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# The Effect of Antibiotic Resistance on the Management of *Helicobacter pylori* Infection

## HIGHLIGHTS

- » *Helicobacter pylori* Diagnosis and Treatment Guidelines
- » Addressing the Unmet Needs of *Helicobacter pylori* Treatment Through Alternative Treatment Options and Antimicrobial Stewardship
- » Renewed Interest in the Management of *Helicobacter pylori* Infection: A Q&A With William D. Chey, MD
- » *Helicobacter pylori*: Current Treatment Options and Challenges: A Q&A With Colin W. Howden, MD

# 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.<sup>1-3</sup> The World Health Organization (WHO) has classified *H pylori* as a top carcinogen since 1994,<sup>4</sup> and it is a common cause for morbidity and mortality. According to one estimate, *H pylori* affected approximately 4.4 billion people in 2015.<sup>5</sup> 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.<sup>6</sup>

## 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.<sup>4</sup> *H pylori* infects the epithelial lining of the stomach and is most commonly acquired through interpersonal contact during childhood.<sup>4,5</sup> 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.<sup>4</sup> 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.<sup>4</sup> *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.<sup>4</sup> 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.<sup>4</sup> 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.<sup>4</sup> A final potential mode of transmission is environmental; in this, contaminated food and water are likely vehicles.<sup>4</sup> 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.<sup>4</sup> 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.<sup>5</sup> The incidence of *H pylori* has changed over time with improvements in sanitation, but its prevalence is still high in certain areas.<sup>5</sup> 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.<sup>5</sup> 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.<sup>6</sup> *H pylori* prevalence varies depending on socioeconomic status, levels of hygiene, and race/ethnicity.<sup>5</sup> 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.<sup>4</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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*.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup> Similar to patients taking aspirin, patients taking NSAIDs and who are positive for *H pylori* have a higher risk for developing ulcer complications.<sup>7</sup> Studies report that patients with an *H pylori* infection are more likely to have ID anemia.<sup>7</sup> Platelet counts may also improve after eradication of *H pylori* infection for some adults with ITP.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup>

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.<sup>8</sup> Invasive techniques involve the use of endoscopy to gather gastric biopsies and include histology, culture, and rapid urease test.<sup>8</sup> 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.<sup>8</sup> 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.<sup>8</sup> 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.<sup>8</sup> 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.<sup>8</sup>

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.<sup>7</sup> Although circumstances may make additional testing impractical and providers or patients may decide that retesting is unnecessary,<sup>7</sup> 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.<sup>8</sup>

### *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.<sup>7</sup>

#### *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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup> The Maastricht/Florence consensus document published in 2012 recommended against triple therapy when the clarithromycin resistance rate exceeds 15% to 20%.<sup>7</sup> At the time the ACG guidance was released in 2017, data suggested that North American resistance rates may fall within that range.<sup>7</sup> The guideline noted that, should clarithromycin resistance indeed exceed 15%, clarithromycin triple therapy should be avoided.<sup>7</sup>

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

Concomitant therapy is a first-line option for patients intolerant of bismuth<sup>8</sup> and includes a PPI, amoxicillin, clarithromycin, and a nitroimidazole (tinidazole or metronidazole) given together for 3 to 10 days.<sup>7</sup> 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.<sup>7</sup> Thus, the ACG guideline recommends considering concomitant therapy as a promising treatment option with high cure rates for North America.<sup>7</sup>

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.<sup>7</sup> 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.<sup>7</sup>

Hybrid therapy consists of 7 days of a PPI and amoxicillin followed by another 7 days of PPI, amoxicillin, clarithromycin, and a nitroimidazole.<sup>7</sup> 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.<sup>7</sup> Because of this, the ACG guideline suggests hybrid therapy as an alternative to clarithromycin triple therapy.<sup>7</sup>

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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup>

### Salvage therapies

Because 10% to 30% of first-line *H pylori* treatments fail, salvage therapy options must be considered.<sup>8</sup> 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.<sup>7</sup> 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.<sup>7</sup>

### Unmet Needs

Treatment guidelines discuss antibiotic resistance as it relates to *H pylori* but also could be considered to be inadvertently promoting misuse.<sup>9</sup> *H pylori* is a high-priority antibiotic-resistant bacterium as defined by the World Health Organization<sup>9</sup> and is included on the FDA's list of qualifying pathogens that have the potential to pose a serious threat to public health.<sup>10</sup> 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.<sup>11</sup> Results showed high rates of resistance for metronidazole, clarithromycin,

and levofloxacin. These rates were highest for adults previously treated with antibiotics, especially metronidazole.<sup>11</sup> Portuguese investigators reviewed the resistance mechanisms of *H pylori* to clarithromycin and found many mutations in the 23S rRNA region of the isolates.<sup>12</sup> 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.<sup>12</sup> 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.<sup>13</sup> 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.<sup>7</sup>

### Antimicrobial sensitivity testing

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

### Costs of *H pylori*

*H pylori* infection is associated with the risk of peptic ulcer, gastritis, and noncardia gastric cancer.<sup>12</sup> It is responsible for 90% of duodenal ulcers and 70% to 90% of gastric ulcers.<sup>16</sup> 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.<sup>17</sup> In 2014, gastritis and dyspepsia accounted for an estimated 2.8 million ambulatory care visits<sup>17</sup> and gastritis/duodenitis resulted in more than 58,000 hospital admissions from emergency departments.<sup>17</sup> 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.<sup>17</sup> Total health care expenses related to gastritis and duodenitis were almost \$1.2 billion in 2015, including \$267 million (22.5%) for prescription medicines.<sup>17</sup> 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.<sup>17</sup> ♦

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# Addressing the Unmet Needs of *Helicobacter pylori* Treatment Through Alternative Treatment Options and Antimicrobial Stewardship

**GASTRIC CANCER** is the third most common cause of cancer death worldwide and is associated with *Helicobacter pylori*,<sup>1</sup> which is classified as a human carcinogen by the International Agency for Research on Cancer.<sup>1</sup> Chronic infection with *H pylori* has been demonstrated to cause noncardia gastric carcinoma and low-grade B-cell gastric mucosa-associated lymphoid tissue (MALT) lymphoma.<sup>2</sup> Over 850,000 deaths were attributed to gastric cancer in 2017. This rate is expected to increase because of increasing life expectancy in developing countries and increased risk in younger generations.<sup>1</sup> Globally, up to 89% of noncardia gastric cancers are attributable to *H pylori*, which is a total of around 780,000 cases and 6.2% of all cancers worldwide. Of the 2.2 million cancers attributable to infection worldwide in 2008, *H pylori* was responsible for 36.3%.<sup>2</sup> Because gastric cancer is a major cause of morbidity and mortality worldwide, the International Agency for Research on Cancer working group recommended that countries explore population-based *H pylori* screening and treatment programs.<sup>1</sup> Additionally, eradication of *H pylori* in asymptomatic individuals has been shown to correlate with a reduction in gastric cancer.<sup>1</sup>

## Circumventing Antibiotic Resistance Through Available Treatment Options

Increasing *H pylori* antibiotic resistance rates are affecting the efficacy of many traditional treatment options.<sup>3-5</sup> Therefore, alternative treatment options are being explored.

### High-dose dual therapy

High-dose dual therapy (HDDT) may be a viable option for first-line therapy. During HDDT, a proton pump inhibitor (PPI) and amoxicillin are given to the patient more than 2 times daily.<sup>6</sup> A systematic review and meta-analysis aimed to compare the efficacy and safety of HDDT with other regimens and found that HDDT was equivalent to recommended first-line or rescue regimens (84% vs 81% eradication rate; relative risk [RR] = 1.00; 95% CI, 0.96-1.05;  $P = .870$ ) with fewer adverse effects (17% vs 37%; RR = 0.48; 95% CI, 0.37-0.64;  $P < .001$ ).<sup>6</sup> In the 15 reviewed trials (11 conducted in Asia, 3 in Europe, 1 in North America), HDDT was given 3 times daily in 4 trials and 4 times daily in the others. HDDT was compared with control regimens that included triple therapy, bismuth quadruple therapy, nonbismuth quadruple therapy, and a

combination of triple therapy and sequential therapy.<sup>6</sup> An open-label, randomized single-center study conducted in China aimed to determine whether bismuth improved the efficacy of HDDT.<sup>7</sup> The cure rates in the nonbismuth group were 96.1% (95% CI, 88.9%-99.2%) compared with 93.3% (95% CI, 85.1%-97.8%) in the bismuth group, but the results were not significant ( $P = .5$ ).<sup>7</sup> Interestingly, adding bismuth to HDDT only improved cure rates for smokers; it did not improve cure rates for nonsmokers.<sup>7</sup> Nevertheless, the study found HDDT to be both an effective and safe candidate for first-line treatment in a population with a high prevalence of antibiotic resistance.<sup>7</sup>

### Rifabutin-based therapy

The 2017 American College of Gastroenterology (ACG) Clinical Guideline discusses high-dose rifabutin-based therapy (300 mg) as a salvage therapy,<sup>4</sup> but does not address the low-dose regimen (150 mg) as a first-line therapy. The omeprazole, rifabutin, amoxicillin combination therapy is designed to combat *H pylori* antibiotic resistance.<sup>8</sup> Rifabutin is ideal for combating *H pylori* because it has in vitro bactericidal activity against the bacterium, it reaches high intracellular and intragastric concentrations, and resistance is rare and typically only occurs when the drug is administered in high doses for long periods.<sup>8</sup> In 2019, the FDA approved the first rifabutin-based therapy for the treatment of *H pylori* infection in adults.<sup>9</sup> This followed ERADICATE Hp (NCT01980095), a phase 3, double-blind trial that tested the efficacy of RHB-105, a fixed-dose treatment containing a low dose of rifabutin (150 mg/d) plus amoxicillin (3000 mg/d) and omeprazole (120 mg/d), given as 4 capsules every 8 hours for 14 days.<sup>9</sup> Study participants included 455 treatment-naive adults who had had dyspepsia for at least 2 weeks and confirmed *H pylori* infection.<sup>8</sup> At baseline, certain patients were found to carry *H pylori* strains that were resistant to amoxicillin, clarithromycin, or metronidazole. Others carried isolates that were resistant to both clarithromycin and metronidazole.<sup>8</sup> In the intention-to-treat data set, the eradication rate was higher with RHB-105 than with the comparator treatment containing amoxicillin (3000 mg/d) and omeprazole (120 mg/d) (83.8% vs 57.7%;  $P < .001$ ).<sup>8</sup> The eradication rate in the RHB-105 group remained high regardless of antibiotic resistance or susceptibility of *H pylori* strains causing the infection.<sup>8</sup> RHB-105

had favorable tolerability and a similar adherence and adverse event profile to those of the comparator group.<sup>8</sup> Given these findings, low-dose rifabutin-based therapy can be an effective first-line option, especially in regions where antibiotic resistance has caused traditional *H pylori* treatment options to fail.

#### *Novel approaches*

Most therapies used for *H pylori* eradication involve combining broad-spectrum antibiotics, bismuth, and acid inhibitors, but increasing resistance rates highlight the importance of developing novel therapeutic approaches. The ACG Clinical Guideline briefly discusses probiotic use as adjuvant therapy for *H pylori* but acknowledges that any data advocating for probiotic use come from clinical trials of low quality. Although certain probiotics might help reduce adverse effects of frontline eradication therapies and increase adherence with these regimens, such use requires further investigation.<sup>4</sup> Additionally, acid suppression using potassium-competitive acid blockers is currently being investigated.<sup>10</sup>

Despite the potential for these novel therapies, rising antibiotic resistance rates underscore the urgency to develop new therapeutic targets and narrow-spectrum antibiotics against *H pylori* to combat resistance. Numerous *H pylori* genomes have been sequenced, but clinical translation of factors targeting *H pylori* major enzymes, such as urease and glutamate racemase, have been disappointing.<sup>11</sup> Several studies have investigated a potential vaccine for *H pylori* but have found limited success. An exception is a large field trial in China that involved a recombinant urease B vaccine given orally with a mucosal adjuvant to teenagers, which resulted in more than 70% efficacy, although further investigation is warranted.<sup>11</sup>

#### **Applying the Principles of Antibiotic Stewardship to Treating *H pylori***

Several *H pylori* consensus treatment guidelines recommend susceptibility-guided therapy. Still, individual antibiotic susceptibility testing is not widely available in North America and antibiotic susceptibility registries akin to those in Europe do not exist on this continent.<sup>11</sup> A comprehensive review from Spain considered the advantages and limitations of susceptibility-guided strategies to treat *H pylori* infection. Assessing the antibiotic susceptibility of the *H pylori* strain in a patient allows a clinician to determine treatment options for that patient that reduce both resistance development and unnecessary antibiotic prescription. Susceptibility testing also prevents additional costs associated with prescribing antibiotics that lack efficacy and induce adverse events. If susceptibility testing is performed before first-line therapy, the

most effective antibiotic regimen can be chosen and administered to the patient.<sup>12</sup> However, obtaining samples for susceptibility testing is difficult and the tests have low sensitivity. Moreover, there is no consensus regarding whether susceptibility testing should be performed before a patient's first treatment or only after eradication failure.<sup>12</sup> Historically, susceptibility testing has involved obtaining cultures, which is time consuming, is not always available, and only provides useful information for clarithromycin, metronidazole, and quinolones.<sup>12</sup>

Importantly, culture is not the only way to determine antibiotic resistance in *H pylori*. Different polymerase chain reaction (PCR)-based techniques have been developed as alternative methods to culture.<sup>12</sup> Molecular tests are faster than conventional culture techniques and do not require the long wait times to obtain cultures or present problems with difficult-to-isolate specimens. They can be performed on either stool or gastric biopsy samples. Molecular tests can also be used in small and medium-sized hospitals, which is ideal for developing countries.<sup>12</sup> Although some investigators and clinicians make the specific point that patients should not undergo endoscopy before treatment, there is consensus that both testing for antimicrobial susceptibility and treating *H pylori* infection in a patient-tailored manner may limit the emergence of antibiotic resistance.<sup>12</sup>

#### *Efficacy and benefits of susceptibility-based therapy*

Though susceptibility-based therapy appears to be at least as effective as empirical therapy and can minimize antimicrobial resistance, *H pylori* treatment regimens are most often prescribed empirically because of the lack of population-based data about antibiotic resistance in *H pylori* strains, availability of sensitivity testing, institutional approval for molecular testing methods, and sensitivity and specificity in tests.<sup>9,13</sup> Moreover, data comparing the efficacy of susceptibility-guided therapy with that of empirical therapy have major limitations that call into question the comparisons' reliability.<sup>12</sup> First among these is that trials to date that compare these therapies have not accurately randomized patients, rendering conclusions about therapy effectiveness unreliable.<sup>12</sup> Second, few data exist comparing susceptibility-based therapy with currently recommended bismuth or nonbismuth quadruple therapies; most studies have considered previously recommended triple therapy.<sup>12</sup> A third limitation is that many comparative studies performed susceptibility testing for only 1 antibiotic (clarithromycin); resistance to other antibiotics was not considered.<sup>12</sup> One consequence of these limitations is that advisers must recommend policy based upon low-quality data: The Maastricht V consensus report, for instance, indicates that susceptibility testing is not recommended in populations

or regions with well-documented low clarithromycin resistance (<15%), even though little scientific evidence supports this.<sup>12</sup>

Despite these limitations in data, susceptibility-based therapy has proven effective compared with empirical treatment. Multiple studies have shown enhanced efficacy with culture-guided treatments for first-line therapy, although data suggest that susceptibility-guided treatment and the most updated empirical regimens may be equally effective.<sup>12</sup> When susceptibility-guided strategies are used in the second line, however, several studies have shown comparable efficacy between the 2 treatments.<sup>12</sup> In the third line, susceptibility-guided strategies have been proven to have similar efficacy to empirical treatment.<sup>12</sup>

The frequent selection of empirical treatment over equally effective susceptibility-based therapy threatens the efficacy of currently available antibiotics and lowers *H pylori* eradication rates.<sup>14</sup> High cure rates for *H pylori* are possible, but current consensus statements and guidelines are based on principles used for other gastrointestinal diseases and rarely consider the different principles and practice of antimicrobial therapy.<sup>14</sup> To minimize antimicrobial resistance and increase eradication rates, susceptibility testing should guide treatment.<sup>9,14</sup>

### Shifting to antimicrobial stewardship

In 2015, *H pylori* was officially recognized as an infectious disease. Because of this, investigators are beginning to accept that *H pylori* should be treated following guidelines and practices governing treatment of other infectious diseases; that is, those of antimicrobial stewardship.<sup>14</sup> These principles prevent antimicrobial misuse, achieve high cure rates, and minimize the risk of developing resistance by optimizing therapy in terms of drugs, dosing, or duration of therapy.<sup>14</sup>

Trial-and-error therapeutic approaches to *H pylori* are a relic of early attempts to treat the disease. Shortly after the discovery of *H pylori*, investigators showed in vitro that it was susceptible to many antimicrobial agents. Unfortunately, the infection had low cure rates using those antimicrobials. Thus, trial-and-error clinical trials were prompted and used many different antimicrobials.<sup>14</sup> *H pylori* therapy was initially focused on treatment of peptic ulcer disease where the ulcer was treated with a histamine-2 receptor antagonist and the infection with bismuth triple therapy, which included metronidazole. Shortly after, *H pylori* developed resistance to metronidazole, so researchers modified the therapy to include a PPI and increase the dosage of metronidazole and the duration of therapy.<sup>14</sup> The development of *H pylori* therapies with different antibiotics has continued according to the trial-and-error approach with a focus on therapy comparisons, but overall cure rates are poor and declining.<sup>14</sup>

### Challenges

Adopting antimicrobial stewardship principles requires a major paradigm shift. Because the diagnosis and management of *H pylori* was the responsibility of gastroenterologists after *H pylori* was discovered, treatment approaches were probably based on experience with common gastroenterology diseases. Most gastroenterology diseases are characterized as having largely unknown etiologies, and treatments are focused on results rather than on explanations for a poor response. This is the opposite in infectious disease, where the cause of a poor response is discovered. The gastroenterology approach focuses on how well a treatment performs relative to a comparator (often a placebo), whereas the infectious disease approach focuses on the absolute cure rate.<sup>14</sup> Clinical trials involving *H pylori* have largely been designed according to the rules of gastroenterology, which has resulted in trial arms achieving poor results.<sup>14</sup> Infectious disease treatment approaches focus on attaining predetermined cure rates and have different clinical trial outcome goals. Comparison trials of effective susceptibility-based therapies are rare and if they are performed, generally only involve limited comparisons of proven and highly reliable regimens using noninferiority methods.<sup>14</sup>

Another challenge in the shift to the antimicrobial stewardship model is that meta-analysis comparisons of *H pylori* treatments have had major flaws and are used inappropriately for assessing *H pylori* therapy. The populations in the trials being compared often have important differences that cannot be compared and trial results are often not generalizable. Generalizability is a key requirement for valid and ethical research according to the guidelines for implementing antimicrobial stewardship for treatment of *H pylori* infections developed by the Infectious Diseases Society of America.<sup>14,15</sup> Meta-analyses have also been misused when being used to provide guidance for therapy. For instance, the 2017 ACG guideline uses a meta-analysis that compares trials achieving clinically unacceptable cure rates to recommend that bismuth quadruple therapy replace triple therapy, whereas an infectious disease perspective would dictate that neither therapy be recommended in the studied regions.<sup>4,14</sup>

The limitations surrounding susceptibility testing present a third challenge for transitioning *H pylori* therapy to the principles of antimicrobial stewardship. Although susceptibility testing for human pathogens is available in most hospitals and clinics throughout the world, susceptibility testing for *H pylori* is almost always unavailable at a local level. In the United States, the Mayo Clinic laboratory and a few commercial laboratories perform culture and susceptibility testing, but the individual physician or endoscopy unit must determine how to take advantage of this service; molecular susceptibility testing is similarly

limited. Current consensus statements recommend testing only patients with 2 or more treatment failures, so the demand in the United States is not high and reimbursement is difficult. The United States also lacks both a tradition of susceptibility-based *H pylori* therapy and the surveillance programs necessary to track resistance patterns and inform therapy.<sup>14</sup> Although hospitals that participate in programs from the Centers for Medicare & Medicaid Services are now required to establish antimicrobial stewardship programs, it appears that *H pylori* is exempt from the provision.<sup>14,16,17</sup>

### Requirements

To address *H pylori* as the infectious disease that it is, treatment guidelines based on the principles of antimicrobial stewardship should be developed and should replace all other recommendations.<sup>14</sup> This will involve adapting clinical trials to focus on achieving high cure rates.<sup>14</sup> It will also involve complying with the Infectious Diseases Society of America's recommendations regarding the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens.<sup>14</sup> Under new *H pylori* guidelines, comparative trials must only compare highly effective therapies that use noninferiority methods.<sup>14</sup> The guidelines should clarify that therapies must be optimized to reliably achieve high cure rates where optimization includes the effects of resistance to the different components and is confirmed in different regions. Surveillance programs should be implemented and consist of routine tests of cure.<sup>14</sup> Treatment should be combined with ongoing or planned prescription and treatment monitoring used for bacterial infections. Data from sites where culture and susceptibility testing and/or molecular testing are performed locally should be published and kept up-to-date.<sup>14</sup> For clinicians to be informed about a regimen that should not be prescribed any longer, the new guidelines should recommend that results be reported in a public location that is easy to access.<sup>14</sup> Developing these new guidelines will be a vast undertaking.

### Primer for guideline development

To facilitate this transition, Graham and Liou developed a primer for the development of guidelines for *H pylori* therapy using antimicrobial stewardship that was published in April 2021. The primer establishes antimicrobial stewardship as a set of practices that promote responsible antibiotic use, measure appropriate use of antimicrobial agents, improve selection of optimal drug regimens, and promote the use of antimicrobials for effective and sustainable therapy.<sup>17</sup>

The primer's first principle is to promote responsible use of antimicrobials.<sup>17</sup> This includes complying with the

general principles of both antimicrobial stewardship and antimicrobial therapy, the latter of which calls for obtaining an accurate diagnosis, understanding the difference between empiric and definitive therapy, understanding drug characteristics that are specific to antimicrobial agents, accounting for host characteristics that influence antimicrobial activity, and recognizing the adverse effects of antimicrobial agents on the host.<sup>17</sup> Only antimicrobials that are known to be effective against the infection should be used, unless any resistance can be overcome with the concomitant use of another agent.<sup>17</sup>

The primer's second principle is to assess and promote optimal drug regimens, which involves measuring appropriate use of antimicrobial agents. An optimal drug regimen achieves the highest cure rate possible. Although a 100% cure rate is ideal, a rate of 95% or greater might be appropriate for *H pylori*, which has proved difficult to cure. If choosing among optimized therapies, the *H pylori* guidelines should consider tolerability, cost, convenience, and other factors.<sup>17</sup>

The primer highlights that determining *H pylori* optimal cure rates for a specific geographic region or population presents several issues. *H pylori* infections are generally asymptomatic and can reappear within a year following therapy, so the accuracy of determining cure rates depends on the type, number, accuracy, and timing of the tests used. In addition, the rate of false-positive and false-negative tests should be considered. Therefore, the operational optimal cure rate should be adjusted to perhaps 93% or higher rather than 95% or higher, and cure rates of 90% to 94% should be considered conditionally acceptable.<sup>17</sup>

In outlining this second principle, the primer highlights how to approach improving cure rates of *H pylori* therapies; reducing further emergence, selection, and spread of antimicrobial resistance; and prolonging the life span of existing antibiotics. It recommends complying with the World Health Organization's AWaRe (Access, Watch, and Reserve) classification of antibiotics according to their potential for resistance. This would privilege *H pylori* therapies using amoxicillin, tetracycline, and metronidazole and emphasize the monitoring of those that use clarithromycin and levofloxacin.<sup>17</sup> The primer also advocates making efforts to expand and utilize susceptibility testing and reporting to reveal regional antimicrobial susceptibility patterns and guide treatment.<sup>17</sup> To the same end of improving *H pylori* care, the primer notes that future treatment guidelines should clarify that only therapies that reliably achieve high cure rates should be compared in clinical trials and that these trials should generally use a noninferiority design.<sup>17</sup>

In the estimation of the primer's authors, introducing antimicrobial stewardship practices will simplify how *H pylori* therapies are classified.<sup>17</sup> Moreover, in focusing

on the need to reliably achieve high cure rates, the new *H pylori* guidelines will need to detail drug specifications, doses, formulations, administration frequency, timing of administration relative to meals, duration, and other topics.<sup>17</sup> Additionally, the primer recommends, the guidelines should use factorial design in complicated therapies and should draw upon head-to-head comparisons in metronidazole-resistant populations to determine the optimal duration of bismuth quadruple therapies.<sup>17</sup>

The primer's third principle is to promote the use of antimicrobials in ways that ensure sustainable access to effective therapy for all who need them. Here, the primer emphasizes the need to optimize therapies and minimize antibiotic misuse.<sup>17</sup> Physicians most often misuse therapy in *H pylori* infection by using an unoptimized treatment regimen.<sup>17</sup> They also prescribe antibiotics that do not cure the infection, such as prescribing 2 antibiotics when only 1 is needed.<sup>17</sup> This third principle advises that new *H pylori* guidelines direct clinicians to stop using an antibiotic, not when an antibiotic resistance exceeds a certain percentage, as the Maastricht IV consensus report had, but when cure rates fall below 90% or another set percentage.<sup>17</sup>

### Recommendations during transition

The primer emphasizes that new guidelines should take into consideration the unique problems that *H pylori* presents and align them with the principles of antimicrobial stewardship. To embrace these antimicrobial stewardship principles, the gastroenterology community will need to discontinue use of current guideline recommendations, optimize antibiotic use, and reduce antimicrobial resistance. The goal is to achieve high cure rates that are reliable for routine clinical practice.<sup>14</sup> While introducing antimicrobial stewardship, Graham recommends the following principles on how to improve empiric therapies. First, only regimens proven to produce high cure rates locally should be included. Next, outcomes obtained using test-of-cure results should be routinely monitored and reported to provide real-time information about whether the goals are being met. Finally, therapies that fail to reliably achieve the desired high cure rates should be stopped or modified.<sup>14</sup> Any antibiotics that do not contribute to a cure rate must be eliminated. Susceptibility testing should be performed; until this is a widely accepted method, the routine test-of-cure data can be used as a surrogate method for susceptibility testing and data should be collected, shared, and integrated into local antimicrobial stewardship programs.<sup>14,17</sup> This will provide real-time information on whether treatments are being successful and permit monitoring and reporting outcomes based on test-of-cure data.<sup>14</sup> All treatment recommendations should comply with the Infectious Diseases Society of

America's white paper on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens.<sup>17</sup>

To track treatment success, a test-of-cure result should be obtained from all patients regardless of the duration of therapy. Clinically, the definition of a cure is a noninvasive test given to the patient at least 4 weeks after therapy has ended that shows a negative result or a negative stool antigen test at least 6 weeks after therapy.<sup>14</sup> The test-of-cure result should also be used as part of ongoing surveillance where results are reported to a central site and results shared.<sup>14</sup> Because noninvasive tests are only 95% sensitive and specific and used to determine cure, Graham proposes a cutoff of 93% or higher until the testing to define a cure allows a more precise estimate. Population-based clinical results should base the cure rate on modified intention-to-treat results that include only those who have test-of-cure data.<sup>14</sup>

While the principles of antimicrobial stewardship are being introduced, the following elements of empiric regimens should be used: (a) experimental identification of antibiotic doses and frequency of administration; (b) unless the regimen has been formally optimized to use a different duration, the duration should be 14 days; and (c) minimum PPI dosage should be 60 mg omeprazole or equivalent (eg, 60 mg omeprazole, 60 mg lansoprazole, 40 mg esomeprazole or rabeprazole).<sup>14</sup> Unneeded antibiotics should not be used and test-of-cure results should be available for ongoing surveillance. Regimens that fail to reach specified end points should be removed from empiric therapies and each approved therapy formally optimized. Therapy optimization should be among the first goals for the implementation of antimicrobial stewardship principles for *H pylori* treatments.<sup>14</sup>

### Conclusions

The rise of antimicrobial resistance and declining *H pylori* eradication rates create a global health challenge that can only be circumvented with new treatment options to address the unmet need. With *H pylori* being a modifiable risk factor for gastric cancer, a potentially fatal malignancy, development of eradication techniques must continue. Current treatment guidelines were last updated in 2017. Although antibiotic resistance rates have increased and reduced the efficacy of recommended treatments since the guideline update, the *H pylori* treatment landscape has seen an FDA approval, in addition to other treatments currently being evaluated. Adoption of antimicrobial stewardship principles for *H pylori* treatments can be useful in reducing antibiotic resistance development and preventing infection spread. Furthermore, coordinated strategies following the Infectious Diseases Society of

## America's guidelines can aid in the transition to antibiotic stewardship principles from current gastroenterological treatment plans. ♦

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# Renewed Interest in the Management of *Helicobacter pylori* Infection

A Q&A With William D. Chey, MD



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**The American Journal of Managed Care® (AJMC®):** What has led to the recent increase in attention given to *Helicobacter pylori* treatments?

**CHEY:** It's been an interesting time because there's been a real renaissance in terms of interest in *H pylori*. There's been a lot of movement in this space over the past year, year and a half, whereas for the previous 20 years there was absolutely no movement in this space whatsoever.

I think the growing recognition and concern with the rising prevalence of clarithromycin-resistant *H pylori* strains have been responsible for this increase in interest. I've been the lead author on the last 2 iterations of the American College of Gastroenterology Clinical Practice Guideline in *H pylori*, and the one that we wrote, I think it was in 2007, we started to look for alternatives to clarithromycin triple therapy because rates of clarithromycin resistance appear to be rising and the eradication rates with that regimen appear to be 80% or less. By the 2017 guideline, we were waving a red flag that we should not be using this regimen except in very specific circumstances.

Our group, as well as other groups in the United States, [has] been tracking the eradication rates associated with clarithromycin triple therapy (PPI [proton pump inhibitor], clarithromycin, amoxicillin) and it is now very consistently under 80%; usually in the mid to high 70% range. Which means that roughly 1 in 4 patients with *H pylori* treated with that regimen isn't going to be successfully cured of their infection. I think increasingly, people have been looking for alternatives and finally, I think we've found some. As far as what I refer to as the legacy regimens—the regimens we've been using for many years—we need to move away from clarithromycin triple therapy and favor bismuth quadruple therapy, which consists of a PPI, bismuth, tetracycline, and metronidazole. Aside from the legacy regimens, there are a number of exciting new combination therapies that I think will provide very viable alternatives and should be preferred over traditional clarithromycin triple therapy.

**AJMC®:** Do you feel that outcome monitoring would be a useful investment, and, if so, how big of a challenge would it be to implement?

**CHEY:** Outcome monitoring is already being done in Europe. What's so interesting about what they're doing in Europe is that it is across many different nations; they've made a conscious effort to collaborate and create a consortium of like-minded investigators across Europe who all submit their data and samples regarding *H pylori* to a central repository. They've been able to do some very interesting and valuable studies looking at resistance patterns as well as real-world eradication rates in association with commonly used *H pylori* treatment regimens. There's nothing that would stop us from doing the same thing here, other than resources and resolve. I hope we can have the vision to make an investment because *H pylori* infection isn't going anywhere anytime soon. The good news is that the United States is a medium- to low-prevalence country relative to many other parts of the world like Asia or Latin America, where *H pylori* infection affects well over 60% of the population. In the United

States, we're probably in a range of around 30% to 35%, so it's substantially lower, but that's still 1 in 3 people who [is] infected. It's also important to remember that [those who] immigrate to the United States, particularly from Russia, Asia, and Latin America, [can be coming from countries that] have a much higher prevalence of *H. pylori* infection. So, as I said, *H. pylori* is going to be around and going to be an issue for the foreseeable future, I think for many years to come.

**AJMC®:** You've noted "resources" and "the resolve to participate" as being roadblocks to outcome monitoring here in the United States. Do you have any ideas on how to overcome that?

**CHEY:** In the 1990s, there was something called the Surveillance of *H. pylori* Antimicrobial Resistance Partnership (SHARP) program, which was a national *H. pylori* antimicrobial resistance monitoring program. So, for a short period of time, there was a surveillance program in the United States. You wonder whether or not there might be the interest or the will at the level of the National Institutes of Health, for example, to fund some type of a consortium that would follow resistance rates and track data around the effectiveness of *H. pylori* treatment regimens in the United States. I think the other possibility is whether the companies that are making these novel regimens might be interested in creating a registry where participants could input data around the regimens that they use—just practical effectiveness data, even that would be potentially helpful.

**AJMC®:** What role does *H. pylori* screening have in patients who are symptomatic compared with patients who are asymptomatic?

**CHEY:** If you first consider symptomatic patients, every clinical guideline recommends that you test and treat patients with dyspepsia. Our guideline also mentions that even for functional dyspepsia where you do an endoscopy and you don't find an ulcer, but you do find *H. pylori* infection, you should treat to eradication. The reason [is that] *H. pylori* infection is one of the few curable and potentially reversible causes of dyspeptic symptoms. If you think about dyspepsia from a pragmatic standpoint, you could make an argument that the inflammation perhaps activates sensory nerves that lead to the symptom experience that we refer to as dyspepsia. There are also patients who probably have ulcers that come and go, so at the time you do the endoscopy maybe it just looks a little bit red but maybe if you did an endoscopy a month or 2 later, you might find erosions or an ulcer. That process of inflammation and mucosal injury is dynamic, and what you find, to some extent, depends on when you look. So, really, I think every organization that I'm aware of recommends that if you have a patient with

uninvestigated dyspepsia or even functional dyspepsia, you should look for *H. pylori* because it offers one of the only reversible or curable causes of these symptoms. That's the good news. The bad news is that in patients with dyspepsia, only around one-third of the patients get better with eradication of *H. pylori* infection. There is also the issue of antibiotic stewardship given the need for multidrug regimens. Still, I side with the guidelines and believe that the upside is enough to justify the downside of treating patients with dyspepsia.

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**I would offer this question: If you're interested enough to find *H. pylori* and treat it, shouldn't you be interested enough to know that it's gone?**

—William D. Chey, MD

It's a completely different discussion in infected people who are asymptomatic. In asymptomatics, you're presumably going after *H. pylori* as a chemopreventive strategy for gastric cancer because *H. pylori*, according to the World Health Organization, is a class 1 carcinogen. There's a very nice meta-analysis that was published in *Gastroenterology* in 2016 by Lee and colleagues<sup>1</sup> that summarized all the data to that point in terms of eradicating *H. pylori* as a chemopreventive strategy for gastric cancer. The investigators came to the conclusion that, yes, there was potential benefit to screening asymptomatic individuals for *H. pylori* and eradicating *H. pylori* in the hopes of reducing the likelihood of developing gastric cancer. But it is important to note that the benefits seem to be confined to countries where the pretest probability of gastric cancer is high, but less robust or even nonexistent in countries like the United States, where the pretest probability of gastric cancer is quite low.

**AJMC®:** Should retesting after therapy be implemented routinely?

**CHEY:** Yes. In our 2017 guideline, we recommended that whenever practically possible, universal posttreatment testing to prove eradication be performed. It should be done with a urea breath test, [with a] stool antigen test, or,

if an esophagogastroduodenoscopy is done, by histology or rapid urease testing at least 4 weeks after the completion of antibiotic therapy.

Unfortunately, retesting is not done consistently. There are many practitioners who have adopted our recommendations, and so if you were to poll gastroenterologists, they largely fall into 3 camps: the providers who routinely retest almost everybody, the ones who do it for certain indications, and the ones who don't think it is important or that the treatments always work, and for those reasons, do not retest to prove eradication. I would offer this question: If you're interested enough to find *H pylori* and treat it, shouldn't you be interested enough to know that it's gone?

**AJMC®: How do you recommend managing a patient who has been treated for *H pylori* and is still infected?**

**CHEY:** Let's say a patient has dyspepsia. You test them for *H pylori*, you find it, you treat them, they come back for follow-up, and they still have symptoms. Don't assume that the symptoms mean that the infection is still present. It's really important to retest because only one-third of the patients with dyspepsia will get better even after

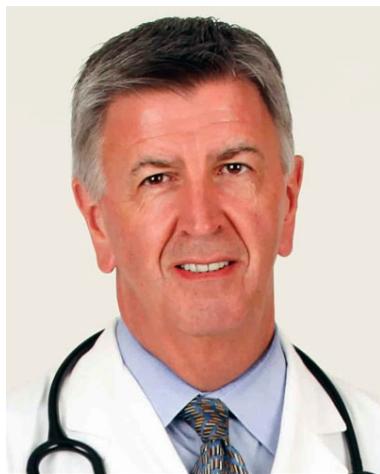
you successfully eradicate *H pylori* infection. Persistent symptoms do not equal persistent infection. You have to do the test because you don't want to give somebody 1, 2, or 3 antibiotics again if they don't actually have the infection. If testing confirms persistent infection, it is important for the treating physician to avoid re-treating with the same antibiotics, to stress the importance of adherence, and to make sure to treat for 14 days. Adherence is key no matter where a patient is in the treatment journey. Remember that with each round of *H pylori* treatment, it becomes progressively more difficult to successfully eradicate the infection, regardless of what you use to treat it. Your first chance is your best chance to cure the infection. After that, things start going downhill really quickly. Other recommendations can be found in our ACG guideline. Also, the American Gastroenterological Association just published a clinical practice update with recommendations for patients with persistent *H pylori* infection. ♦

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# *Helicobacter pylori*: Current Treatment Options and Challenges

A Q&A With Colin W. Howden, MD



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**The American Journal of Managed Care® (AJMC®):** What treatment options or regimens for *Helicobacter pylori* exist that are not reflected in the 2017 American College of Gastroenterology (ACG) guidelines?

**HOWDEN:** The most important one that's not present in the 2017 ACG guideline is the triple combination of rifabutin, amoxicillin, and omeprazole, which was approved by the FDA in late 2019. It wasn't included in the 2017 guideline because we didn't have data about its efficacy at that time. Also of note is a clinical trial using the potassium-competitive acid blocker vonoprazan, which is not currently approved in the United States, with either amoxicillin alone or with the combination of amoxicillin and clarithromycin. Top-level results from that should be available shortly. No other established treatments have become available since 2017.

**AJMC®:** Which treatment regimens are currently used most often to treat *H pylori*?

**HOWDEN:** I don't know the exact rates at which they are used, but I suspect that the so-called legacy triple therapy (proton pump inhibitor [PPI], amoxicillin, clarithromycin) is still the most widely used regimen in this country. It was endorsed in the 2017 guideline with certain reservations: It should not be used in patients who have previously received a macrolide antibiotic for any reason; it should also not be used unless you know that the patient comes from a region where clarithromycin resistance is below 15%. If people actually followed those recommendations, legacy triple therapy would hardly be used at all, but that's not the case. Bismuth-based quadruple therapy (bismuth, a PPI, tetracycline, and metronidazole) is also widely used. Unfortunately, it can be difficult for patients to take because it contains 4 different medicines and several tablets to be taken daily, so it can be confusing and difficult for patients to follow. The rifabutin-based regimen is a combination capsule. It should be straightforward for patients to take, but I don't have any recent data on how widely it's being used.

**AJMC®:** What type of information about *H pylori* would be helpful to improving treatment outcomes?

**HOWDEN:** We still have a lack of information about the prevalence of resistance to commonly used antibiotics for *H pylori* infection. That's why, to some extent, the treatment of the infection is largely empiric. We usually don't know what antibiotics it might be sensitive or resistant to, and we don't know that because we have very limited access to antimicrobial sensitivity testing. If doctors were able to use simpler and more effective regimens that limited the number of antibiotics but were still efficacious in getting rid of the infection, treatment outcomes for patients with *H pylori* infection would be improved. We would also be at less risk of producing resistance among bacteria other than *H pylori*; it would be a win-win situation.

**AJMC®:** How challenging would it be to adopt and implement antibiotic stewardship principles to *H pylori* treatment? Do you think that clinicians would support a movement toward treating *H pylori* based upon these principles?

**HOWDEN:** That's difficult to answer because we need to use multiple antibiotics to treat *H pylori* infection. As I indicated, I suspect that the most widely used regimen in this country is still so-called legacy triple therapy. However, its efficacy has diminished recently because of increasing rates of clarithromycin resistance, and that has led people to use a broader combination. Instead of prescribing 3 drugs—a PPI, clarithromycin, and amoxicillin—some have gone to prescribing 4, which would be a PPI, clarithromycin, amoxicillin, and metronidazole. If we knew in advance which of those antibiotics the bug was sensitive or resistant to, based on the availability of reliable pretreatment sensitivity testing, we would be able to practice much better antibiotic stewardship than we currently are. However, we usually don't have that ability. For patients who are using that 4-drug combination, there will inevitably be some who receive an antibiotic unnecessarily. If we're treating a clarithromycin-sensitive infection, we didn't really need to give them metronidazole, and similarly, if we're treating a metronidazole-sensitive infection, maybe we didn't need to give them amoxicillin.

All physicians should be aware of the problems of increasing antibiotic resistance—not just by *H pylori* but by other organisms. I hope that physicians would welcome any chance to improve and limit their use of antibiotics where appropriate. Limiting the number of antibiotics used would simplify things for patients and physicians. Very recent data from the United States suggest that amoxicillin resistance by *H pylori* remains very low. That often comes as a surprise to nongastroenterologists who are used to seeing amoxicillin-resistant urinary and pulmonary infections, but *H pylori* is different. I can't explain why, but *H pylori* appears not to acquire resistance to amoxicillin with anything like the same frequency that some other bacteria do.

**AJMC®:** Given the challenges of antibiotic resistance that exist and the limited access to antimicrobial sensitivity testing, what treatments are most effective?

**HOWDEN:** Two regimens do not require antibiotic sensitivity testing because they don't contain clarithromycin. One is bismuth-based quadruple therapy, which consists of a PPI, bismuth, tetracycline, and metronidazole. The other is the triple combination of rifabutin, omeprazole, and amoxicillin. In the case of the rifabutin regimen, we

know from recent US data that resistance to rifabutin and amoxicillin is very low to nonexistent.

**AJMC®:** How significant is the association of *H pylori* infection and gastric cancer?

**HOWDEN:** Important developments in recent years show increasing evidence that getting rid of *H pylori* infection in asymptomatic adults is associated with reduced risk of gastric cancer. That's been relatively straightforward to demonstrate in studies conducted in Asia where there's much more *H pylori* infection, and there's probably a greater risk of gastric cancer from it. However, it may also be true in the United States.

**Evidence is increasing that eradication of *H pylori* in asymptomatic adults may ultimately reduce the risk of gastric cancer in the United States.**

—Colin W. Howden, MD

There was a study published in *Gastroenterology* in 2020 from the University of Pennsylvania<sup>1</sup> that looked at the Veterans Administration database. They found that veterans with *H pylori* infection who were successfully treated for it and had a confirmed posttreatment test of eradication ultimately had a reduced incidence of gastric cancer during follow-up compared with those who weren't treated or weren't successfully treated. There's increasing evidence of the benefits of getting rid of *H pylori*. On a worldwide basis, *H pylori* is probably responsible for more stomach cancers than both hepatitis B and C viruses combined are for hepatocellular cancers. Gastric cancer continues to be either the second or the third most common cause of cancer-related death worldwide. Most of those cancers are due to *H pylori* infection. Evidence is increasing that eradication of *H pylori* in asymptomatic adults may ultimately reduce the risk of gastric cancer in the United States. ♦

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