*Helicobacter pylori* Treatment Regimens: A US Perspective

Jonathan J. C. Ho, MD, Erick A. Argueta, MD, and Steven F. Moss, MD

1Department of Internal Medicine, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island

2Division of Gastroenterology, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island

**Abstract:** *Helicobacter pylori* infects nearly one-third of the US population. *H pylori* is a significant cause of gastroduodenal disease, including peptic ulcers and cancers. However, rising antibiotic resistance has complicated management of *H pylori*. This article provides a practical review of management strategies, including first-line empiric therapies and how to treat patients when prior therapies fail. Bismuth-based quadruple therapy remains the standard initial empiric regimen, although a rifabutin-based triple regimen is another approach for empiric therapy in the United States. Clarithromycin and levofloxacin therapies should be avoided except when treating a strain of known susceptibility. When therapies fail, resistance should be tested with molecular or culture-based methods. Knowing local resistance patterns and/or using practice-based eradication rates is important for devising logic-based clinical choices. Ultimately, shared decision-making, patient counseling, and careful attention to drug type and dosage are essential for refractory cases.

*Helicobacter pylori* is a highly prevalent organism, infecting more than one-half of the global population. Within the United States, the estimated prevalence is around 35% with significant variance by location and socioeconomic factors.

Because *H pylori* infection is a strong risk factor for peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric cancer, it should be eradicated whenever detected. Many guidelines review the management of *H pylori*, but most relevant for the United States are those from the American College of Gastroenterology and the Maastricht consensus of international *H pylori* experts, which is updated approximately every 5 years. Growing concerns about increasing antibiotic resistance, coupled with new modalities for resistance testing and new regimens, are changing the approach to the management of *H pylori*. This article highlights current and emerging treatment regimens for practitioners in the United States, based on the available evidence and guidelines.

**Keywords**

*Helicobacter pylori*, antibiotics, management, treatment, resistance
Empiric Treatment With Bismuth-Based Quadruple Therapy

Despite recent advances in susceptibility testing, as well as the recognition that the principles of antibiotic stewardship should apply to *H pylori* infection, the treatment of *H pylori* infection remains empiric for most patients. Multiple factors should be taken into consideration prior to making an antibiotic regimen selection for *H pylori*, but most important is choosing a regimen that achieves reliably high cure rates. However, unlike for other infections, there is very little knowledge of current local, regional, and national *H pylori* success rates, or of resistance patterns. In a recent meta-analysis of a limited number of published US studies, resistance rates for clarithromycin, metronidazole, and levofloxacin have been found to be higher than 30% for each. Based upon these limited data, such high resistance rates for clarithromycin and levofloxacin are not compatible with their use with proton pump inhibitors (PPIs) and amoxicillin in the triple regimens that had been the standard for many years. Instead, clarithromycin and levofloxacin should be used only in refractory cases in which the *H pylori* strain is proven to be susceptible, based on resistance testing for that individual patient. In contrast, amoxicillin, tetracycline, and rifabutin offer better options for empiric treatment of first-line or refractory cases, given their low rates of resistance (Table 1).

Several national and international guidelines have coalesced around 14 days of bismuth-based quadruple therapy containing tetracycline and metronidazole as first-line therapy for the empiric treatment of *H pylori* infection. Although more complex than traditional clarithromycin-based triple therapy, this regimen has reliably achieved higher eradication rates. As an alternative to prescribing the individual components of bismuth-based quadruple therapy, a branded option (Pylera, AbbVie) significantly simplifies this regimen by decreasing the total pill burden to a single capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline. However, its widespread use has been cost prohibitive, and the standard prescription is for a 10-day course vs the 14-day optimal duration of bismuth-based quadruple therapy.

The overall efficacy of empiric bismuth-based quadruple therapy is limited primarily by metronidazole-resistant *H pylori*. However, metronidazole resistance is a complex issue, as in vitro resistance is only weakly predictive of failure in bismuth-based quadruple therapy. Indeed, metronidazole resistance can be partially or almost completely overcome by increasing the total daily dosage to 1.5 to 2 g divided into 3 or 4 doses throughout.

### Table 1. Empiric First-Line Therapies for *Helicobacter pylori* Infection

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Agents</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard bismuth-based quadruple therapy</td>
<td>PPI</td>
<td>BID</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td>Bismuth</td>
<td>QID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metronidazole 250 mg or 500 mg</td>
<td>QID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetracycline 500 mg</td>
<td>QID</td>
<td></td>
</tr>
<tr>
<td>Branded bismuth-based quadruple therapy</td>
<td>PPI</td>
<td>BID</td>
<td>10 days</td>
</tr>
<tr>
<td></td>
<td>Combination bismuth subcitrate potassium + metronidazole + tetracycline, 3 capsules</td>
<td>QID</td>
<td></td>
</tr>
<tr>
<td>Rifabutin-based triple therapy</td>
<td>PPI</td>
<td>BID</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td>Rifabutin 150 mg</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amoxicillin 750 mg</td>
<td>TID</td>
<td></td>
</tr>
<tr>
<td>Branded rifabutin-based triple therapy</td>
<td>Combination omeprazole magnesium + amoxicillin + rifabutin, 4 capsules</td>
<td>TID</td>
<td>14 days</td>
</tr>
</tbody>
</table>

BID, twice daily; PPI, proton pump inhibitor; QID, 4 times daily; TID, 3 times daily.
the day and increasing the total duration of therapy. If unsuccessful despite this attempt, alternative forms of bismuth-based quadruple therapy could be considered, such as substituting metronidazole with amoxicillin, although this has not been studied much outside East Asia.

### High-Dose Dual Therapy

Given its simplicity, high-dose dual therapy consisting of high-dose amoxicillin (2-3 g daily) and PPIs is an attractive option for *H. pylori* treatment. Eradication success with high-dose dual therapy has been shown to be comparable with bismuth-based quadruple therapy in some studies from East Asia. However, results from studies outside East Asia have demonstrated less success. For example, with treatment of 3 g of amoxicillin and 120 mg of omeprazole daily for 14 days, eradication rates in a US multicenter trial were only 58%. However, emerging evidence supports the potential use of vonoprazan, a drug from a new and more potent class of acid-suppressing agents, instead of a PPI in dual therapy. In a recent phase 3 clinical trial from the United States and Europe, vonoprazan-based dual and triple therapy (with clarithromycin) achieved similar eradication rates (77.2% and 80.8%, respectively). For the primary endpoint in strains not resistant to amoxicillin or clarithromycin, both dual and triple therapies with vonoprazan were non-inferior to lansoprazole-based triple therapy (78.5% and 84.7% vs 78.8%, respectively). For the secondary endpoint in strains with clarithromycin resistance, both dual and triple therapies with vonoprazan were significantly superior to lansoprazole-based triple therapy (69.6% and 65.8% vs 31.9%, respectively).

### Rifabutin-Based Triple Therapy

Rifabutin-based triple therapy has generally been considered an appropriate regimen after patients fail 1 or more therapies against *H. pylori*. However, a recent study from the United States found evidence suggesting a role for rifabutin-based triple therapy in the first line, leading to its US Food and Drug Administration approval. In a clinical trial of treatment-naïve patients, rifabutin-based triple therapy (with omeprazole and amoxicillin in a single capsule [Talicia, RedHill]) produced a greater eradication rate (83.8%) than high-dose dual therapy with...
Treatment Regimens for Refractory Helicobacter pylori

When deciding among regimens for refractory H pylori infection, providers should first consider patient tolerance, ability to adhere to treatment, prior antibiotic exposure, and the presence or absence of a true penicillin allergy. If available, local H pylori resistance patterns to the most commonly prescribed antibiotics should also be reviewed and used to help guide selection (Table 2). Additionally, a bismuth-based quadruple therapy or a rifabutin-based triple therapy could be used empirically as a second-line therapy if it had not been used as the initial treatment regimen. Finally, a thorough review of the patient’s medical record and detailed shared decision-making with the patient can help determine the best next course of action.7,19

When an initial therapy fails, providers should avoid antibiotics that were previously used, particularly clarithromycin and levofloxacin, for which resistance is very likely. However, as resistance to amoxicillin, tetracycline, and rifabutin is low in the United States, these antibiotics can generally be used in subsequent treatment regimens.

If a patient declares a penicillin allergy, testing should be performed because most patients will not exhibit a true allergy. If testing reveals no evidence of penicillin allergy, there are several treatment options. First, empiric rifabutin-based triple therapy can be considered because H pylori is rarely resistant to the drugs in this combination. Rifabutin-based triple therapy includes twice-daily high-dose PPI, rifabutin 150 mg once daily, and amoxicillin 750 mg 3 times daily for a total of 14 days. The combination omeprazole, amoxicillin, and rifabutin pill simplifies this regimen and contains omeprazole 10 mg, amoxicillin 250 mg, and rifabutin 12.5 mg in each capsule, and the treatment involves taking 4 capsules 3 times daily for 14 days. The other option for patients who are not allergic to penicillin depends on antibiotic susceptibility data. If levofloxacin or clarithromycin resistance locally is known to be less than 15% (unlikely in the United States) or the strain is known to be sensitive to levofloxacin or clarithromycin, either antibiotic could be used in a triple therapy with high-dose PPI twice daily and amoxicillin 750 mg 3 times daily, or in a quadruple therapy with high-dose PPI, bismuth, levofloxacin 500 mg daily, and amoxicillin 750 mg 3 times daily. For patients allergic to penicillin and in a region with low levofloxacin resistance or with a known levofloxacin-sensitive H pylori strain, a regimen with PPI, bismuth, levofloxacin, and tetracycline or a regimen with PPI, bismuth, levofloxacin, and metronidazole can also be considered, bearing in mind that there are very little to no data on these combinations in US patients. In general, if a strain is sensitive to both clarithromycin and levofloxacin, clarithromycin is preferred, given that fluoroquinolones may have potential adverse effects such as tendonitis and cardiac arrhythmia.20

Testing for Resistance

Antimicrobial resistance testing is recommended after a patient has failed 1 or more empiric therapies. In the United States, culture-based approaches using agar dilution or an epilometer test have been available in a very limited number of hospitals or via a send-out service to a small number of commercial laboratories. Owing to its fastidious properties, culturing H pylori from gastric biopsy samples is not easy and in some cases fails because of problems with specimen handling and processing leading to a loss of viability during shipping. As a result, most gastroenterologists have underutilized resistance testing despite declining eradication rates.

H pylori resistance testing has entered a new era in which awareness of its necessity has increased and molecular techniques are commercially available using fresh or formalin-fixed gastric biopsies or stool samples (Table 3).21 For endoscopists, molecular approaches are easier because sample processing is simpler and specimen recovery is greater. Polymerase chain reaction (PCR) assays, including real-time PCR, digital PCR, and PCR enzyme immunoassay, with sequencing of amplified segments are faster than culture-based methods with a turnaround time of a few days.13 However, they are limited to identifying known regions of mutation, cannot determine minimum inhibitory concentrations, and cannot distinguish between live organisms and the presence only of H pylori DNA.

Molecular susceptibility testing can also be performed using next-generation sequencing (NGS) of gastric biopsies (using fresh or formalin-fixed paraffin-embedded tissues) and now even with stool samples.22,23 This approach utilizes knowledge of the molecular underpinnings of phenotypic resistance to assess for the presence of gene mutations to the 6 most commonly prescribed antibiotics in H pylori regimens: clarithromycin, amoxicillin, tetracycline, metronidazole, rifabutin, and levofloxacin. The test
has been commercialized with proprietary methodology to offer a turnaround time of 24 to 72 hours. However, full prospective evaluation of NGS with phenotypic methods and, more importantly, outcome measures is awaited because the correlation between resistance prediction by NGS and phenotypic resistance and eradication rates in US populations is not yet clear. The test appears highly predictive for levofloxacin or clarithromycin in triple therapy, but perhaps less predictive for metronidazole-containing regimens.24,25

Optimizing Proton Pump Inhibition

PPIs are essential components of current eradication therapies. PPIs synergize with antibiotics by suppressing gastric acidity, increasing the proportion of bacteria in the dividing and growing state, and allowing for better antibiotic efficacy.26 PPIs also inhibit urease, which helps H pylori adapt to and survive the acidity of the gastric environment. Standard PPI doses are pantoprazole 40 mg, omeprazole 20 mg, lansoprazole 30 mg, esomeprazole 20 mg, and rabeprazole 20 mg. PPIs administered at twice the standard dosage in H pylori eradication regimens are typically referred to as high-dose PPIs.27 Some studies demonstrate that high-dose PPIs may allow for improved eradication rates, overcoming variances in PPI metabolism.27

The variability in how PPIs are metabolized can contribute to differences in treatment efficacy owing to polymorphisms in the CYP2C19 and CYP3A4 genes that create inactive metabolites. Poor PPI metabolism has been found in a larger percentage of East Asian patients than White patients (15%-20% vs 3%, respectively).28 Eradication rates are higher in poor metabolizers as a result of greater acid suppression.29,30 The pharmacokinetics, and to a lesser extent pharmacodynamics, of the earlier generation of PPIs (omeprazole, lansoprazole, and pantoprazole) are significantly impacted by CYP2C19 polymorphisms. This is much less of an issue for rabeprazole and esomeprazole.26 Vonoprazan, a drug in the class of potassium-competitive acid blockers (PCABs), may have advantages over PPIs in combination with antibiotics for improved H pylori eradication success. Compared with PPIs, PCABs are faster-acting and are not significantly affected by CYP2C19 polymorphisms.31 Vonoprazan has shown considerable promise in Japan, where it was first approved for use.32,33 As discussed previously, US clinical trials have recently been completed and the final results are awaited.18

Table 3. Laboratories in the United States Offering Helicobacter pylori Susceptibility Testing

<table>
<thead>
<tr>
<th>Culture-Based Resistance Testing</th>
<th>Catalog Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARUP Laboratories</td>
<td>2006686</td>
</tr>
<tr>
<td>Mayo Clinic Laboratories</td>
<td>HELIS</td>
</tr>
<tr>
<td>Labcorp</td>
<td>18085</td>
</tr>
<tr>
<td>Quest Diagnostics</td>
<td>369949</td>
</tr>
<tr>
<td>Microbiology Specialists Inc</td>
<td>058, 238</td>
</tr>
<tr>
<td>Molecular Resistance Testing</td>
<td>Catalog Code</td>
</tr>
<tr>
<td>Mayo Clinic Laboratories (stool PCR)</td>
<td>HPFRP</td>
</tr>
<tr>
<td>American Molecular Laboratories (next-generation sequencing of gastric biopsies or stool specimens)</td>
<td>PyloriAR/AmHPR</td>
</tr>
</tbody>
</table>

Adapted from Graham DY, Moss SF.31

PCR, polymerase chain reaction.

Probiotics

Probiotic adjuncts have been studied in an effort to improve eradication rates and/or reduce the adverse effects of current H pylori therapies. A network analysis of studies predominantly from Asia reported that the use of probiotics slightly improved eradication with triple therapy (intent-to-treat, 81.5% vs 71.6%).34 The probiotic arms of these studies had approximately one-half the rate of antibiotic side effects compared with the placebo group. Similarly, a recent randomized controlled trial from Greece using probiotics as an adjunct to concomitant therapy reported greater eradication rates with the addition of a probiotic compared with placebo (92.0% vs 86.8%).35 However, given the significant heterogeneity between studies in the meta-analysis and concerns over the quality of many of the studies, the use of probiotics should still be considered experimental.

Patient and System-Related Risk Factors for Failure

Antibiotic resistance is the most common reason that H pylori therapies may fail, but many other factors can also contribute. For example, socioeconomic status in
childhood is known to affect acquisition of H pylori and its transmission. A crowded household, unstable housing situation, and parents’ occupation as unskilled rather than skilled workers have all been associated with increased H pylori infection risk. 36 Although relatively few studies have attempted to directly assess possible correlations between such socioeconomic factors and H pylori eradication success, 1 study reported that annual household income less than $54,000 was associated with a decreased probability of eradication. 37 Higher odds of therapy failure noted in studies performed outside the United States include body mass index greater than 30 and smoking. 38-40 Further, nonadherence can be a significant issue. Adherence to greater than 60% of the course of antibiotics is considered necessary for successful eradication efforts. 41 A high pill burden, increased regimen complexity, high drug costs, and poor patient-provider communication can each hinder medication adherence. 42 Many of these issues can be addressed with shared physician-patient decision-making and are particularly important to consider in treating refractory H pylori infections.

Conclusion

Treating H pylori infection remains a common issue for gastroenterologists and has become more challenging during the past 20 years because of increased antimicrobial resistance. Practitioners should aim to prescribe antibiotics based on the local H pylori resistance pattern wherever possible. However, as these data are generally not available, bismuth-based quadruple therapy containing tetracycline and metronidazole for 14 days is now the preferred empiric choice. If this therapy fails, rifabutin-based triple therapy is recommended. If a patient is concerned about a possible penicillin allergy, prompt referral to an allergist should be made in order to enable the use of amoxicillin. Because clarithromycin resistance and levofloxacin resistance are now common among US H pylori strains, these antibiotics should generally be avoided and used only when strains are known to be susceptible to them, as determined by resistance testing. Providers should also appreciate the essential role of acid suppression and consider doubling the PPI dosage, especially in refractory cases or when their rates of primary treatment with empiric regimens are suboptimal. When the treatment choice is unclear, several commercial laboratories now offer antimicrobial susceptibility testing to guide regimen selection. Finally, effective communication with patients and consideration of potential demographic, social, cultural, and financial barriers to treatment adherence can help increase the success of H pylori eradication efforts.

Disclosures

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References