Practice Tips From the Updated *Helicobacter pylori* Treatment Guidelines

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Abstract: In 2024, the American College of Gastroenterology released updated guidelines for managing *Helicobacter pylori* infection, replacing the previous 2017 guidelines. Since that time, 3 new first-line treatment options have been approved in the United States and knowledge of rising antimicrobial resistance (now above 30% for clarithromycin, levofloxacin, and metronidazole) has been accumulating. Key clinical updates in the 2024 guidelines include new recommendations on screening practices, selecting the most appropriate treatment regimens for initial *H pylori* infection, and using antimicrobial susceptibility testing in cases where the infection does not respond to initial therapy. This article summarizes these updates with an emphasis on how the current guidelines differ from the previous version. The aim of this article is to present this information in a digestible manner for practicing gastroenterologists and other clinicians who treat patients with *H pylori* infection.

Keywords
Helicobacter pylori, guidelines, screening, treatment, antimicrobial stewardship, gastric cancer prevention

Helicobacter pylori causes chronic gastritis that can lead to peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. Infection with *H pylori* is also associated with certain other conditions and symptom complexes such as iron-deficiency anemia, idiopathic thrombocytopenic purpura, and dyspepsia.[1] Although there has been a progressive gradual decline in the global prevalence of infection from 58.2% in 1980 to 1990 to 43.1% in 2011 to 2022, more than 40% of the adult population of the world remains infected.[2] Approximately one-third of people in the United States are estimated to be *H pylori*–positive, although precise estimates are lacking in recent years. The distribution of *H pylori* infection in the US population is heterogeneous, with the highest prevalence in elderly individuals (owing to the age cohort effect), minority populations, and first-generation immigrants from endemic areas such as Central and South America, East Asia, Sub-Saharan Africa, and Eastern Europe.[3-5]

The American College of Gastroenterology (ACG) recently published *H pylori* management guidelines[6] with significant updates to the prior recommendations published in 2017.[7] Importantly, the 2017 management guidelines relied heavily upon extrapolation from studies

performed outside of North America. Since then, new data from US patients have become available that highlights the rising rates of resistance of commonly used antibiotics for treatment of *H pylori*. The new guidelines describe the efficacy of new treatment regimens with alternate antibiotics and acid-suppressive agents and review several regimens in common clinical use.[6] They also contain important information on identifying patients at high risk for *H pylori* infection, as well as advice on selecting a suitable regimen for both first-line treatment and refractory infections. Notably, for the first time, the updated guidelines incorporate information about antimicrobial resistance testing into regimen selection as well as guidance on its clinical utility. This is particularly important as the management of this infection shifts from an empiric approach to more targeted, evidence-based therapy guided by antimicrobial stewardship principles.[8]

As with all ACG guidelines, the authors of the 2024 *H pylori* management document were selected based upon their clinical expertise, working in concert with gastroenterology methodologists who helped formulate the clinical questions, conducted literature searches, and assessed the quality of the evidence for each recommendation statement based upon the well-established Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. The guidelines were then revised in response to comments from external peer reviewers and by the ACG itself prior to publication.

The goal of this primer is to update clinicians on the appropriate treatment of *H pylori* infection.

Table 1. Key Takeaways From the ACG 2024 *Helicobacter pylori* Treatment Guidelines

First-line treatment (treatment-naive patients)
• Optimized bismuth quadruple therapy for 14 days is preferred
• Rifabutin triple therapy or potassium-competitive acid blocker dual therapy for 14 days are suitable empiric alternatives in patients without penicillin allergy
Subsequent treatments (refractory/salvage cases)
• Optimized bismuth quadruple therapy for 14 days is preferred, if not treated with this previously
• If previously treated with bismuth quadruple therapy and not penicillin-allergic, rifabutin triple therapy is recommended
• If optimized bismuth quadruple therapy failed and either rifabutin triple therapy also failed or if penicillin-allergic, use antimicrobial susceptibility testing to guide next choice of regimen
Antimicrobial susceptibility testing
• Regimens containing clarithromycin or levofloxacin should only be used if antibiotic susceptibility is confirmed
• Use antibiotic susceptibility testing whenever the choice of therapy remains unclear
Screening
• Focused screening for *H pylori* is appropriate in high-risk populations (non-White racial/ethnic groups) at age 45-50 years for cancer prevention

ACG, American College of Gastroenterology.

Changes From the 2017 Guidelines

The 2024 ACG guidelines include 5 recommendations for treatment-naive patients and 7 for patients with persistent infection after at least 1 failed treatment attempt. In addition, there are 6 key concepts (statements that could not be formally tested using the GRADE methodology). This article focuses on the novel aspects of the guidelines, when compared with the ACG guidelines from 2017 (Table 1). Key areas of *H pylori* management guidance are discussed in the following sections.

Bismuth Quadruple Therapy Is First Line and Should Be Optimized

In 2017, bismuth quadruple therapy, or a concomitant quadruple therapy consisting of a proton pump inhibitor (PPI), clarithromycin, amoxicillin, and metronidazole, was recommended as first-line therapy over clarithromycin triple therapy. This had been the standard treatment for many years based on concerns over clarithromycin resistance, although data on that subject were very limited. It is now clear that clarithromycin resistance is common in the United States (over 30%, as discussed in the following section) and that clarithromycin triple therapy has unacceptable efficacy. Therefore, an optimized bismuth quadruple therapy is now recommended as the preferred first-line option in the 2024 guidelines. Data supporting this recommendation have come from 3 reasonably large retrospective US series from the past 5 years, demonstrating clear superiority of the bismuth quadruple regimen over clarithromycin triple therapy (85%-87% eradication rates compared with 76%-80%, respectively) in cohorts of patients from Rhode Island, the US military, and a national medical claims database.[9-11] Fourteen days is the recommended duration of this therapy, as with all regimens in the 2024 guidelines. This is an important recommendation because the prior (2017) guidelines had included various 5-, 7-, 10-, or 14-day options as first-line recommendations. (An exception is Pylera [AbbVie], the single drug combination of bismuth subcitrate [not salicylate], tetracycline, and metronidazole, which is marketed

Table 2. Optimized Bismuth Quadruple Therapy (14 Days)

Drug	Dosing	Notes
PPI	Twice-daily standard dose, 30-60 min before breakfast/dinner	Esomeprazole or rabeprazole preferred, pantoprazole nonpreferred (based on relative acid-inhibitory activities)
Bismuth	Bismuth subsalicylate ≥300 mg 4 times daily	In event of salicylate allergy, substitute bismuth subcitrate or use the branded bismuth subcitrate/metronidazole/tetracycline combination tablet (10-day course with PPI)
Tetracycline	500 mg 4 times daily	Do not use doxycycline as substitute
Metronidazole	500 mg 3 or 4 times daily	

PPI, proton pump inhibitor.

as a 10-day pack to be taken with a PPI.) Because bismuth quadruple therapy does not contain a penicillin, it is safe to use in the small number of patients who have a true penicillin allergy.

In practice, there are a variety of bismuth quadruple regimens, but they are not all equally effective. The 2024 ACG guidelines define the specifics of an optimized bismuth quadruple therapy (Table 2) primarily based upon efficacy studies conducted outside of the United States demonstrating that substitution of doxycycline for tetracycline should be avoided[9] and that more efficacious PPIs (less prone to metabolism by the CYP2C19 polymorphism) were preferred over other PPIs. Additionally, the appropriate bismuth dose is specified (greater than 300 mg of bismuth subsalicylate or 120-300 mg of bismuth subcitrate 4 times daily), as is the appropriate dose of metronidazole in quadruple therapy (greater than 1.5 g daily), which can help eradicate strains that may be resistant to metronidazole in vitro.

New Treatment Regimens With Potent Acid Suppression Are Included As Suggested First-Line Choices; Rifabutin Triple Therapy Can Also Be Used Empirically If Bismuth Quadruple Therapy Fails

Over the past few years, 3 new regimens have received US Food and Drug Administration (FDA) approval for *H pylori* therapy, each based on high levels of gastric acid inhibition. The first is a combination tablet of rifabutin with amoxicillin and omeprazole (Talicia, RedHill Biopharma), given in daily doses of 150 mg, 3 g, and 120 mg, respectively. In modified intention-to-treat analysis, the eradication success rate in treatment-naive US patients was 84% compared with 58% in the comparator arm that included amoxicillin and omeprazole only (at identical doses).[12] It is noteworthy that this dual treatment was ineffectual despite much higher eradication rates reported in studies in East Asian patients, a familiar theme in US *H pylori* clinical trials. If the combination tablet is not available, generic equivalents can be substituted at similar doses (omeprazole 40 mg and amoxicillin 1 g each 3 times daily). Because the lowest available dose of generic rifabutin is only 150 mg, the best option is likely 150 mg twice daily, as pharmacokinetic modeling suggests that generic rifabutin 150 mg once daily is inferior to 50 mg rifabutin 3 times daily (as dosed in the combination tablet).[13]

The second regimen is based on vonoprazan (Voquezna, Phathom Pharmaceuticals), the first potassium-competitive acid blocker (P-CAB) approved in the United States. P-CABs target the parietal cell proton pump, but compared with PPIs, they are more potent acid inhibitors, are faster-acting, and their efficacy is independent of the timing of dosing with regard to meals. In a multicenter study of treatment-naive patients from the United States and Europe, substituting the P-CAB vonoprazan for lansoprazole in clarithromycin triple therapy produced higher eradication rates (81% compared with 69%). Similar statistically high rates (77%) were achieved with a dual vonoprazan-amoxicillin combination in the same trial, leading to FDA approval of both the triple and dual regimens.[14] It is too early to know how well these new regimens will perform in real-world clinical practice, and they were not compared directly with bismuth quadruple therapy.

Given these concerns and the preference to avoid clarithromycin unless susceptibility testing is performed, the ACG guidelines made conditional recommendations based on low quality and moderate quality of evidence in favor of rifabutin triple therapy, as well as dual therapy with a P-CAB and amoxicillin, respectively, as suggested first-line treatment options in treatment-naive patients with *H pylori* infection. Importantly, the term *suggested* is a weaker endorsement than *recommended*, which is used for the bismuth quadruple regimen. It should also be noted that dual PPI-amoxicillin therapy was not recommended.

Rifabutin triple therapy was also suggested for patients with persistent *H pylori* infection who failed

bismuth quadruple therapy (based on low quality of evidence). There was insufficient evidence from North America to recommend high-dose PPI or P-CAB dual therapy as a salvage regimen.

Finally, both rifabutin- and vonoprazan-containing regimens use amoxicillin and cannot be used in the confirmed penicillin-allergic patient. For patients with unproven penicillin allergy (approximately 10% of the US population), allergy testing is recommended. This is an important step, as amoxicillin is a mainstay of most salvage therapies.

Use Clarithromycin or Levofloxacin Only If Antimicrobial Susceptibility Is Confirmed

Although only a key concept and not a formal recommendation (based on insufficient evidence), this may be the most significant statement in the new guidelines, as it represents a major shift in the approach to management of *H pylori* infection from empiric to biologically based.

Increasing antimicrobial resistance has been well documented for *H pylori*, with primary and secondary resistance rates to clarithromycin, metronidazole, and levofloxacin rising above 15% globally.[15] In the United States, a meta-analysis of data published between 2011 and 2021 reporting the resistance patterns of *H pylori* strains has described rates of resistance of 42.1% for metronidazole, 37.6% for levofloxacin, 31.5% for clarithromycin, 2.6% for amoxicillin, 0.87% for tetracycline, and 0.17% for rifabutin. Additionally, 11.7% of the strains exhibited dual clarithromycin and metronidazole resistance.[16] Using data from 907 US and European participants from the trial that led to vonoprazan approval,[14] 22.2% of the *H pylori* isolates were resistant to clarithromycin, 1.2% to amoxicillin, and 69.2% to metronidazole.[17] The high rates of clarithromycin and levofloxacin resistance in the United States and the clear link between resistance to these antimicrobials and their failure in triple therapies[18] underlie the strong recommendation against continued empiric use. In the 2017 guidelines, prior antibiotic exposure history was used as a surrogate or predictor of likely resistance to clarithromycin or levofloxacin. The current guideline encourages antimicrobial susceptibility testing, particularly in refractory cases if the choice of therapy is unclear, and especially in cases of definite penicillin allergy.

Antimicrobial susceptibility testing has had limited use in clinical practice in the United States to date, primarily owing to difficulty with culture-based methods. The biggest drawback to using culture has been the exacting requirements for gastric biopsy tissue collection and the need to transport the specimens to laboratories far from the endoscopy suite, which can hinder successful bacterial growth. The emergence of molecular-based methods (polymerase chain reaction and next-generation sequencing) using either gastric biopsies or stool provides a more practical clinical pathway.[19] Although issues over the costs and reimbursements for molecular-based methods remain to be resolved, the emphasis in the guidelines on antimicrobial susceptibility testing in general should prompt providers treating *H pylori* to explore how they can obtain such testing in their practices. As this is a rapidly evolving area with more laboratories offering molecular testing, ongoing discussion with infectious disease, microbiology, and pathology colleagues locally is encouraged in order to develop easily applicable best practice models.

Acknowledging that antimicrobial susceptibility testing is only now becoming widely available, the 2024 ACG guidelines include 2 separate algorithms to guide the management of refractory cases—one that incorporates the results of antimicrobial susceptibility testing while the other does not. Without antimicrobial susceptibility testing, the choice of therapies is extremely limited, essentially just optimized bismuth quadruple therapy for those patients who are penicillin-allergic.

In refractory cases, for patients who have not previously received bismuth quadruple therapy, optimized bismuth quadruple therapy is suggested and recommended over quinolone-based therapy. In patients who had previously received PPI-clarithromycin triple therapy, optimized bismuth quadruple therapy is suggested. In

Table 3. Evidence for *Helicobacter pylori* Eradication Reducing Risk of Gastric Cancer

Evidence	Risk reduction
Randomized controlled trials in *H pylori*–positive healthy individuals	36% reduction (meta-analysis)[20]
Randomized controlled trials in *H pylori*–positive patients undergoing endoscopic resection of gastric cancer	48% reduction (meta-analysis)[20]
Randomized controlled trial in first-degree relatives of gastric cancer patients	55% reduction[21]
Population screening/treating (Matsu Islands, Taiwan)	50% reduction[22]
Retrospective (United States)	76% reduction in Veterans Affairs cohort[23] 63% reduction in Kaiser Permanente Northern California cohort[24] (noncardia cancer; after ≥8 years follow-up)

patients who had received bismuth quadruple therapy, rifabutin triple therapy is suggested. The guidelines also state that clarithromycin-containing regimens should be avoided in the absence of demonstrated antimicrobial susceptibility. Levofloxacin-based triple therapy is suggested in patients with known levofloxacin-sensitive strains only when other treatments have been tried or are unavailable, owing to the adverse side-effect profile and black-box warning of levofloxacin. Acknowledging the dearth of clinical trials of salvage treatments in US populations, it is important to note that all recommendations regarding refractory treatment were conditional and based on low- or very low-quality evidence.

Consider Screening of High-Risk Populations to Prevent Gastric Cancer

The World Health Organization declared *H pylori* to be a definite (group one) carcinogen in 1994 based upon emerging evidence linking *H pylori* to gastric cancer. Since that time, the evidence base has increased enormously and there are now numerous studies demonstrating the benefit of eradication of *H pylori* in gastric cancer prevention, including in primary prevention randomized controlled trials, after endoscopic resection of early gastric cancer, and in first-degree relatives of gastric cancer patients.[20,21] In these studies, which were mainly performed in East Asia,[22] *H pylori* eradication was associated with a 30% to 50% decrease in subsequent gastric cancer development (Table 3).

Prospective randomized *H pylori* eradication studies in the United States are lacking, but 2 retrospective cohort studies have been recently published, each demonstrating significant gastric cancer risk reduction. The first study, which analyzed data from 371,813 Veterans Health Administration patients, reported significantly higher risks of gastric cancer among racial and ethnic minorities as well as smokers. It also showed eradication of *H pylori* decreased risk by 75% compared with those with persistent infection.[23] The second cohort consisted of 716,567 enrollees in the Kaiser Permanente Northern California program with a history of *H pylori* testing and/or treatment. Eradication therapy was associated with a significantly reduced incidence of noncardia gastric adenocarcinoma by 63% after 8 years compared with those who received no treatment.[24] The evidence linking *H pylori* eradication to a reduced risk of gastric cancer has prompted the adoption of *H pylori* screening programs in Japan and Korea, as two examples, and the implementation of *H pylori* screening trials in several European countries.[25] Although universal screening is not currently recommended in the current iteration of the recently published ACG guidelines, the authors state that "focused testing and treatment is appropriate" starting at age 45 to 50 years in non-White racial/ethnic groups and immigrants from high cancer incidence regions, as these groups have the highest rates of gastric cancer among people in the United States.

Pros and Cons of the Guidelines

Numerous guidelines for *H pylori* management exist based on different health systems and drug availability in nations and regions of the world. There are also global guidelines, particularly intended for resource-poor countries.[26] The Maastricht guidelines are arguably the most important of these because they are updated every few years based on input from experts around the world.[27] Important differences between the ACG 2024 guidelines and the latest (2022) Maastricht guidelines include the use of rifabutin in first- or second-line therapy by the ACG, whereas the Maastricht guidelines reserve rifabutin for failure after at least 2 prior therapies (likely owing to concerns over adverse effects). The Maastricht guidelines also recommend levofloxacin-based therapies as suitable empiric second-line choices, whereas the ACG 2024 guidelines recommend against this, based on the high rate of levofloxacin resistance in the United States and its concerning adverse-event profile. Importantly, the ACG 2024 guidelines emphasize avoiding empiric use of clarithromycin and levofloxacin and to only use these agents in known susceptible strains (in other words, mandating susceptibility testing before using either antimicrobial); in contrast, this is not mandated in the Maastricht guidelines. The 2024 ACG guidelines on *H pylori* treatment are the third iteration of the ACG guidelines, following previous versions published in 2017 and 2007.[7,28] Changes in the latest ACG guidelines reflect not only the evolution of knowledge of this subject and the results of recent clinical trials, but also a move toward a more robust review of the evidence, using systematic searching tools together with formal evaluation of the quality of the evidence, to inform the strength of specific recommendations. However, guidelines are never perfect products; they are often criticized for being out-of-date, inaccessible, irrelevant, and subject to bias.[29] Potential conflicts of interest are inevitable when recruiting subject matter experts on a topic of pharmacologic therapy, such as *H pylori* eradication, although mechanisms exist to mitigate this, including declaring such potential conflicts openly for others to judge.

Although clinical practice guidelines are intended to complement, not replace, clinical judgment, they are published with the intention of changing clinical practice for the better. In this respect, how can the *H pylori* management guidelines in the *American Journal of Gastroenterology* be expected to improve clinical practice?

Readers of this article are likely gastroenterologists, gastroenterology trainees, or nurse practitioners or are already very interested in *H pylori* management. However, most prescriptions for *H pylori* therapy are from primary care practitioners who may not be aware of every single guideline. The majority of practitioners continue to use clarithromycin-based triple therapy and have not followed the 2017 ACG *H pylori* guidelines that state prominently (in the abstract): "For first-line treatment, clarithromycin triple therapy should be confined to patients with no previous history of macrolide exposure who reside in areas where clarithromycin resistance amongst *H pylori* isolates is known to be low." It is striking that clarithromycin-PPI triple therapy still dominates the US market, comprising greater than 80% of all treatments in 2016 to 2019.[11] Notably, in approximately half of the cases where clarithromycin-PPI triple therapy failed, exactly the same prescription was given a second time.[11] Thus, a massive implementation gap exists, and whether it will shrink with time is uncertain. Publishing guidelines for general use in a specialty-specific journal is a necessary first step, but much wider dissemination is needed for primary care adoption. This could be achieved through changing the recommendations in various platforms that primary care providers turn to in daily practice (eg, UpToDate or OpenEvidence), as well as through modifying the care algorithms used in electronic medical record systems and pharmacy and insurance plans.

Conclusions: Filling the Knowledge Gaps

One of the important features of the 2024 ACG guidelines is the identification of important knowledge gaps, which are listed as future research priorities. Identifying which individuals are likely to benefit from *H pylori* screening to prevent gastric cancer is particularly important given the established benefits of primary prevention in regions and populations with high gastric cancer incidence. The authors also point out the need for randomized controlled trials directly comparing novel treatments with optimized bismuth quadruple therapy in treatment-naive patients, as well as in patients with persistent infection. The lack of US data regarding the efficacies of refractory treatments is disappointing and should be addressed, and trials of antibiotic susceptibility testing–based treatment compared with empiric treatments are needed to formally test the hypothesis that outcomes will be improved when tailoring therapy based on the antimicrobial susceptibility testing results. Ongoing efforts to establish an *H pylori* treatment registry in the United States, as in Europe and Latin America,[30] may help with some of these issues and can allow clinicians to make more informed and evidence-based decisions for their patients.

The field will undoubtedly continue to evolve rapidly. For example, P-CABs will probably replace PPIs in eradication regimens, given the importance of acid suppression in killing the organism in vivo.[31] Since the ACG guidelines were published in the fall of 2024, a recent network meta-analysis has recommended P-CAB–amoxicillin as the most efficacious regimen overall, although it should be noted that 24 of the 25 included studies were from East Asia, where dual therapies work better than they do in the West, for unclear reasons.[32] To achieve eradication rates of 90% or greater in the United States, it is likely that novel combinations of drugs will be needed, such as combining P-CAB–amoxicillin dual therapy with rifabutin and/or bismuth and/or tetracycline.

Disclosures

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