitivity testing.

Bismuth quadruple therapy (PPI, bismuth, tetracycline, metronidazole) for 14 days or levofloxacin triple therapy (PPI, levofloxacin, amoxicillin) for 14 days are the recommended salvage regimens. Other suggested regimens include concomitant therapy (PPI, clarithromycin, amoxicillin, nitroimidazole) for 10 to 14 days, rifabutin triple therapy (PPI, amoxicillin, and rifabutin) for 10 days, and high-dose dual therapy (PPI and amoxicillin) for 14 days. Clarithromycin triple therapy is not recommended for salvage therapy.

When Should Penicillin Allergy Testing Be Considered in Patients with *H. pylori* Infection?

Amoxicillin is an important component of *H. pylori* treatment regimens. However, there are alternatives that do not include amoxicillin, most notably bismuth quadruple therapy. Allergy testing may be considered after one or two failures of first-line therapy. Most often, a true penicillin allergy will be excluded, and amoxicillin-containing salvage therapy can be initiated safely.

Guideline source: American College of Gastroenterology

Evidence rating system used? Yes

Systematic literature search described? Yes

Guideline developed by participants without relevant financial ties to industry? No

Recommendations based on patient-oriented outcomes? Yes

Published source: *Am J Gastroenterol.* February 2017;112(2):212-239

Available at: https://www.nature.com/ajg/journal/v112/n2/full/ajg2016563a.html [login required]

Amber Randel

AFP Senior Associate Editor ■