Diagnosis and Treatment of *Helicobacter pylori*

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Opinion statement

Helicobacter pylori infection remains a ubiquitous infection, especially in populations with poor socioeconomic conditions. Severe clinical outcomes of chronic infection include peptic ulcer disease and gastric cancer. Consensus meetings have developed guidelines for diagnosis, treatment, and management of *H. pylori* infection and related disorders in various populations. Clear benefits are obtained for *H. pylori* eradication in peptic ulcer disease and gastric mucosa-associated lymphoid tissue lymphoma. Most authorities agree that first-degree relatives of gastric cancer patients should undergo testing for *H. pylori* infection. *H. pylori* eradication in dyspepsia remains controversial. Global investigations continue to identify specific host and bacterial factors that are responsible for *H. pylori*-related inflammatory processes and development of clinical disease. Effective eradication regimens have been identified. The proton pump inhibitor (PPI)-based triple therapies are considered first-line therapy because of high patient compliance and good eradication rates. "Quadruple therapy" with bismuth-metronidazole-tetracycline plus a PPI is another first-line therapy with a similar eradication rate. This therapy is preferred in patients with penicillin allergy or prior exposure to clarithromycin. Rescue regimens are being developed because of rising antimicrobial resistance to metronidazole and clarithromycin in *H. pylori* strains. Emerging rescue combination therapies include furazolidone, rifabutin, and quinolones. These combination regimens are still preliminary and should be reserved for patients who have failed first-line therapies. Vaccine development remains elusive.

Introduction

The successful culture of *Helicobacter pylori* infection discovered by Barry Marshall and Robin Warren 20 years ago revolutionized our understanding of many upper gastrointestinal tract disorders. Acid was assumed to be the sole culprit in the etiology of peptic ulcers until the discovery of *H. pylori*. Our understanding of this microorganism has matured so we are beyond the observational studies, and global investigations are focused on effective treatment (eradication) of the infection and elucidation of its role in a multitude of clinical disorders [1••]. *H. pylori* infection remains a ubiquitous infection. This bacterial infection can be found in an estimated 50% of the world's population. It is concentrated in populations with poor socioeconomic conditions where associated diseases remain relatively common.

Virtually everyone infected has chronic active gastritis, but it remains unclear which individuals will develop one of the severe clinical outcomes associated with this infection. Some of the clinical outcomes are peptic ulcer disease, gastric cancer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or dyspepsia. The infection is most frequently acquired in childhood and can be transmitted from person to person likely by the gastro-oral and fecal-oral routes. The prevalence of the infection usually reflects a birth cohort effect in developed countries, although the prevalence in many developing countries is often high from childhood throughout adulthood. Factors that likely promote acquisition of the infection include poor socioeconomic conditions, large families, and residence in endemic areas [2,3].

Table 1. Tests to detect *Helicobacter pylori* infection

	Sensitivity	Specificity
Nonendoscopic		
Blood antibody test	85%	70%–80%
Urea breath test (^{13}C , ^{14}C)	95%	95%
Stool antigen test	90%–95%	85%–90%
Endoscopic		
Rapid urease test	90%–95%	90%–95%
Histology	90%–95%	90%–95%
Culture	50%	100%

DIAGNOSIS OF *HELICOBACTER PYLORI* INFECTION

Eradication of the infection should not be attempted without a positive test result. Eradication treatment should be offered if a positive test result is obtained. Diagnostic tests are well established and widely available (Table 1). Selection of a noninvasive test should be based on prevalence of *H. pylori* infection in the population, past exposure to antibiotics, and availability of the tests [4]. General categories of diagnostic tests for *H. pylori* infection include those that are biopsy-based, utilizing endoscopy (invasive), and those that do not (noninvasive). Noninvasive tests include blood/serum antibody tests, urea breath tests, and the stool antigen test.

Serologic or IgG antibody tests indicate past exposure to the infection; these tests cannot determine whether infection is present. Rapid qualitative immunoassays that can be performed in the office and quantitative enzyme-linked immunosorbent assay formats are available. Antibody tests can be very useful in a primary care setting where the prevalence is high and patients have not had frequent exposure to antimicrobial agents that affect *H. pylori*. The sensitivity and specificity of approved antibody tests are 85% to 90% and 78% to 80%, respectively. Because antibodies may remain positive for years after successful eradication and many people have received eradication treatment, the accuracy of serologic tests may now be lower. In general, the antibody test should not be used as follow-up to confirm eradication of the infection. The antibody titer does not help discriminate active or more severe infection. However, laboratory experts suggest that serologic titers can be helpful for long-term follow-up after eradication treatment if the follow-up sample can be compared with the initial diagnostic serum sample. A significant decrease in the titer may be seen 6 months after the infection has been eradicated. Antibodies against *H. pylori* are often present for years after successful treatment, so the presence of blood antibodies does not indicate presence of infection.

Urea breath tests contain either ^{13}C - or ^{14}C -labelled urea as the active ingredient. If *H. pylori* infection is present in the stomach, its urease will metabolize the urea to generate excess ^{13}C - or ^{14}C -labelled carbon dioxide in collected breath samples. Urea breath tests

can determine presence of active infection both before and after eradication treatment. Both types of urea breath tests have been approved by the US Food and Drug Administration (FDA) with an accuracy of 95% to diagnose and confirm eradication of *H. pylori* infection. The *H. pylori* stool antigen test is an enzyme-based immunoassay that is also useful for diagnosing active infection [5]. Ideally, the patient should submit a fresh stool to the laboratory. Sensitivity and specificity have been reported at 93% and 92%, respectively, but some single-center studies suggest that it may be less useful in some populations. European studies indicate that this test is useful for confirming eradication of the infection. Enhanced *H. pylori* detection has been reported in a European study using a rapid qualitative monoclonal version of the stool antigen test. Pretreatment *H. pylori* sensitivity and specificity were 91.3% and 93.5%, respectively; post-treatment sensitivity and specificity were 92% and 100%, respectively [6].

Endoscopic tests for *H. pylori* diagnosis are based upon gastric biopsies obtained from the antrum and/or corpus. These biopsy-based tests can detect active (current) infection. The most cost-effective biopsy-based test is the rapid urease test. Biopsies are placed in a gelatin or filter strip containing urea and a pH color indicator. When *H. pylori* bacteria are present in the biopsy, the microorganisms will metabolize the urea to generate an alkaline pH-causing a color change. Gastric biopsies for histology are useful if there is concern about underlying disease or a permanent record is needed. Histology is more expensive than the rapid urease test, but specimens can be reexamined using special stains to confirm diagnoses. Accuracy of the rapid urease test and histology are reported to be about 90% to 95%. Although culture is typically used to diagnose an infection, it is not recommended for *H. pylori*. Culture is labor-intensive and many hospital laboratories are not successful in culturing this infection because of its need for specific (microaerophilic) culture conditions, special media, and also because of its slow growth.

It is important to note that accuracy of tests for "active" *H. pylori* infection will be decreased if the patient is taking proton pump inhibitors (PPIs), high-

dose H₂-receptor antagonists, or antibiotics [7]. These agents can suppress growth of *H. pylori* such that a false-negative result may be obtained. Authorities recommend "holding" these drugs for 1 to 2 weeks prior to performing the diagnostic test in order to ensure an accurate test result.

GUIDELINES FOR MANAGEMENT OF *HELICOBACTER PYLORI* INFECTION

Consensus conferences have been convened in many geographic locations to establish guidelines for diagnosis and treatment of this prevalent infection. These guidelines help provide consistent management approaches, testing for the infection, and recommended eradication treatments to patients with *H. pylori*-associated diseases. The guidelines address issues for the primary care physician and also the specialist. These regional meetings reflect differences in population demographics, *H. pylori*-associated disease burden, economic conditions, and health-delivery systems. Many of these guidelines are relevant to the US population because of its heterogeneous population. For example, if a patient population includes many immigrants from Asia, Latin America, or Eastern Europe, the frequency of the infection is likely to be greater than in the general US population. These individuals are at greater risk for developing peptic ulcer disease and gastric malignancy in the setting of chronic *H. pylori* infection.

The National Institutes of Health Consensus Panel in 1994 was one of the first consensus conferences to examine the potential role of *H. pylori* in gastrointestinal disorders [8]. This panel recommended testing for the infection in patients with current peptic ulcer disease or a history of peptic ulcer disease. Eradication treatment was recommended for those with a positive test result. Proceedings of the International Update Conference on *H. pylori* confirmed the important role of *H. pylori* in peptic ulcer disease, in gastric cancer, and gastric MALT lymphoma [9]. Practice guidelines from the American College of Gastroenterology have also been published for the US population [10]. The European *H. pylori* Study Group has held two consensus meetings in which guidelines for their populations are listed [11]. The Japanese Society for Helicobacter Research published guidelines for the diagnosis and treatment of *H. pylori* infection for routine medical practice in Japan [12]. The Latin American Consensus meeting discussed its guidelines within the context of its population because of the variability in the prevalence and clinical outcomes observed in its different member populations [13]. The recent Canadian Consensus conference is particularly pertinent because of its adherence to an evidence-based approach to diagnosis and treatment of *H. pylori* [14••].

All consensus meetings recommend testing for and eradicating *H. pylori* infection in peptic ulcer disease and gastric MALT lymphoma. The European guidelines recommend *H. pylori* eradication in the patient on

chronic PPI therapy due to its potent acid suppression and concern about increased risk for gastric malignancy. Recommendations for eradication of the infection in the setting of gastric hyperplastic polyps, chronic atrophic gastritis, dyspepsia, the patient on chronic PPIs, and postgastrectomy for gastric cancer were variable from region to region. Studies in the Japanese population have confirmed the significant role of *H. pylori* in gastric cancer with recommendations to eradicate the infection to prevent subsequent gastric cancer. The prevalence of gastric cancer has declined in many developed countries with a corresponding uncertainty about screening for this infection to prevent gastric cancer. In those countries where gastric cancer has decreased and is less of a public health burden, few standard guidelines are available. Most authorities agree that first-degree relatives of patients with gastric cancer should be tested for the infection, and eradication treatment should be offered to those with a positive test result.

***HELICOBACTER PYLORI* INFECTION AND ASSOCIATED DISORDERS**

Helicobacter pylori is accepted as the most common cause of peptic ulcer in the absence of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). A recent meta-analysis confirmed the significant increased risk of peptic ulcer and ulcer bleeding in patients with *H. pylori* [15••]. All patients with a history of ulcers or a current ulcer should be tested for *H. pylori* infection. Eradication of the infection has resulted in decreased recurrence of peptic ulcer disease [16]. An increasing proportion of peptic ulcers are now found to be *H. pylori* negative. This is probably due to the combination of the eradication of the infection, the increasing NSAID use, and a decline in *H. pylori* prevalence. This emphasizes the need to confirm *H. pylori* infection prior to prescribing *H. pylori* therapy. If a patient is beginning chronic NSAID therapy and has had a prior ulcer, it is prudent to check for *H. pylori* infection.

There has been some concern that eradication of *H. pylori* infection may cause or exacerbate gastroesophageal reflux disease (GERD) symptoms. Recent studies have shown that many patients have simultaneous peptic ulcer and GERD. Much of the controversy related to this issue is based on the variability in study design, sample size, and endpoint measurements. When *H. pylori* infection is eradicated and the ulcer healed, the GERD symptoms may become apparent. A posthoc analysis of US clinical trials of patients with duodenal ulcer showed no significant differences in erosive esophagitis or GERD after *H. pylori* eradication [17]. A recent systematic review [18] and a randomized controlled trial [19] concluded that there is little evidence to support an interaction between *H. pylori* infection and GERD. Currently, there is no known causal relationship between GERD and *H. pylori* infection. The impact of *H. pylori* infection in erosive esophagitis heal-

ing and GERD symptom control were studied in a large European study [20]. Findings from this study indicated that if *H. pylori* infection were present, pantoprazole was more effective in erosive esophagitis healing and symptom control. However, there was no impact of *H. pylori* in erosive esophagitis in clinical trials with esomeprazole or rabeprazole [21,22]. This suggests that there may be differences in acid suppression with different PPIs in the presence or absence of *H. pylori* infection but its overall clinical impact is likely to be small.

Gastric adenocarcinoma remains the second most common cause of worldwide cancer-related deaths. Gastric cancer is often the outcome of a multifactorial process in susceptible individuals with *H. pylori* infection that causes the onset of chronic gastric inflammatory cascade [23]. *H. pylori* infection was categorized as a Group 1 (definite) carcinogen by the World Health Organization [24]. Seroepidemiologic studies support a four- to sixfold increased risk of gastric cancer in the susceptible individual with chronic *H. pylori* infection [25], although the prevalence of the infection is not a consistent or reliable indicator of the risk within a specific population. Patients with atrophic gastritis who originate from countries such as Japan where gastric cancer remains relatively common are at increased risk for gastric cancer. Uemura *et al.* [26] have shown that eradication of *H. pylori* can decrease gastric cancer outcome in that population. However, whether or not premalignant gastric histology with intestinal metaplasia and gastric atrophy can be reversed after *H. pylori* eradication with decreased risk remains unclear. Lifestyle and environmental factors as well as host genetic factors are important in this clinical outcome. Studies from El-Omar *et al.* [27,28] demonstrated that increased interleukin (IL)-1 β expression and proinflammatory cytokine profiles are more commonly seen in gastric cancer. The Maastricht meeting has recommended that individu-

als taking chronic potent acid-suppressing medications should be tested for *H. pylori* infection because of the potential increased risk of gastric cancer [11].

Helicobacter pylori infection has been implicated in more than 85% of cases of low-grade gastric MALT lymphoma. This is a rare and indolent malignancy. Partial or complete regression of this tumor has been observed in over 70% of cases with eradication of the infection. Patients with advanced (high-grade) stages of this malignancy are likely to require surgery and/or chemotherapy.

Whether *H. pylori* infection has a causal role in dyspepsia continues to be debated. Dyspepsia is common and likely related to many different etiologies, as a subset of patients may well have dyspepsia related to this infection [29]. The challenge is identifying patient characteristics or predictors if *H. pylori* infection is implicated in their symptoms. When considering *H. pylori* eradication in dyspepsia, uninvestigated dyspepsia versus nonulcer dyspepsia should be considered [30]. Studies in many primary care settings indicate that the "test and treat" strategy for *H. pylori* infection is effective and reduces cost [31]. A large screening program for *H. pylori* in the United Kingdom showed no statistical benefit in quality of life after eradication in the setting of dyspepsia [32]. No global consensus has been reached about the long-term benefits of *H. pylori* eradication in the patient with nonulcer dyspepsia. This is largely due to variations in the study design, small sample sizes, and differences in follow-up duration and criteria. One meta-analysis showed no benefit for eradication in these patients [33]. A subsequent meta-analysis suggested that there is a small but statistically increased benefit for *H. pylori* eradication in this common clinical disorder [34]. A number of small or single-center studies suggest that eradication of the infection in this population may reduce overall costs by decreasing endoscopy workloads [35].

Treatment

Diet and lifestyle

- No particular foods or diet have been shown to eradicate or prevent *H. pylori* infection. A study of *H. pylori* infection in the Andes suggested that inadequately washed foods were associated with an increased infection rate [36]. Because infection prevalence is increased in lower socioeconomic conditions, it is recommended that foods be washed with clean water. A decline in *H. pylori* prevalence in the general population has been linked to improved socioeconomic conditions with good sanitation and dietary practices. Antioxidant supplements have been suggested because *H. pylori* infection decreases gastric ascorbic acid levels. An intervention study in Latin America showed a similar decrease in premalignant gastric histologic markers using antimicrobial therapy with or without ascorbic acid and beta-carotene [37]. Foods such as garlic, broccoli, and honey have been examined for inhibition of *H. pylori* growth in in vitro studies, but these findings have not been confirmed in human control patients. Probiotics with *Lactobacillus* have decreased *H. pylori* loads in humans and animal models [38,39]. Some postulate that probiotics

may be useful as a supplement to antimicrobial therapy. Smoking should be discouraged as it may delay or prolong healing of ulcer disease. Smoking and high dietary salt intake may enhance development of gastric cancer particularly in the setting of *H. pylori*-induced inflammation [40]. Interestingly, an inverse relationship between alcohol intake and *H. pylori* infection has been observed [41,42]. Laboratory studies suggest that alcohol suppresses growth of *H. pylori* but this has not been prospectively demonstrated in human studies.

Pharmacologic treatment

Proton pump inhibitors

	Five PPIs are available in the United States; they are omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. These prodrugs are the most potent acid inhibitory agents and act by inhibiting the H ⁺ /K ⁺ proton pump in gastric parietal cells.
Standard dosage	For the "PPI-based triple" regimen, most PPIs are prescribed twice daily. Omeprazole, 20 mg twice daily; lansoprazole, 30 mg twice daily; rabeprazole, 20 mg twice daily; and esomeprazole, 40 mg once daily. No clinical trials using pantoprazole in <i>H. pylori</i> eradication have been performed in the United States, so clinical efficacy in the US population is unproven, but many formularies permit use of pantoprazole, 40 mg twice daily for 10 to 14 days
Contraindications	Individual hypersensitivity to the various PPIs appear to be idiosyncratic reactions. Because the duration of treatment using these drugs in eradication treatment is short; there are no major contraindications.
Main drug interactions	Interaction of the PPIs with hepatic cytochrome P450 family is a potential source of drug interactions. Omeprazole, lansoprazole, and esomeprazole may induce these enzymes and affect metabolism of other drugs such as diazepam, warfarin, phenytoin, and ketoconazole. Rabeprazole and pantoprazole have the lowest induction of cytochrome P450 and may have the lowest drug interactions. Reported drug interactions with the PPIs are uncommon.
Main side effects	Diarrhea, constipation, headache, and abdominal pain
Special points	All PPIs are prescribed twice daily except esomeprazole, which is prescribed once daily. FDA-approved duration of treatment is 10 to 14 days except for the rabeprazole-based regimen, which has been approved for 7-day eradication treatment by the FDA.
Cost effectiveness	Pricing often depends on formulary with branded PPIs moderately expensive. Branded Prilosec (Procter & Gamble, Cincinnati, OH) is available over the counter. Generic omeprazole available.

Antibiotics

- Successful treatment (eradication) of *H. pylori* infection has been proven only with combination antimicrobial treatment. A positive *H. pylori* test result should be obtained prior to prescribing *H. pylori* treatment. Monotherapy should not be considered because no single-drug therapy has effective killing rates of *H. pylori* infection.
- Antibiotics used for first-line eradication treatment include clarithromycin, metronidazole, and amoxicillin. Most treatment durations in the United States have been approved at 10- and 14-day duration. Current FDA-approved combination therapies include two treatment categories (Table 2). First-line treatments include the "PPI-based triple therapy," that consists of a PPI, amoxicillin, and clarithromycin, or "quadruple therapy," that includes bismuth, metronidazole, tetracycline (BMT), and a PPI. Rabeprazole-based triple therapy has been approved by the FDA for 7-day treatment [43••]. Effective 7-day eradication treatment with esomeprazole, omeprazole, lansoprazole, and pantoprazole has been shown in non-US populations, but no clinical trials using this shorter treatment duration have been performed in the United States.

Table 2. Antibiotic regimens approved by the US Food and Drug Administration for *Helicobacter pylori*

Bismuth-metronidazole-tetracycline therapy for 14 days
Pepto-Bismol (Proctor & Gamble, Cincinnati, OH), 2 tablets orally 4 times daily
Metronidazole, 250 mg orally 4 times daily
Tetracycline, 500 mg orally 4 times daily
Plus H2RA for 8 weeks or PPI for 4 to 6 weeks
PPI triple therapy twice daily for 10 or 14 days
Omeprazole, 20 mg or lansoprazole, 30 mg orally twice daily
Amoxicillin, 1 g orally twice daily
Clarithromycin, 500 mg twice daily
PPI triple therapy twice daily for 7 days
Rabeprazole, 20 mg orally twice daily
Amoxicillin, 1 g orally twice daily
Clarithromycin, 500 mg twice daily
PPI triple therapy with once daily PPI for 10 days
Esomeprazole, 40 mg daily
Amoxicillin, 1 g orally twice daily
Clarithromycin, 500 mg twice daily

PPI—proton pump inhibitor.

- Proton pump inhibitor-based triple therapy is more frequently prescribed in the United States because of better patient compliance with fewer pills to take. Omeprazole, lansoprazole, and rabeprazole are prescribed twice daily; esomeprazole has received FDA approval for once-daily administration. Regimens have been approved by the FDA for 7, 10, and 14 days with intent-to-treat eradication rates of 80% to 85% and per protocol eradication rates greater than 90%. PPI triple therapy with clarithromycin and metronidazole can be highly effective for *H. pylori* eradication. Because of the increasing resistance to both these antibiotics, this regimen is not generally recommended for initial treatment.
- The BMT quadruple regimen antibiotics are taken four times daily and this regimen has been approved for 14-day treatment. In the absence of *H. pylori* antimicrobial resistance, eradication rates are similar among these regimens of greater than 85% to 90%. If the patient has a penicillin allergy, the BMT quadruple regimen should be prescribed. Other drugs should not be substituted in these approved regimens. For example, azithromycin should not be substituted for clarithromycin. *H. pylori* treatment trials with azithromycin demonstrate much lower eradication rates compared with clarithromycin.

Clarithromycin

	A member of the macrolide antibiotics with antibacterial activity based on binding to the 50S subunit of the bacterial ribosome and inhibiting protein synthesis. The 500-mg doses are preferred because lower doses may yield lower eradication rates [44].
Standard dosage	500 mg twice daily.
Contraindications	Hypersensitivity to this drug or other macrolides; avoid concomitant use with cisapride, astemizole, and terfenadine.
Main drug interactions	Warfarin, statins, phenytoin, rifabutin, and fluconazole.
Main side effects	Metallic taste, abdominal cramping, headache, and dyspepsia.
Special points	Patients previously exposed to this medication may be infected by <i>H. pylori</i> resistance to this antibiotic.
Cost effectiveness	Moderately expensive.

Amoxicillin

	Member of the penicillin family with a broad-spectrum antibacterial activity that inhibit the synthesis of the bacterial cell wall. It is well tolerated and widely available. It should not be substituted with ampicillin.
Standard dosage	1 g orally twice daily.
Contraindications	Do not use in those with penicillin allergy.
Main drug interactions	Ethotrexate and allopurinol.
Main side effects	Diarrhea, nausea, vomiting, and abdominal pain.
Special points	Reports of oral thrush development while on this drug.
Cost effectiveness	Available in generic form that is inexpensive.

Metronidazole

	Nitroimidazole with antiprotozoal and antibacterial activity.
Standard dosage	500 mg twice daily or 250 mg orally twice daily.
Contraindications	Hypersensitivity to metronidazole or other nitroimidazole derivatives; do not use in first trimester of pregnancy.
Main drug interactions	Warfarin.
Main side effects	Nausea and abdominal pain.
Special points	Potential disulfiram-like interaction of metronidazole and alcohol.
Cost effectiveness	Available in generic form that is inexpensive.

Tetracycline

	Inhibits protein synthesis by disrupting RNA translation in microorganisms.
Standard dosage	500 mg orally four times daily.
Contraindications	Hypersensitivity to tetracyclines; patients in the last part of pregnancy; children up to 8 years of age.
Main drug interactions	Compounds containing aluminum, iron, or calcium may decrease absorption of tetracyclines.
Main side effects	Diarrhea, nausea, vomiting, rash, and photosensitivity.
Special points	Do not use doxycycline as a substitute.
Cost effectiveness	Use generic form that is inexpensive.

Pepto-Bismol

	Pepto-Bismol (Proctor & Gamble, Cincinnati, OH) is the only available bismuth-containing drug in the United States.
Standard dosage	525 mg (2 tablets) orally four times a day.
Contraindications	Hypersensitivity to bismuth or salicylates.
Main drug interactions	Can interact with warfarin.
Main side effects	Constipation, diarrhea, nausea, and vomiting.
Special points	Darkening of the tongue and stool; patients should be warned that this is due to the drug and not gastrointestinal tract bleeding.
Cost effectiveness	Inexpensive. Available over the counter.

The eradication regimen

- Factors to consider in the selection of *H. pylori* eradication treatment include patient compliance, prior exposure to the antibiotics, safety, and allergy. Select a regimen with antibiotics to which the patient has not been previously exposed. If a patient has not been previously treated for *H. pylori* infection and has had little exposure to antibiotics, either regimen is useful but many practitioners would prescribe the PPI triple therapy because it contains significantly fewer pills. If the patient has been exposed to clarithro-

mycin, it may be prudent to prescribe the BMT quadruple therapy. If the patient has been previously treated with metronidazole, clarithromycin triple therapy is more likely to be successful. Obviously, if the patient has a penicillin allergy, amoxicillin should not be used. If there is known prolonged exposure to metronidazole and clarithromycin, a metronidazole-containing regimen should be prescribed for a longer duration to “overcome” potential metronidazole resistance.

- Educate the patient in the importance of taking all the prescribed medications to achieve the highest efficacy and to prevent antimicrobial resistance. The patient should be warned about possible side effects because these are multidrug therapies.

Management after a treatment failure

- Repeat eradication treatment for *H. pylori* infection should be guided by previously administered treatment regimens. Prior exposure to antibiotics may increase the risk of treatment failure if the same antibiotics are used [45]. Bacterial resistance to metronidazole and clarithromycin increases significantly in patients who have failed previous eradication treatments. Antimicrobial resistance in *H. pylori* includes genetic and metabolic processes. Recent estimates include clarithromycin resistance of 10% to 12% and metronidazole resistance of 30% to 40% in the US adult population [46]. Clarithromycin resistance in *H. pylori* is strongly correlated to treatment failure. Clarithromycin resistance is based on point mutations of the 16S RNA. By contrast, although metronidazole resistance is much more prevalent, resistance is based on *H. pylori* factors such as the RDX gene and appears to be “overcome” by repeat or longer duration regimens that include metronidazole.

Testing for *Helicobacter pylori* infection after eradication treatment

- Tests to confirm eradication include the urea breath, the *H. pylori* stool antigen, biopsy urease test, and histology. Follow-up testing should be undertaken no sooner than 4 to 6 weeks after completion of treatment. As mentioned above, patients should not be on acid-suppressing drugs such as PPIs or high-dose H₂-receptor antagonists or antibiotics because these drugs can suppress the density of *H. pylori* infection in the stomach. This decreased density can result in a false-negative test result with the urea breath test, stool antigen test, and all biopsy-based tests. Confirmation of eradication is important in complicated ulcer disease. There are no guidelines about follow-up testing in other *H. pylori*-related disorders. Some authorities recommend follow-up testing in all treated patients, particularly because diagnostic tests have become widely available and are much less expensive.

Emerging therapies

- Increased treatment failures related to noncompliance and antimicrobial resistance are pushing the search for new antibiotic combinations. A multicenter randomized trial evaluated a “single-triple” capsule of BMT plus omeprazole [47••]. Omeprazole, 20 mg twice daily plus three oral BMT (OBMT) capsules four times daily was compared with omeprazole, amoxicillin, clarithromycin (OAC) twice daily for 10-day treatment; modified intent-to-treat eradication rates were 87.7% for OBMT and 83.2% for OAC (95% CI, 3.9% to 12.8%; *P* = 0.29). Compliance was high. OBMT eradicated 91.7%

of *H. pylori* strains that were metronidazole sensitive and 80.4% metronidazole-resistant strains. OAC eradicated 92.1% of strains that were clarithromycin sensitive; only 21.4% with clarithromycin resistance were eradicated with OAC. This study confirmed that OBMT can “overcome” *H. pylori* with metronidazole resistance.

Rifabutin

Rifabutin is a rifamycin-like antimycobacterial drug. It has been designated as an orphan product for use in the prevention or treatment of disseminated *Mycobacterium avium* complex disease. Rifabutin has been used in pilot and single-center studies for *H. pylori* eradication in patients who have failed other approved *H. pylori* therapies. Perri *et al.* [48] used 300 mg daily with pantoprazole, 40 mg twice daily and amoxicillin, 1 g twice daily for 1-week treatment in 41 patients who had failed other PPI-based triple therapies. Intent to treat and per protocol analyses were similar at 71% (95% CI, 57% to 85%) and 74%, respectively. It appeared to be well tolerated with all subjects taking at least 80% compliance. Pilotto *et al.* [49] determined rifabutin's minimal inhibitory concentration to be 0.0003 to 0.0097 mg/mL for 87 different strains. This drug is not available in the United States. It is moderately expensive in countries where it is available [50].

- Standard dosage** Rifabutin has been prescribed at 300 mg daily and 150 mg daily in *H. pylori* eradication studies.
- Contraindications** Hypersensitivity to this drug and hepatic impairment.
- Main drug interactions** Rifampin is known to induce cytochrome P450 enzymes so similar interactions are considered possible for rifabutin. Increased warfarin metabolism and decreased zidovudine serum concentrations may be observed. Concurrent use with azithromycin or clarithromycin has been associated with an increased risk of neutropenia.
- Main side effects** Nausea, vomiting, diarrhea, rash, and abdominal pain. Neutropenia and uveitis have been reported.

Furazolidone

Furazolidone is a nitrofurantoin derivative with both antibacterial and antiprotozoan activity. It acts by interfering with bacterial enzyme systems. It is extensively metabolized in the intestines and excreted renally. A US single-center study of 27 patients evaluated 14-day furazolidone combination therapy including furazolidone, 100 mg three times daily; tetracycline, 500 mg three times daily; omeprazole 20 mg daily; and metronidazole, 500 mg three times daily or clarithromycin, 500 mg three times daily depending on antimicrobial susceptibility [51]. Overall eradication rate was 97%, but side effects were common and resulted in discontinuation of therapy by 26% of patients. Eradication rate of only 72% was obtained with a PPI-triple therapy including furazolidone, tetracycline, and lansoprazole, 30 mg twice daily. Improved *H. pylori* eradication rates were obtained with higher (200 mg twice daily) doses compared with lower doses (100 mg twice daily) [52].

- Standard dosage** Available in the United States as a 100-mg tablet. Many small studies of *H. pylori* eradication have been conducted with moderate to good efficacy. It should be reserved for those who have failed first-line treatments.
- Contraindications** Hypersensitivity and hepatic and renal impairment. Allergic angioedema reactions have been reported. It is structurally similar to nitrofurantoin; similar acute pulmonary reactions have been seen with furazolidone. Hemolytic anemia may occur in those with glucose-6-phosphate dehydrogenase deficiency.
- Main drug interactions** It has monoamine oxidase inhibitory properties, so it may interact with sympathomimetics, tyramine, and amine-containing foods, such as aged cheese, wine, or smoked/pickled meats.
- Main side effects** Nausea, vomiting, rash, and abdominal pain.
- Special point** May darken the urine. A disulfiram-like reaction may occur with alcohol-intake.

Quinolones

Ofloxacin and levofloxacin have been evaluated in combination therapies for *H. pylori* eradication in patients who have failed prior eradication therapies. Levofloxacin is the S-enantiomer of ofloxacin, and it is the primary isomer for antibacterial activity. Antibacterial activity for the quinolones occurs through inhibition of DNA gyrase activity. An open label study using twice daily doses of ofloxacin, 400 mg; amoxicillin, 1 gm; and rabeprazole, 20 mg had significantly better eradication rates with 14-day compared with 7-day therapy (92% versus 62%, respectively) [53]. Preliminary results of 10-day rescue therapy in 107 patients treated with levofloxacin, 250 mg twice daily; amoxicillin, 1 g twice daily; and esomeprazole, 40 mg twice daily for 10 days yielded an 87% eradication rate [54]. Studies of *H. pylori* eradication are still preliminary, and the use of the quinolones should be reserved for those who have failed first-line treatments.

Standard dosage	250-mg and 500-mg doses of levofloxacin are available.
Contraindications	Hypersensitivity to quinolones. Hyperglycemia has been reported in diabetic patients.
Main drug interactions	Increased prothrombin time with bleeding in patients on warfarin; chelated complexes with aluminum, iron, and zinc compounds may occur.
Main side effects	Nausea, diarrhea, and headache.

Vaccine development

- In regions with a high prevalence of *H. pylori* infection and where clinical outcomes such as peptic ulcer disease and gastric cancer are common, the ideal intervention would be a vaccine. The ideal vaccine should be prophylactic, therapeutic, safe, and well tolerated. However, no commercial vaccine is currently available. The large genetic heterogeneity of the microorganism is one of the challenges delaying development of an effective vaccine. Current investigations are evaluating various vectors, adjuvants, and routes of administration in animal models [55].

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