

REVIEW OF THERAPEUTICS

Treatment of *Helicobacter pylori* in Special Patient PopulationsCynthia T. Nguyen^{*1}  Kyle A. Davis,² Sarah A. Nisly,³  and Julius Li⁴

¹Department of Pharmacy, University of Chicago Medicine, Chicago, Illinois; ²Department of Pharmacy, Wake Forest Baptist Medical Center, Winston Salem, North Carolina; ³School of Pharmacy, Wingate University, Wingate, North Carolina; ⁴Department of Pharmacy, Southeast Louisiana Veteran Health Care System, New Orleans, Louisiana

Helicobacter pylori infection can lead to gastritis, gastric and duodenal ulcers, and gastric cancer. Consequently, complete eradication is the goal of therapy. First-line therapy for *H. pylori* infection includes clarithromycin triple therapy (clarithromycin, proton pump inhibitor [PPI], and amoxicillin or metronidazole), bismuth quadruple therapy (bismuth salt, PPI, tetracycline, and metronidazole or amoxicillin), or concomitant therapy (clarithromycin, PPI, amoxicillin, and metronidazole). However, many patients have relative contraindications to the antibiotics included in these regimens, making therapy selection difficult. Furthermore, failure of initial therapy makes selection of second-line therapy challenging due to concerns for potential resistance to agents included in the initial regimen. This review discusses *H. pylori* microbiology, including antibiotic resistance, and summarizes the existing evidence for first- and second-line treatment regimens that may be considered for special populations such as patients with penicillin allergies, patients with or at risk for QTc-interval prolongation, and patients who are pregnant, breastfeeding, or elderly.

KEY WORDS *Helicobacter pylori*, hypersensitivity, QT prolongation, pregnancy, breastfeeding, elderly. (Pharmacotherapy 2019;39(10):1012–1022) doi: 10.1002/phar.2318

Helicobacter pylori infection is common; however, the prevalence is generally low in the United States and varies with socioeconomic status, race, and ethnicity.¹ *Helicobacter pylori* infection is a common cause of gastritis, gastric and duodenal ulcers, and gastric cancer. Consequently, if diagnosed, the goal of therapy is complete eradication.² Worldwide, the treatment of *H. pylori* is complicated by antibiotic resistance, complex medication regimens, and adverse effects of the medications.

In the United States, the American College of Gastroenterology (ACG) clinical guideline for the treatment of *H. pylori* provides recommendations for first-line and salvage therapy.² Treatment typically consists of a combination of at least two antibiotics along with a proton pump inhibitor (PPI) (Table 1 and Table S1). Clarithromycin triple therapy for 14 days is recommended as first-line therapy in regions with low (less than 15%) clarithromycin resistance. In areas with higher resistance rates or among patients with previous macrolide exposure, bismuth quadruple therapy for 10–14 days is recommended. Concomitant therapy with a PPI, amoxicillin, clarithromycin, and metronidazole is also a likely efficacious first-line regimen, although data from North America are lacking.

Unfortunately, many patients have relative contraindications to the antibiotics included in first-line *H. pylori* regimens, making therapy

Conflict of interest: The authors have declared no conflicts of interest for this article.

*Address for correspondence: Cynthia T. Nguyen, Department of Pharmacy, University of Chicago Medicine, 5841 S. Maryland Avenue, MC0010 TE019, Chicago, IL 60637-1470; e-mail: cynthnguyen@gmail.com
© 2019 Pharmacotherapy Publications, Inc.

Table 1. Recommended *Helicobacter pylori* Treatment Regimens Based on Clinical Scenario

Clinical scenario	First-line regimens	Alternative regimens
General population ²	• Clarithromycin triple (when clarithromycin resistance is < 15% and no previous history of macrolide exposure) • Bismuth quadruple • Concomitant therapy	• Sequential therapy • Hybrid therapy • Levofloxacin based
β -Lactam allergy ²	• Clarithromycin triple with metronidazole (when clarithromycin resistance is < 15% and no previous history of macrolide exposure) • Bismuth quadruple	• Levofloxacin based excluding amoxicillin • Rifabutin-based triple or quadruple excluding amoxicillin
QTc-interval prolongation	• Bismuth quadruple	• Amoxicillin-based dual • Rifabutin-based triple or quadruple • Triple therapy with amoxicillin, metronidazole, and PPI
Elderly	• Clarithromycin triple (when clarithromycin resistance is < 15% and no previous history of macrolide exposure) • Bismuth quadruple	• Sequential therapy
Pregnancy and breastfeeding	• Without symptoms or with mild symptoms: postpone treatment until after pregnancy and breastfeeding • With hyperemesis gravidarum, weigh risks against benefits. If treatment is pursued, consider limiting therapy to 7 days. ■ first trimester: triple therapy with amoxicillin, metronidazole, and PPI; ■ second trimester, third trimester, or breastfeeding: clarithromycin triple therapy with amoxicillin	

PPI = proton pump inhibitor.

selection difficult. Furthermore, failure of initial therapy makes selection of second-line therapy challenging due to concerns for potential resistance to agents included in the initial regimen. Eradication rates with second-line therapy are often lower, and these regimens frequently have decreased tolerability. Consequently, thoughtful selection of initial therapy is critical. This review discusses *H. pylori* microbiology including antibiotic resistance and summarizes the evidence for treatment regimens among three commonly encountered special populations: patients with penicillin allergies, patients with or at risk for QTc-interval prolongation, and patients who are pregnant, breastfeeding, or elderly.

Data Sources and Extraction

A search of the PubMed database for human studies published in English from inception to May 2019 was performed using a combination of these terms: *Campylobacter pyloridis*, *H. pylori*, penicillin allergy, cephalosporins, carbapenems, fluoroquinolone, rifabutin, QT prolongation, bismuth quadruple therapy, triple therapy, breastfeeding, breast milk, pregnancy, geriatrics, and elderly. Our search yielded 1612 results

(Table S2). References of the included studies were reviewed to identify additional relevant studies. Titles, abstracts, and articles were evaluated for relevance, and trials evaluating the efficacy of medication regimens for the treatment of *H. pylori* were included.

Microbiology and Pharmacology

Colonization with *H. pylori* is generally attained during childhood across most populations and can persist for an entire lifetime.³ However, because the prevalence and incidence of colonization is higher in areas of suboptimal sanitary conditions, the acquisition of *H. pylori* varies significantly among persons from different regions of the world and depends not only on age but was also linked to socioeconomic status.^{1, 3} In the United States and other developed countries, the incidence of *H. pylori* has been progressively declining, with less than 10% of children carrying *H. pylori*, whereas in many developing parts of the world (e.g., Latin America, Southeast Asia, Middle East, and Africa), *H. pylori* prevalence remains high, with more than 70% of children colonized with *H. pylori*.⁴ Consequently, risk factors for *H. pylori*

colonization include immigration from or residence in developing countries and lower socioeconomic status.

Antibiotic resistance is the most important factor impacting eradication rates of *H. pylori* regimens. The primary resistance mechanisms for commonly used antibiotics along with estimated rates of resistance are described in Table S3.^{5, 6} Unlike most other bacteria, *H. pylori* acquires resistance through mutations.⁶ Therefore, rates of resistance increase progressively through selective pressures including previous antibiotic use and antibiotic consumption among the general population, especially for macrolides, metronidazole, and fluoroquinolones.^{7, 8} Global resistance rates should be considered when attempting to translate eradication rates from published studies to an individual patient because these data may not be generalizable. With the rise in *H. pylori* resistance, a paradigm shift to more patient-specific regimens, including susceptibility testing, may be required to reduce the potential for treatment failures.⁹ However, in the absence of susceptibility testing, patient-specific information, such as age, travel and immigration history, and socioeconomic status, can provide insight on the time and place of acquisition of *H. pylori*. When combined with global patterns of resistance (Table S3) and prior antibiotic use, these demographic data can inform treating clinicians on the likelihood of primary resistance.

Helicobacter pylori is intrinsically resistant to several antibiotic classes including glycopeptides, polymyxins, nalidixic acid, trimethoprim, and sulfonamides.⁶ Wild-type strains are susceptible to β -lactams, fosfomycin, macrolides, aminoglycosides, tetracyclines, chloramphenicol, rifamycins, fluoroquinolones, 5-nitroimidazoles, and nitrofurans.⁶ Other than aminoglycosides and chloramphenicol, these antibiotics were all trialed in various *H. pylori* eradication regimens.^{10, 11} The Clinical and Laboratory Standards Institute (CLSI) provides clinical breakpoints for the primary antibiotics used against *H. pylori* including clarithromycin, amoxicillin, tetracycline, rifabutin, ciprofloxacin, and metronidazole.¹² Importantly, the CLSI does not specifically describe the use of these breakpoints as surrogates for similar agents within the same antibiotic class (e.g., ampicillin and amoxicillin). Although many agents within the same class of antibiotics may exhibit similar antibiotic activity, the potential for reduced activity in acidic environments may result in discordance

between in vitro and in vivo activity.¹³ Antibiotics that may be subject to these effects include erythromycin, ampicillin, and select cephalosporins.¹³ In the absence of clinical data, providers should use acid-stable agents (e.g., amoxicillin, azithromycin, clarithromycin) when substituting within a class of antibiotics, particularly in the setting of less than maximal acid suppression.

Some nonantibiotic agents also demonstrate selective activity against *H. pylori*. Both bismuth salts and PPIs are active in vitro, whereas histamine H₂-receptor antagonists (H₂RAs) lack activity against *H. pylori*.¹⁴ Although the different bismuth salts vary in their in vitro activity, high concentrations achieved in the gastric lumen after oral administration may mitigate these differences, making all bismuth salts similarly efficacious.¹⁵ Of the various PPIs, lansoprazole and rabeprazole have the most potent antibacterial activity, and pantoprazole has the least.^{14, 16, 17} Omeprazole and esomeprazole have intermediate activity, with esomeprazole slightly more active than omeprazole.^{16, 18}

In addition to direct antibacterial activity, both bismuth salts and PPIs demonstrate indirect effects, such as inhibition of urease enzymes as well as disruption of adenosine triphosphate synthesis that may further alter the pathogenicity of *H. pylori*.^{15, 16} All acid-suppressive agents contribute to increased activity of antibacterial agents by increasing the pH level of the gastric lumen.⁶ Minimum inhibitory concentrations of many antibiotics become more favorable in less acidic environments.⁶ Elevated gastric pH levels lead to increases in the population of dividing *H. pylori* and, consequently, greater susceptibility to antibiotics such as amoxicillin and clarithromycin.¹⁹

Lastly, the degree of acid suppression is critical to the eradication of *H. pylori*. Several studies demonstrated that multiple pharmacologic factors can contribute to increased eradication when using PPIs, such as using twice/day dosing over once/day dosing, using high doses versus standard doses, and using more potent agents (e.g., rabeprazole over omeprazole).^{20, 21} The potential impact of genetic polymorphisms, particularly polymorphisms of cytochrome P450 (CYP) 2C19, should also guide selection of PPIs.^{22, 23} Two meta-analyses demonstrated that *H. pylori* eradication rates are inversely correlated with the capacity to metabolize PPIs.^{22, 23} Therefore, in populations with high proportions of ultra-rapid metabolizers (e.g., whites), it may

be prudent to favor use of PPIs less influenced by CYP2C19 polymorphisms, such as esomeprazole or rabeprazole.

Taken together, consideration of local resistance rates and selection of maximal acid suppression therapy can contribute to the overall effectiveness of eradication regimens for *H. pylori*. Appropriate evaluation of demographic data can inform clinicians on the probability of primary resistance based on age and location of initial acquisition of *H. pylori*. Current guidelines recommend avoiding clarithromycin-based triple therapy for empirical treatment when regional clarithromycin resistance exceeds a threshold of 15–20%.^{2, 9} Similar thresholds were suggested for both metronidazole and fluoroquinolones.⁶ Because of both their direct and indirect effects, PPIs may provide for better eradication rates than H₂RAs. Although microbiological and pharmacologic factors have important implications for the eradication of *H. pylori*, additional patient-specific factors, such as medication allergies and relative contraindications, can further complicate the selection of optimal treatment regimens. Commonly encountered special populations are discussed in detail next.

Penicillin Allergy

The treatment of *H. pylori* among patients with a true penicillin allergy represents a significant challenge. Amoxicillin is one of the most effective antibiotics against *H. pylori*, and acquired resistance is rare in most regions.²⁴ Consequently, amoxicillin is a component of many first- and second-line treatment regimens.² However, ~10% of the population report having a penicillin allergy, leaving providers with fewer options for treating *H. pylori*.²⁵ As such, it is imperative to obtain a complete and accurate allergy history including the description and timing of the reaction because many of these reported reactions may not be true allergies. Early evaluation with penicillin skin testing should also be considered to determine if a patient may be able to tolerate a penicillin or amoxicillin challenge.⁹

First-line β -lactam-sparing treatment regimens for *H. pylori* include clarithromycin triple therapy (clarithromycin, PPI, and metronidazole) and bismuth quadruple therapy (PPI, bismuth, tetracycline, and metronidazole).² The ACG recommends clarithromycin triple therapy for 14 days in regions with low (less than 15%) macrolide resistance.² Eradication rates for clarithromycin triple therapy rely heavily on

clarithromycin susceptibility. A meta-analysis of 93 European studies (68% randomized controlled trials [RCTs]) found that clarithromycin resistance reduced the eradication rates of clarithromycin triple therapy by ~35%.²⁶ Unfortunately, local and regional resistance patterns are commonly unknown. In the absence of *H. pylori* resistance testing, providers can use national resistance trends (Table S3), as well as evaluate if patients have had recent macrolide use before using this regimen.²⁷ Metronidazole resistance also plays a role because resistance was shown to reduce eradication rates of clarithromycin triple therapy by 18%.²⁶ Still, several studies have suggested adequate (76–82%) eradication rates among metronidazole-resistant compared with metronidazole-susceptible strains (Table S4),^{28, 29} which may be a function of the ability to overcome metronidazole resistance with more frequent dosing, longer durations of therapy, and concomitant therapy with a PPI or bismuth.^{24, 26, 30}

Among patients with previous macrolide exposure or in countries with higher rates of macrolide resistance (Table S3), bismuth quadruple therapy is the preferred initial β -lactam-sparing regimen.^{2, 9} Two multinational meta-analyses comparing bismuth quadruple therapy with clarithromycin triple therapy that included amoxicillin demonstrated similar, yet notably low, eradication rates for first-line therapy (69–78%).^{31, 32} However, because bismuth quadruple therapy maintained high eradication rates (more than 80%) in the presence of metronidazole resistance, this regimen remains an option for patients who have failed initial therapy with clarithromycin triple therapy containing metronidazole.^{31–33} Still, it remains important to recognize the potential for reduced eradication rates with bismuth quadruple therapy in the presence of metronidazole resistance, particularly if the dosages and duration of therapy are not optimized.³⁴ Consequently, some providers may elect to use bismuth quadruple therapy as initial therapy even when macrolide resistance is not a concern, to preserve the efficacy of metronidazole.³⁵

Selection of therapy after failure of first- or second-line therapy depends on a variety of factors including the previous regimens received, national resistance trends, and patient-specific factors (e.g., previous antibiotic use and drug-drug interactions). Levofloxacin and rifabutin are two agents that have been more commonly evaluated in this setting and remain options for

penicillin-allergic patients. However, resistance, adverse effects, and drug-drug interactions are important considerations when using these agents.²⁷ Levofloxacin-based regimens are favored due to improved tolerability and more consistent efficacy data compared with rifabutin-based therapies.^{9, 36–39} Although several meta-analyses of RCTs evaluating levofloxacin-based regimens containing amoxicillin as second-line therapy have yielded favorable results,^{40, 41} there are fewer studies evaluating specific levofloxacin-based regimens that excluded amoxicillin. Two RCTs found high eradication rates (more than 90%) with a levofloxacin, PPI, and metronidazole combination among treatment-naïve patients in Italy⁴⁰ and with a levofloxacin, rifabutin, and rabeprazole combination for patients who failed clarithromycin triple therapy in China.³⁶ Favorable eradication rates were observed in both countries despite having differing rates of fluoroquinolone resistance (Table S3), suggesting that primary resistance to levofloxacin may not have played a role. However, neither study performed levofloxacin susceptibility testing on the clinical *H. pylori* isolates. Levofloxacin-based regimens containing clarithromycin have also been evaluated and are discussed later.

Two large studies specifically compared *H. pylori* treatment regimens in penicillin-allergic patients.^{35, 39} One such study conducted in Spain compared clarithromycin triple therapy with metronidazole for 7 days (112 patients) with bismuth quadruple therapy for 10 days (50 patients).³⁵ Eradication rates with bismuth quadruple therapy were significantly higher than those with clarithromycin triple therapy (74% vs 57%, $p < 0.05$). Patients who failed clarithromycin triple therapy were retreated with either bismuth quadruple therapy or levofloxacin-based triple therapy consisting of levofloxacin, omeprazole, and clarithromycin. Patients who failed bismuth quadruple therapy were given levofloxacin-based triple therapy. Overall, the eradication rate of retreating with levofloxacin-based triple therapy with clarithromycin was 64%. Following clarithromycin triple therapy failures, retreatment with levofloxacin-based triple therapy resulted in higher eradication rates compared with retreatment with bismuth quadruple therapy (64% vs 37%, $p < 0.05$). A second study among 50 penicillin-allergic patients found similar eradication rates (73%) with levofloxacin, omeprazole, and clarithromycin for 10 days among patients failing clarithromycin triple therapy

with metronidazole.³⁹ Together, these two studies suggest that levofloxacin-based triple therapy with clarithromycin may be a reasonable second-line option for penicillin-allergic patients.

To our knowledge, only three studies have evaluated the use of a nonpenicillin β -lactam antibiotic (e.g., cephalosporin) for the treatment of *H. pylori*.^{41–43} One small study of 12 patients found cefprozil monotherapy to be ineffective at eradicating *H. pylori*.⁴³ Cefixime-based triple therapy, consisting of cefixime (200–400 mg twice/day), a PPI, and clarithromycin, was moderately effective when administered as initial therapy to 49 patients in Italy.³⁸ The eradication rate was 71% (24/34) among patients receiving cefixime 200 mg twice/day and 73% (11/15) among patients receiving cefixime 400 mg twice/day. In a single-center RCT of 400 treatment-naïve patients in China, patients were randomized to receive levofloxacin-based quadruple therapy with either amoxicillin or cefuroxime for 14 days. Both arms achieved similar eradication rates (84% vs 81%, $p = 0.513$).⁴³ Together, these data suggest that substitution of amoxicillin with a cephalosporin may be an option for patients with a penicillin allergy.^{2, 9} However, eradication rates appear less than optimal for first-line therapy. Consequently, clarithromycin triple therapy with metronidazole and bismuth quadruple therapy remain first-line therapy for penicillin-allergic patients. More clinical data are required to make general recommendations regarding the best cephalosporin to use and the optimal combination regimen when using alternative β -lactam agents for salvage therapy.

In summary, when resistance is not a concern, clarithromycin triple therapy with metronidazole and bismuth quadruple therapy are equally efficacious first-line regimens for patients with a penicillin allergy. Among patients failing clarithromycin triple therapy with metronidazole, bismuth quadruple therapy may still be considered as second-line therapy, as long as the dosages and duration of therapy are optimized. Levofloxacin-based triple therapy may be considered as second-line therapy for patients failing initial therapy and is preferred over rifabutin-based regimens for second-line and salvage therapy due to improved tolerability and eradication rates and decreased drug interaction potential.

QTc-Interval Prolongation

Of the available treatment options for *H. pylori*, both clarithromycin and levofloxacin are

associated with significant prolongation of the QTc interval.⁴⁴ Because many of the first-line treatment options include clarithromycin or levofloxacin, selection of the most appropriate regimen in patients at risk for QTc-interval prolongation can be challenging. Briefly, the QT interval, as measured on an electrocardiogram, represents a marker of ventricular repolarization time and can be corrected for factors such as heart rate.⁴⁵ In general, a corrected QT (QTc) interval greater than 450 milliseconds (ms) in men and greater than 470 ms in women is considered moderately prolonged, whereas a QTc of 500 ms or greater is considered severely prolonged and can be associated with torsade de pointes (TdP), a life-threatening ventricular arrhythmia, and death.^{46, 47}

Identifiable risk factors for QTc-interval prolongation include electrolyte abnormalities, cardiovascular disease, genetics, female sex, increasing age, and, most notably, certain medications.⁴⁸ Electrolyte abnormalities including hypokalemia, hypomagnesemia, and hypocalcemia were associated with significant elevations (more than 10 ms) in the QTc interval. The presence of one QTc-interval-prolonging medications such as a macrolide antibiotic was associated with an increase of roughly 10–15 ms, with additional medications contributing to a much smaller degree (~5 ms). In general, the risk of TdP in patients receiving fluoroquinolone and macrolide antibiotics is very low, even in patients with additional risk factors.⁴⁹ However, a case report described a 63-year-old woman with risk factors for QTc-interval prolongation who received clarithromycin for *H. pylori* treatment and subsequently developed TdP.⁵⁰ When initiating therapy, providers should consider obtaining a baseline electrocardiogram and a basic metabolic panel in patients at high risk for QTc-interval prolongation with concomitant cardiac conditions to determine optimal treatment regimens.

Among the available first-line treatment strategies recommended by the ACG, only bismuth quadruple therapy excludes clarithromycin and levofloxacin, which remains an option for patients with or at risk for QTc-interval prolongation.² In patients unable to receive or who have failed bismuth quadruple therapy, providers are forced to select a salvage treatment regimen. For patients with QTc-interval prolongation, salvage therapies include rifabutin-based triple therapy, amoxicillin-based dual therapy, and amoxicillin-based triple therapy (Table S1). Selection of the optimal salvage regimen requires a careful

evaluation of resistance patterns, prior antibiotic exposure, and tolerability. As such, the following section focuses on the comparative efficacy of these second-line regimens.

Studies evaluating the effect of rifabutin-based triple therapy have yielded mixed results when compared with first-line therapies. One multicenter RCT conducted in Spain compared PPI, amoxicillin, and rifabutin with bismuth quadruple therapy for 7 days.⁵¹ Rifabutin-based triple therapy was associated with a significantly lower rate of eradication than bismuth quadruple therapy (44% vs 70%, $p=0.009$). Alternatively, another study conducted in Italy found that the use of rifabutin-based triple therapy was an effective first-line (eradication rate 88%) and second-line treatment (eradication rate 79%).⁵² Finally, in a meta-analysis of 21 RCTs, rifabutin-based triple therapy was associated with inferior eradication rates when compared with amoxicillin-based triple therapy (68% vs 82%, $p=0.283$) and similar eradication rates when compared with bismuth quadruple therapy (66% vs 67%, $p=0.87$).⁵³

Amoxicillin-based dual therapy, consisting of amoxicillin and a PPI, has demonstrated favorable eradication rates. In a prospective multicenter RCT conducted in Taiwan, amoxicillin-based dual therapy was evaluated for first-line treatment of *H. pylori*.⁵⁴ Patients were randomized to amoxicillin and rabeprazole for 14 days (amoxicillin dual therapy), amoxicillin and rabeprazole for 5 days followed by metronidazole, clarithromycin, and rabeprazole for 5 more days (sequential therapy), or amoxicillin-based triple therapy for 7 days. Rates of eradication 4–8 weeks following treatment completion were significantly greater for patients receiving amoxicillin dual therapy (95%) compared with study-defined sequential therapy (85%) and amoxicillin-based triple therapy (81%) ($p<0.001$). These findings were echoed in a meta-analysis that found that high-dose amoxicillin dual therapy (amoxicillin of 2 g/day or more and PPI given more than twice/day) was associated with similar efficacy to other salvage treatments including rifabutin-based triple therapy and bismuth quadruple therapy.⁵⁵

Amoxicillin-based triple therapy, consisting of amoxicillin, metronidazole, and a PPI, may also be an option in patients with a prolonged QTc interval, particularly among patients with a low risk for metronidazole resistance.⁹ A large meta-analysis of more than 90 trials demonstrated an eradication rate of up to 70% with this regimen when used as first-line treatment, which was

significantly lower compared with clarithromycin triple therapy with amoxicillin (70% vs 77%, $p < 0.002$) or clarithromycin triple therapy with metronidazole (66% vs 78%, $p = 0.0003$).⁵⁶ However, eradication rates for amoxicillin-based triple therapy depend highly on metronidazole resistance rates, and further analysis identified longer treatment durations and higher amoxicillin and metronidazole doses (every 8 hours) as factors closely associated with the improved efficacy of amoxicillin-based triple therapy. When high doses were administered for 14 days, eradication rates for amoxicillin-based triple therapy were similar to first-line treatment regimens.

In summary, bismuth quadruple therapy should be considered the treatment of choice in patients with QTc-interval prolongation. The efficacy of this regimen was demonstrated in several large RCTs as both first-line and salvage treatment of *H. pylori*. In patients with a contraindication, patients who are unable to tolerate bismuth quadruple therapy, or patients who have failed initial therapy, alternative options include rifabutin-based triple therapy, amoxicillin-based dual therapy, and amoxicillin-based triple therapy. Given the similar efficacy, lower pill burden, lack of major drug-drug interactions, and lower potential for adverse reactions, amoxicillin-based dual therapy may be considered an alternative to bismuth quadruple therapy in patients at risk for or with prolonged QTc intervals.

Pregnancy and Breastfeeding

The presence of *H. pylori* was associated with an increased risk (odds ratio 3.34, 95% confidence interval [CI] 2.32–4.81) of hyperemesis gravidarum, a condition characterized by severe nausea, vomiting, or weight loss during pregnancy.⁵⁷ Hyperemesis gravidarum can lead to fetal complications, such as low birth weight, prematurity, and malformation.^{58, 59} Additionally, maternal complications of hyperemesis gravidarum include dehydration, electrolyte disturbances, and hospitalizations.^{52, 53} Eradication of *H. pylori* led to symptom alleviation of hyperemesis gravidarum in case reports, case series, and small research reports starting in the late 1990s.^{60–63} Early therapy consisted of treatment with erythromycin, clarithromycin, metronidazole, and amoxicillin, alone or in combination. H₂RAs and PPIs were consistently used for acid suppression in the corresponding treatment

regimens. Treatment durations varied in the reports from 5 to 14 days.

Use of the limited clinical data available to guide therapy in pregnant and breastfeeding patients must be balanced with consideration for fetal toxicity from select drug therapies. Specifically, tetracyclines carry the highest teratogenic potential, with concerns for bone growth inhibition and teeth discoloration, thereby prohibiting the use of bismuth quadruple therapy in this population. The remaining first-line regimens contain at least one agent carrying a pregnancy category C with no data to support use in pregnancy or during breastfeeding. Consequently, the decision to provide treatment should involve careful evaluation of the patient's symptoms and the goals of therapy.

Based on available data and current U.S. Food and Drug Administration pregnancy and lactation standards, asymptomatic pregnant patients testing positive for *H. pylori* should be treated postpartum and following cessation of breastfeeding.^{57–60, 68} However, some situations, such as hyperemesis gravidarum, may dictate the need for treatment during pregnancy. The largest study, to our knowledge, is a retrospective cohort study of 24 pregnant women in the United States with prolonged nausea and vomiting.⁶⁴ All patients were evaluated for *H. pylori* using serology testing. Half of the patients tested positive and were prescribed treatment with clarithromycin triple therapy for 2 weeks. Although only three patients completed treatment, all patients experienced symptomatic relief. Furthermore, 23 patients (96%) had adequate total weight gain during pregnancy, suggesting that treatment and *H. pylori* infection alike did not impact fetal growth. The remaining clinical data are limited to case reports and small case series, but the compilation of available data provides some understanding of treatment risks and benefits.

For patients experiencing hyperemesis gravidarum, careful consideration of risks versus benefits of therapy should be discussed before proceeding with treatment. Patients electing to undergo treatment may benefit from clarithromycin triple therapy. However, those undergoing treatment during the first trimester should substitute metronidazole for clarithromycin. Studies demonstrated that use of clarithromycin in the first trimester leads to an increased risk of miscarriage (hazard ratio 1.56, 95% CI 1.14–2.13) but did not increase risks for congenital malformations.^{65, 66} Balancing risk of maternal

and fetal harm and benefit of symptom resolution should be used to decide treatment duration. Initial conservative treatment with a short course of 7 days may alleviate symptoms and minimize risks.^{61, 67}

For medication use during breastfeeding, the World Health Organization (WHO) considers macrolides and penicillin antibiotics safe in usual dosages but recommends monitoring the infant for rash, thrush, and diarrhea.⁶⁸ Additionally, the WHO suggests avoiding metronidazole use, when possible, citing animal data demonstrating potential carcinogenic effects. Although clinical data in this population are limited, these recommendations support the use of clarithromycin triple therapy for breastfeeding mothers.

The limited options for safe medication use in pregnancy and lactation make treating *H. pylori* challenging in these scenarios. In the rare case that an asymptomatic patient is tested and is positive for *H. pylori*, treatment should be delayed until delivery or cessation of breastfeeding. Symptomatic pregnant patients in the second or third trimester and breastfeeding mothers should be offered clarithromycin triple therapy, if treatment is warranted. Careful discussion with the mother regarding fetal risk, potential retreatment necessity, and antibiotic adverse effects alongside benefit of symptom relief is needed when deciding treatment duration between 7 and 14 days.

Elderly

Increasing age is a risk factor for *H. pylori* infection and related complications such as peptic ulcer disease, functional dyspepsia, and gastric malignancies.^{1, 69, 70} Treatment of *H. pylori* in the elderly was also associated with improved gastrointestinal symptoms including gastritis and peptic ulcers.^{71–73} Consequently, early effective therapy is important in this population. There are no specific contraindications to the recommended *H. pylori* therapies, and first-line clarithromycin triple therapy and bismuth quadruple therapy demonstrated good eradication rates among elderly patients.^{71, 73, 74} However, to ensure that therapy is safe and appropriate, patient-specific considerations should include potential antibiotic resistance, appropriate antibiotic dosing, drug-drug interactions, and adverse event monitoring. As previously discussed, antibiotic resistance reduces the efficacy of many treatment regimens. Because

elderly patients are more likely to have received previous antibiotic therapy, a thorough antibiotic history can help determine if specific antibiotic classes should be avoided, and their dosages and durations should be optimized.

Pharmacokinetic changes associated with advanced age, such as reduced renal function, may predispose this population to higher antibiotic serum concentrations and subsequent treatment-related adverse reactions.^{75, 76} Consequently, clarithromycin and fluoroquinolone doses should be reduced in patients with significant renal impairment to avoid the increased risk of adverse effects such as gastrointestinal upset and central nervous system effects, respectively.^{77, 78} In a single-center study of 154 patients older than 60 years with *H. pylori* infection, patients were randomized to receive clarithromycin triple therapy with either clarithromycin 250 mg twice/day or 500 mg twice/day.⁶⁹ Numerically more patients receiving the higher clarithromycin dose reported having adverse events (9% vs 5%, *p* value not significant). Notably, this study did not evaluate serum creatinine concentration or other markers of renal function.

Due to the common occurrence of polypharmacy and increased sensitivity to adverse reactions, drug-drug interactions should be monitored closely in this population. Clarithromycin and other macrolides, excluding azithromycin, carry the highest potential for drug-drug interactions. Caution is also advised among older patients taking ciprofloxacin with theophylline and warfarin.⁷⁷ Although drug-drug interactions may be identified, the consequences of these interactions must be weighed against the benefits of providing optimal therapy. Some interactions may be managed with close monitoring during the short period of concomitant therapy. Additionally, the American Geriatrics Society 2019 Beers Criteria discourages the scheduled use of PPIs for more than 8 weeks due to the risk of *Clostridium difficile*-associated diarrhea and bone loss.⁷⁷ This may become a concern among relapsed or recurrent *H. pylori* infections, requiring repeated and prolonged durations of therapy.

The optimal duration of therapy in elderly patients is unclear. Given the potential increased sensitivity for treatment-related adverse effects, providers may wish to shorten the duration of therapy. Unfortunately, to our knowledge, no studies have compared durations of therapy among elderly patients. Seven days of therapy were generally associated with low rates of

treatment-related adverse effects (4–7%),^{69, 71, 73} whereas studies evaluating 10–14 days of therapy reported variable rates (3–33%).^{72, 74, 79} However, this potential advantage should be balanced with the risk of treatment failure. Eradication rates tend to be higher with longer treatment durations. A multicenter RCT conducted in Italy of 179 patients older than 65 years compared 10-day sequential therapy with 7-day clarithromycin triple therapy and demonstrated significantly higher eradication rates in the sequential therapy arm compared with the triple therapy arm (94% vs 80%, $p=0.008$) and no significant difference in the occurrence of adverse effects (10% vs 12%).⁷⁹ A smaller prospective single-center study of 93 patients also demonstrated a high eradication rate of 91% with twice/day quadruple therapy for 10 days.⁷⁴ Mild adverse effects, such as fatigue, discomfort, and gastrointestinal symptoms, were reported in 28% of patients. Resistance testing was not performed in these trials. Taken together, the longer durations of therapy recommended in the ACG guidelines for the general population are also preferred among the elderly population due to the high eradication rates, lack of data suggesting that longer durations of therapy are associated with severe adverse effects among elderly patients, and the data among the general population demonstrating the ability for longer durations to overcome the risk of resistance.

The *H. pylori* treatment recommendations among the elderly population are the same as those for the general population. Furthermore, clarithromycin triple therapy, bismuth quadruple therapy, and sequential therapy have specifically been studied in well-designed trials among the elderly population. Increased vigilance should be taken regarding the proper dosing and management of potential drug-drug interactions due to the increased likelihood of renal impairment and polypharmacy. Proper monitoring and follow-up are important to evaluate for potential treatment-related adverse reactions that may influence adherence and subsequent efficacy of medication regimens.

Conclusion

For patients with a penicillin allergy, clarithromycin triple therapy with metronidazole and bismuth quadruple therapy are recommended first-line regimens. In patients with a prolonged QTc interval at risk for TdP, bismuth quadruple therapy is the preferred treatment regimen. Although several second-line options

exist, amoxicillin dual therapy provides optimal benefit with the lowest risk of medication-related events. Treatment of symptomatic pregnant patients requires careful consideration of the risks and benefits, and clarithromycin triple therapy can be considered if treatment is warranted. Finally, among elderly patients, clarithromycin triple therapy or bismuth quadruple therapy is recommended, and careful attention to dosing and drug-drug interactions is necessary.

Although antibiotic resistance is the primary challenge to effective treatment of *H. pylori* infection, providers are often faced with patient-specific challenges when prescribing antibiotic therapy. Selecting an appropriate regimen based on patient allergies and coexisting conditions is crucial to ensuring patient safety without compromising treatment efficacy. Although efficacious regimens exist for initial therapy in these situations, second- and third-line regimens are limited and complex. When barriers to antibiotic selection exist, providers should conduct a thorough investigation (e.g., penicillin allergy history, modifiable risk factors for QT prolongation) and attempt to address these situations as appropriate (e.g., penicillin skin testing, electrolyte replacement). In the absence of any mitigating solutions, providers should carefully consider the risks versus benefits of available options when selecting treatment regimens in these common but challenging scenarios.

References

1. Everhart JE, Kruszon-Moran D, Perez-Perez GI, Tralka TS, McQuillan G. Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in the United States. *J Infect Dis* 2000;181:1359–63.
2. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guidelines: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol* 2017;112:212–39.
3. Taylor DN, Blaser MJ. The epidemiology of *Helicobacter pylori* infection. *Epidemiol Rev* 1991;13:42–59.
4. Zamani M, Ebrahimitabar F, Zamani V, et al. Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2018;47:868–76.
5. Megraud F, Lehours P. *Helicobacter pylori* detection and antimicrobial susceptibility testing. *Clin Microbiol Rev* 2007;20:280–322.
6. Thung I, Aramin H, Vavinskaya V, et al. Review article: the global emergence of *Helicobacter pylori* antibiotic resistance. *Aliment Pharmacol Ther* 2016;43:514–33.
7. Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013;62:34–42.
8. Perez Aldana L, Kato M, Nakagawa S, et al. The relationship between consumption of antimicrobial agents and the prevalence of primary *Helicobacter pylori* resistance. *Helicobacter* 2002;7:306–9.

9. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht V/Florence consensus report. *Gut* 2017;66:6–30.
10. Lambert T, Megraud F, Gerbaud G, Courvalin P. Susceptibility of *Campylobacter pyloridis* to 20 antimicrobial agents. *Antimicrob Agents Chemother* 1986;30:510–1.
11. McNulty CA, Dent J, Wise R. Susceptibility of clinical isolates of *Campylobacter pyloridis* to 11 antimicrobial agents. *Antimicrob Agents Chemother* 1985;28:837–8.
12. Clinical and Laboratory Standards Institute. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria. CLSI guideline M45, 3rd ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2016.
13. Cover TL, Blaser MJ. *Helicobacter pylori* and other gastric *Helicobacter* species. In: Bennett JE, Dolin R, Basler MJ, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 8th ed. Philadelphia, PA: Elsevier, 2015:2494.
14. Iwahi T, Satoh H, Nakao M, et al. Lansoprazole, a novel benzimidazole proton pump inhibitor, and its related compounds have selective activity against *Helicobacter pylori*. *Antimicrob Agents Chemother* 1991;35:490–6.
15. Alkim H, Koksai AR, Boga S, Sen I, Alkim C. Role of bismuth in the eradication of *Helicobacter pylori*. *Am J Ther* 2017;24:e751–7.
16. Nakao M, Malfertheiner P. Growth inhibitory and bactericidal activities of lansoprazole compared with those of omeprazole and pantoprazole against *Helicobacter pylori*. *Helicobacter* 1998;3:21–7.
17. Kawakami Y, Akahane T, Yamaguchi M, et al. In vitro activities of rabeprazole, a novel proton pump inhibitor, and its thioether derivative alone and in combination with other antimicrobials against recent clinical isolates of *Helicobacter pylori*. *Antimicrob Agents Chemother* 2000;44:458–61.
18. Gatta L, Perna F, Figura N, et al. Antimicrobial activity of esomeprazole versus omeprazole against *Helicobacter pylori*. *J Antimicrob Chemother* 2003;51:439–42.
19. Scott D, Weeks D, Melchers K, Sachs G. The life and death of *Helicobacter pylori*. *Gut* 1998;43(Suppl 1):S56–S60.
20. Vallve M, Vergara M, Gisbert JP, Calvet X. Single vs. double dose of a proton pump inhibitor in triple therapy for *Helicobacter pylori* eradication: a meta-analysis. *Aliment Pharmacol Ther* 2002;16:1149–56.
21. Villoria A. Acid-related diseases: are higher doses of proton pump inhibitors more effective in the treatment of *Helicobacter pylori* infection? [in Spanish]. *Gastroenterol Hepatol* 2008;31:546–7.
22. Tang HL, Li Y, Hu YF, Xie HG, Zhai SD. Effects of CYP2C19 loss-of-function variants on the eradication of *H. pylori* infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. *PLoS One* 2013;8:e62162.
23. Zhao F, Wang J, Yang Y, et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication: a meta-analysis. *Helicobacter* 2008;13:532–41.
24. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut* 2010;59:1143–53.
25. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014;133:790–6.
26. Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. *Aliment Pharmacol Ther* 2007;26:343–57.
27. McNulty CA, Lasseter G, Shaw I, et al. Is *Helicobacter pylori* antibiotic resistance surveillance needed and how can it be delivered? *Aliment Pharmacol Ther* 2012;35:1221–30.
28. Gisbert JP, Gonzalez L, Calvet X, et al. Proton pump inhibitor, clarithromycin and either amoxicillin or nitroimidazole: a meta-analysis of eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther* 2000;14:1319–28.
29. Houben MH, Hensen EF, Rauws EA, et al. Randomized trial of omeprazole and clarithromycin combined with either metronidazole or amoxicillin in patients with metronidazole-resistant or -susceptible *Helicobacter pylori* strains. *Aliment Pharmacol Ther* 1999;13:883–9.
30. van der Wouden EJ, Thijs JC, van Zwet AA, Sluiter WJ, Kleibeuker JH. The influence of in vitro nitroimidazole resistance on the efficacy of nitroimidazole-containing anti-*Helicobacter pylori* regimens: a meta-analysis. *Am J Gastroenterol* 1999;94:1751–9.
31. Luther J, Higgins PD, Schoenfeld PS, Moayyedi P, Vakil N, Chey WD. Empiric quadruple vs. triple therapy for primary treatment of *Helicobacter pylori* infection: systematic review and meta-analysis of efficacy and tolerability. *Am J Gastroenterol* 2010;105:65–73.
32. Venerito M, Krieger T, Ecker T, Leandro G, Malfertheiner P. Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of *Helicobacter pylori* infection. *Digestion* 2013;88:33–45.
33. O'Morain C, Borody T, Farley A, et al. Efficacy and safety of single-triple capsules of bismuth biskalcitrate, metronidazole and tetracycline, given with omeprazole, for the eradication of *Helicobacter pylori*: an international multicentre study. *Aliment Pharmacol Ther* 2003;17:415–20.
34. Peitz U, Sulliga M, Wolle K, et al. High rate of post-therapeutic resistance after failure of macrolide-nitroimidazole triple therapy to cure *Helicobacter pylori* infection: impact of two second-line therapies in a randomized study. *Aliment Pharmacol Ther* 2002;16:315–24.
35. Gisbert JP, Barrio J, Modolell I, et al. *Helicobacter pylori* first-line and rescue treatments in the presence of penicillin allergy. *Dig Dis Sci* 2015;60:458–64.
36. Wong WM, Gu Q, Lam SK, et al. Randomized controlled study of rabeprazole, levofloxacin and rifabutin triple therapy vs. quadruple therapy as second-line treatment for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2003;17:553–60.
37. Ierardi E, Giangaspero A, Losurdo G, et al. Quadruple rescue therapy after first and second line failure for *Helicobacter pylori* treatment: comparison between two tetracycline-based regimens. *J Gastrointest Liver Dis* 2014;23:367–70.
38. Gisbert JP, Gisbert JL, Marcos S, Olivares D, Pajares JM. *Helicobacter pylori* first-line treatment and rescue options in patients allergic to penicillin. *Aliment Pharmacol Ther* 2005;22:1041–6.
39. Gisbert JP, Perez-Aisa A, Castro-Fernandez M, et al. *Helicobacter pylori* first-line treatment and rescue option containing levofloxacin in patients allergic to penicillin. *Dig Liver Dis* 2010;42:287–90.
40. Cammarota G, Cianci R, Cannizzaro O, et al. Efficacy of two one-week rabeprazole/levofloxacin-based triple therapies for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2000;14:1339–43.
41. Fagoonee S, Astegiano M, Smedile A, et al. Efficacy of cefixime-based triple therapy for *Helicobacter pylori* eradication: a retrospective study. *Panminerva Med* 2013;55(3):309–10.
42. Malaty H, Klein PD, Graham DY. Short report: cefprozil for the eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1992;6(4):503–6.
43. Fu W, Song Z, Zhou L, et al. Randomized clinical trial: esomeprazole, bismuth, levofloxacin, and amoxicillin or cefuroxime as first-line eradication regimens for *Helicobacter pylori* infection. *Dig Dis Sci* 2017;62(6):1580–9.
44. Roden M. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013–22.
45. Nielsen JB, Graff C, Rasmussen PV, et al. Risk prediction of cardiovascular death based on the QTc interval: evaluating age and gender differences in a large primary care population. *Eur Heart J* 2014;35:1335–44.
46. Pickham D, Helfenbein E, Shinn JA, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: results of the QT in Practice (QTIP) Study. *Crit Care Med* 2012;40:396–9.

47. Vandael E, Vandenberg B, Vandenberghe J, Spriet I, Willems R, Foulon V. Development of a risk score for QTc-prolongation: the RISQ-PATH study. *Int J Clin Pharm* 2017;39:424–32.
48. Heemskerk CPM, Pereboom M, van Stralen K, et al. Risk factors for QTc interval prolongation. *Eur J Clin Pharmacol* 2018;74:183–91.
49. Niedrig D, Maechler S, Hoppe L, Corti N, Kovari H, Russmann S. Drug safety of macrolide and quinolone antibiotics in a tertiary care hospital: administration of interacting co-medication and QT prolongation. *Eur J Clin Pharmacol* 2016;72(7):859–67.
50. Chang NL, Shah P, Bikkina M, et al. Clarithromycin-induced torsades de pointes. *Am J Ther* 2016;23(3):e955–6.
51. Navarro-Jarabo JM, Fernandez N, Sousa FL, et al. Efficacy of rifabutin-based triple therapy as second-line treatment to eradicate *Helicobacter pylori* infection. *BMC Gastroenterol* 2007;7:31.
52. Toracchio S, Capodicasa S, Soraja DB, et al. Rifabutin based triple therapy for eradication of *H. pylori* primary and secondary resistant to tinidazole and clarithromycin. *Dig Liver Dis* 2005;37:33–8.
53. Liu X, Wang H, Lv Z, et al. Rescue therapy with a proton pump inhibitor plus amoxicillin and rifabutin for *Helicobacter pylori*: a systematic review and meta-analysis. *Gastroenterol Res Pract* 2015;2015:415648.
54. Yang JC, Lin CJ, Wang HL, et al. High-dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* infection. *Clin Gastroenterol Hepatol* 2015;13:895–905.
55. Gao CP, Zhou Z, Wang JZ, Han SX, Li LP, Lu H. Efficacy and safety of high-dose dual therapy for *Helicobacter pylori* rescue therapy: a systematic review and meta-analysis. *J Dig Dis* 2016;17:811–9.
56. Puig I, Baylina M, Sanchez-Delgado J, et al. Systematic review and meta-analysis: triple therapy combining a proton-pump inhibitor, amoxicillin and metronidazole for *Helicobacter pylori* first-line treatment. *J Antimicrob Chemother* 2016;71:2740–53.
57. Li L, Li L, Zhou X, Xiao S, Gu H, Zhang G. *Helicobacter pylori* infection is associated with an increased risk of hyperemesis gravidarum: a meta-analysis. *Gastroenterol Res Pract* 2015;2015:278905.
58. Cardaropoli S, Rolfo A, Todros T. *Helicobacter pylori* and pregnancy-related disorders. *World J Gastroenterol* 2014;20:654–64.
59. Grooten IJ, Den Hollander WJ, Roseboom TJ, et al. *Helicobacter pylori* infection: a predictor of vomiting severity in pregnancy and adverse birth outcome. *Am J Obstet Gynecol* 2017;216:512.e1–9.
60. Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and *Helicobacter pylori* infection: a systematic review. *Obstet Gynecol* 2007;110:695–703.
61. Ono Y, Shiozaki A, Yoneda N, Yoneda S, Toshino O, Saito S. Effectiveness of *Helicobacter pylori* eradication in pregnant women with idiopathic thrombocytopenic purpura. *J Obstet Gynaecol Res* 2017;43:1212–6.
62. Mansour GM, Nashaat EH. *Helicobacter pylori* and hyperemesis gravidarum. *Int J Gynaecol Obstet* 2009;106:63–4.
63. Mansour GM, Nashaat EH. Role of *Helicobacter pylori* in the pathogenesis of hyperemesis gravidarum. *Arch Gynecol Obstet* 2011;284:843–7.
64. Penney DS. *Helicobacter pylori* and severe nausea and vomiting during pregnancy. *J Midwifery Womens Health* 2005;50:418–22.
65. Muanda FT, Sheehy O, Berard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. *CMAJ* 2017;189:E625–33.
66. Anderson JT, Petersen M, Jimenez-Solem E, et al. Clarithromycin in early pregnancy and the risk of miscarriage and malformation: a register based nationwide cohort study. *PLoS One* 2013;8:e53327.
67. Strachan BK, Jokhi RP, Filshie GM. Persistent hyperemesis gravidarum and *Helicobacter pylori*. *J Obstet Gynaecol* 2000;20(4):427.
68. World Health Organization. Breastfeeding and maternal medication: recommendations for drugs in the Eleventh WHO Model List of Essential Drugs. Geneva, Switzerland: World Health Organization, 2002. Available from <http://www.who.int/iris/handle/10665/62435>. Accessed March 7, 2019.
69. Pilotto A, Franceschi M, Leandro G, et al. Cure of *Helicobacter pylori* infection in elderly patients: comparison of low versus high doses of clarithromycin in combination with amoxicillin and pantoprazole. *Aliment Pharmacol Ther* 2001;15(7):1031–6.
70. de Martel C, Forman D, Plummer M. Gastric cancer: epidemiology and risk factors. *Gastroenterol Clin North Am* 2013;42(2):219–40.
71. Pilotto A, Di Mario F, Franceschi M, et al. Cure of *Helicobacter pylori* infection in the elderly: effects of eradication on gastritis and serological markers. *Aliment Pharmacol Ther* 1996;10(6):1021–7.
72. Catalano F, Branciforte G, Brogna A, et al. *Helicobacter pylori*-positive functional dyspepsia in elderly patients: comparison of two treatments. *Dig Dis Sci* 1999;44(5):863–7.
73. Pilotto A, Franceschi M, Leandro G, et al. Efficacy of 7 day lansoprazole-based triple therapy for *Helicobacter pylori* infection in elderly patients. *J Gastroenterol Hepatol* 1999;14(5):468–75.
74. Dore MP, Farina V, Cuccu M, et al. Twice-a-day bismuth-containing quadruple therapy for *Helicobacter pylori* eradication: a randomized trial of 10 and 14 days. *Helicobacter* 2011;16(4):295–300.
75. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Curr Drug Metab* 2011;12(7):601–10.
76. Ammon S, Treiber G, Kees F, et al. Influence of age on the steady state disposition of drugs commonly used for the eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther* 2000;14(6):759–66.
77. American Geriatrics Society. Updated AGS Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019;67(4):674–94.
78. Harb AH, Chalhoub JM, Abou Mrad R, et al. Systematic review and meta-analysis: full- vs. half-dose anti-microbials in clarithromycin-based regimens for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2015;42(2):131–41.
79. Zullo A, Gatta L, De Francesco V, et al. High rate of *Helicobacter pylori* eradication with sequential therapy in elderly patients with peptic ulcer: a prospective controlled study. *Aliment Pharmacol Ther* 2005;21(12):1419–24.

Supporting Information

The following supporting information is available in the online version of this paper:

Table S1. *Helicobacter pylori* treatment regimens.^{2,9}

Table S2. Search methodology and results.

Table S3. Antibiotic resistance mechanisms and estimated rates of resistance.^{5,6}

Table S4. Data summary of clinical studies evaluating eradication rates of treatment regimens.

Supplementary Material

Supplementary Table 1. *Helicobacter pylori* treatment regimens [2] [9]

Name of regimen	Components of regimen	Duration of therapy
Clarithromycin triple	• Clarithromycin + PPI + amoxicillin • Clarithromycin + PPI + metronidazole	14 days
Bismuth quadruple	• Bismuth salt + PPI + tetracycline + metronidazole • Bismuth salt + PPI + tetracycline + amoxicillin	10 – 14 days
Concomitant therapy	• Clarithromycin + PPI + amoxicillin + metronidazole	14 days
Sequential therapy	• PPI + amoxicillin x 5-7 days followed by PPI + clarithromycin + nitroimidazole x 5-7 days	10 – 14 days
Hybrid therapy	• PPI + amoxicillin x 7 days followed by PPI + amoxicillin + clarithromycin + metronidazole x 7 days	14 days
Levofloxacin-based triple	• Levofloxacin + PPI + amoxicillin • Levofloxacin + PPI + metronidazole • Levofloxacin + PPI + clarithromycin	10 – 14 days
Rifabutin-based quadruple	• Rifabutin + minocycline + rabeprazole + bismuth	7 – 14 days
Rifabutin-based triple	• Rifabutin + clarithromycin + omeprazole • Rifabutin + amoxicillin + PPI	7 – 14 days
Amoxicillin-based dual	• Amoxicillin + PPI	14 days
Amoxicillin-based triple	• Amoxicillin + metronidazole + PPI	14 days

Supplementary Table 2. Search methodology and results

Search Terms in addition to "helicobacter pylori"[MeSH Terms] OR ("helicobacter"[All Fields] AND "pylori"[All Fields]) OR "helicobacter pylori"[All Fields] OR ("campylobacter"[All Fields] AND "pyloridis"[All Fields]) OR "campylobacter pyloridis"[All Fields] AND English[lang]	Results	Add humans-only filter
((("penicillins"[MeSH Terms] OR "penicillins"[All Fields] OR "penicillin"[All Fields]) AND ("hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields] OR "allergy"[All Fields] OR "allergy and immunology"[MeSH Terms] OR "allergy"[All Fields] AND "immunology"[All Fields]) OR "allergy and immunology"[All Fields]))	65	61
("cephalosporins"[MeSH Terms] OR "cephalosporins"[All Fields] OR "cephalosporin"[All Fields]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms])	46	29
("carbapenems"[MeSH Terms] OR "carbapenems"[All Fields] OR "carbapenem"[All Fields])	12	6
("fluoroquinolones"[MeSH Terms] OR "fluoroquinolones"[All Fields] OR "fluoroquinolone"[All Fields])	463	413
("rifabutin"[MeSH Terms] OR "rifabutin"[All Fields])) NOT ("amoxicillin"[MeSH Terms] OR "amoxicillin"[All Fields])	47	36
(qt[All Fields] AND prolongation[All Fields])	1	—
((("bismuth"[MeSH Terms] OR "bismuth"[All Fields]) AND quadruple[All Fields])) AND triple[All Fields]	370	320
("breast feeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "breast feeding"[All Fields] OR "breastfeed"[All Fields])	42	38
"human"[All Fields] OR "human milk"[All Fields] OR ("breast"[All Fields] AND "milk"[All Fields]) OR "breast milk"[All Fields])	93	66
("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])	222	194
("gravity"[MeSH Terms] OR "gravity"[All Fields] OR "pregnant"[All Fields])	121	106
("geriatrics"[MeSH Terms] OR "geriatrics"[All Fields])	65	52
"elderly"[All Fields]	327	291

Supplementary Table 3. Antibiotic resistance mechanisms and estimated rates of resistance [5] [6]

Antibiotics	Primary Mechanisms of Resistance	Rates of Resistance	
		United States	Global
Macrolides	Altered binding site in ribosome Drug efflux systems	13-18%	Europe: 18% Japan: 27-30% China: 53%
Amoxicillin	Altered binding site in penicillin binding proteins	<1%	Europe: <2% Japan: <1% China <10%
Metronidazole	Inactivation of nitroreductase enzyme required to “activate” drug Drug efflux systems	22%	Europe: 35% Japan: 9-12%
Tetracyclines	Altered binding site in ribosome Drug efflux systems	<1%	Europe: <1% China <10%
Fluoroquinolones	Altered binding site in DNA gyrase	32%	Europe: 3-14% China: 35%
Rifamycins	Altered binding site in RNA polymerase	Unknown	Europe: 1%

Supplementary Table 4. Data summary of clinical studies evaluating eradication rates of treatment regimens

Reference	Country of study	Study design	Sample size	Treatment regimens and eradication rates (ITT)
[26]	Multinational	Meta-analysis	93 studies (68% RCTs)	- PPI/H2RA + CLA + NMZ = 91% (NMZ susceptible), 72% (NMZ resistant) - PPI/H2RA + AMX + NMZ = 63% (NMZ resistant) - PPI/H2RA + BIS + MET + TET = 59% (MET resistant, with LAN or RAN), 90% (MET resistant, with OME or PAN or RAB) - RAN + BIS + CLA + MET = 97% (CLA susceptible, MET resistant)
[28]	Multinational	Meta-analysis	22 RCTs	- PPI + CLA + AMX = 81% - PPI + CLA + NMZ = 81%
[29]	Netherlands	Single-center RCT	122 patients	- OME + CLA + MET = 81% (MET susceptible), 83% (MET resistant) - OME + CLA + AMX = 88% (MET susceptible), 86% (MET resistant)
[30]	Multinational	Meta-analysis	91 treatment arms including NMZ among 4823 patients	- BIS + NMZ + AMX/TET = 89% (NMZ susceptible), 64% (NMZ resistant) - PPI + NMZ + AMX/CLA = 93% (NMZ susceptible), 69% (NMZ resistant) - PPI + BIS + NMZ + AMX/TET = 91% (NMZ susceptible), 71% (NMZ resistant)
[31]	Multinational	Meta-analysis	9 RCTs	- PPI + BIS + MET + TET = 78% - PPI + CLA + AMX = 77%
[32]	Multinational	Meta-analysis	12 RCTs (4 RCTs evaluated antibiotic susceptibility on eradication rates)	- PPI + BIS + MET + TET = 78%, 92% (MET susceptible), 84% (MET resistant) - PPI + CLA + AMX = 69%, 88% (CLA susceptible), 14% (CLA resistant)
[33]	Multinational	Prospective, multicenter	170 patients	- OME + BIS + MET + TET = 93%
[34]	Germany	Multicenter RCT	84 patients who failed triple therapy with PPI/H2RA, CLA, and NMZ	- OME + CLA + AMX = 43% - OME + BIS + MET + TET = 68%
[35]	Spain	Prospective, multicenter	162 patients with a documented penicillin allergy	- OME + CLA + MET = 57% - OME + BIS + TET + MET = 74% - OME + CLA + LVX = 64% - OME + CLA + RFB = 22%
[36]	China	Single-center RCT	109 patients who failed at least 1 course of therapy	- RAB + LVX + RFB = 91% - RAB + BIS + MET + TET = 91%
[37]	Italy	RCT	54 patients who failed first-line therapy (triple	- RAB + BIS + MIN + RFB = 77% - RAB + BIS + MIN + TIN = 52%

Formattato: Italiano (Italia)

			or sequential) and second-line LVX-based triple therapy	
[38]	Spain	Prospective, single-center	40 treatment courses among patients with a documented penicillin allergy	- OME + CLA + MET = 58% (12 treatment-naïve patients) - RAN + BIS + MET + TET = 47% (17 patients, 2nd course) - OME + CLA + RFB = 11% (9 patients, 3rd course) - OME + CLA + LVX = 100% (2 patients, 4th course)
[39]	Spain	Prospective, multicenter	50 patients with a documented penicillin allergy	- OME + CLA + MET = 54% (1st-line therapy) - OME + CLA + LVX = 73% (among 15 patients who failed 1st-line therapy)
[37]	Italy	Single-center RCT	100 patients	- RAB + LVX + AMX = 92% - RAB + LVX + MET = 90%
[38]	Italy	Prospective, single-center	49 patients	- PPI + CLA + CFM 200 mg twice daily = 71% - PPI + CLA + CFM 400 mg twice daily = 73%
[42]	United States	Prospective, single-center	12 patients	- CPZ 250 mg 4 times daily = 0%
[43]	China	RCT	400 patients	- ESO + BIS + AMX + LVX = 84% - ESO + BIS + CFX + LVX = 81%
[51]	Spain	Multicenter RCT	99 patients	- RFB + OME + AMX x 7 days = 70% - BIS + OME + MET + TET = 44.4%
[52]	Italy	Prospective, single-center	524 patients	- RFB + PAN + AMX = 88% (1st-line) 79% (2nd-line)
[53]	Multinational	Meta-analysis	21 RCTs	- RFB + PPI + AMX = 68.4% - "Other triple regimens" = 81.9% - BIS + OME + MET + TET = 67%
[54]	Taiwan	Multicenter RCT	450 treatment-naïve patients	- AMX + RAB = 95% - AMX + RAB followed by MET + RAB + CLA = 85% - AMX + RAB + CLA = 81%
[55]	Multinational	Meta-analysis	4 RCTs	- AMX + PPI = 81.3% - "Rescue therapy" = 81.5%
[56]	Multinational	Meta-analysis	91 RCTs	- AMX + MET + PPI = 70% - AMX + CLA + PPI = 77% - CLA + MET + PPI = 69%
[69]	Italy	Single-center RCT	154 patients aged > 60 years old	- PAN + CLA 250 mg twice daily + AMX = 83% - PAN + CLA 500 mg twice daily + AMX = 79%
[71]	Italy	RCT	121 patients aged > 60 years old	- OME + CLA + MET = 85% - OME + CLA + MET = 83% - OME + AZI + MET = 50% (OME 20 mg daily), 65% (OME 40 mg daily) - OME + CLA = 47%

				- OME + AZI = 39%
[72]	Unable to determine	RCT	126 patients aged > 60 years old	- BIS + MET + AMX = 66% - OME + AMX = 64%
[73]	Italy	RCT	150 patients aged > 60 years old	- LAN + CLA + MET = 86% - LAN + AMX + MET = 80% - LAN + CLA + AMX = 82%
[74]	Italy	Prospective, single-center	93 patients aged > 65 years old	- ESO + BIS + MET + TET = 91%
[79]	Italy	Multicenter RCT	179 patients aged > 65 years old	- RAB + AMX x 5 days, then RAB + CLA + TIN x 5 days = 94% - RAB + CLA + AMX x 7 days = 80%

AMX = amoxicillin; AZI = azithromycin; BIS = bismuth; CFM = cefixime; CPZ = cefprozil; CFX = cefuroxime; CLA = clarithromycin; ESO = esomeprazole; FAM = famotidine; H2RA = histamine H₂-receptor antagonist; ITT = intention to treat; LAN = lansoprazole; LVX = levofloxacin; MET = metronidazole; MIN = minocycline; NMZ = nitroimidazole; OME = omeprazole; PAN = pantoprazole; PPI = proton pump inhibitor; RAB = rabeprazole; RAN = ranitidine; RCT = randomized controlled trial; RFB = rifabutin; TET = tetracycline; TIN = tinidazole.