# Treatment regimens for Helicobacter pylori in adults

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Literature review current through: **Sep 2023.**
This topic last updated: **Oct 05, 2023.**

## INTRODUCTION

Multiple antibiotic regimens have been evaluated for *Helicobacter pylori* (*H. pylori*) therapy [1-6]. However, few regimens have consistently achieved high eradication rates. There are also limited data on *H. pylori* antibiotic resistance rates to guide therapy. The treatment regimen that is selected must consider local antibiotic resistance patterns (if known), previous exposure and allergies to specific antibiotics, cost, side effects, and ease of administration.

This topic will review treatment regimens for *H. pylori*. The bacteriology, epidemiology, and diagnostic tests for *H. pylori* infection are discussed elsewhere. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults" and "Bacteriology and epidemiology of Helicobacter pylori infection".)

## INDICATIONS FOR TREATMENT

All patients with evidence of active infection with *H. pylori* should be offered treatment. Indications for testing for *H. pylori* infection are discussed in detail separately. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Indications for testing'.)

## INITIAL ANTIBIOTIC THERAPY

**Approach to selecting an antibiotic regimen** — The choice of initial antibiotic regimen to treat *H. pylori* should be guided by the presence of risk factors for macrolide resistance and the presence of a penicillin allergy [7]. In patients with one or more risk factors for macrolide resistance, clarithromycin-based therapy should be avoided. A suggested approach to the selection of antibiotics for initial treatment of *H. pylori* infection is outlined in the algorithm ( algorithm 1 and table 1). (See 'Clarithromycin-based therapy' below.)

Risk factors for macrolide resistance include:

- Prior exposure to macrolide therapy at any time for any reason
- High local clarithromycin resistance rates ≥15 percent or eradication rates with clarithromycin triple therapy ≤85 percent

A resistance threshold of ≥15 percent is commonly used for choosing alternative empiric antibiotic regimen for *H. pylori* [8,9]. In the United States, given the limited information on antimicrobial resistance rates, we generally assume clarithromycin resistance rates are greater than 15 percent unless local data indicate otherwise [10]. Data suggest that *H. pylori* antibiotic resistance rates are high worldwide. In a systematic review and meta-analysis that included 178 studies, comprising 66,142 isolates from 65 countries, primary and secondary resistance to clarithromycin, metronidazole, and levofloxacin were high (≥15 percent) in the majority of WHO regions [11]. The pooled prevalence of primary clarithromycin resistance was >15 percent in European, Eastern Mediterranean and Western regions but were lower in the Americas (10 percent, 95% CI 4-16) and the South East Asia region (10 percent, 95% CI 5-16). Resistance to clarithromycin was significantly associated with failure of *H. pylori* eradication with a clarithromycin-containing regimen (odds ratio, 6.97; 95% CI, 5.2-9.3). However, the study was limited by significant heterogeneity and 10 of the 13 studies contributing to the pooled data for the Americas region were derived from South America. Local surveillance data are needed guide the choice of eradication regimens.

**Patients with risk factors for macrolide resistance** — In patients with risk factors for macrolide resistance, we use bismuth quadruple therapy ( algorithm 1 and table 1) [7-9,12-16]. (See 'Bismuth quadruple therapy' below and 'Levofloxacin based therapy' below.)

**Patients without risk factors for macrolide resistance** — In patients without risk factors for macrolide resistance, we use clarithromycin-based triple therapy with a proton pump inhibitor (PPI), amoxicillin, and clarithromycin ( algorithm 1 and table 1). Other first-line antibiotic regimens for these patients include bismuth quadruple therapy and clarithromycin-based concomitant therapy. In penicillin-allergic individuals, metronidazole can be substituted for amoxicillin. In patients with metronidazole exposure within the past few years, we use bismuth

quadruple therapy. (See 'Clarithromycin-based therapy' below and 'Bismuth quadruple therapy' below and 'Concomitant therapy' below.)

Other potential first-line treatment regimens include clarithromycin-based hybrid or sequential therapy [7]. However, the clarithromycin-based hybrid therapy has not been universally endorsed as an option for first-line therapy given its complexity [8]. In addition, some North American guidelines recommend against the use of sequential therapy as a first-line regimen given the lack of data from North American trials [8].

**Duration of therapy** — We recommend clarithromycin-based triple therapy and bismuth quadruple treatment regimens for *H. pylori* be administered for 14 days. Our recommendations are largely consistent with guidelines that recommend extended (10 to 14 days) treatment with all antibiotic regimens for *H. pylori* ( table 1) [8,9,12].

**Tolerability and compliance** — Side effects are reported in up to 50 percent of patients taking one of the triple therapy regimens [3,17]. The adverse effects are usually mild; fewer than 10 percent of patients stop treatment due to side effects [17]. Clarithromycin-based triple therapy and bismuth quadruple therapy appear to have similar efficacy, compliance, and tolerability [18]. While the tolerability and compliance of sequential, hybrid, and concomitant therapies appears to be similar to triple therapy in clinical trials, these regimens are more complex. Side effects of individual drugs are discussed in detail separately. (See "Metronidazole: An overview" and "Azithromycin and clarithromycin", section on 'Adverse reactions' and "Tetracyclines", section on 'Adverse reactions' and "Fluoroquinolones", section on 'Adverse effects' and "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Adverse effects' and "Antiulcer medications: Mechanism of action, pharmacology, and side effects", section on 'Adverse effects'.)

**Antibiotic regimens** — Initial antibiotic regimens for *H. pylori* can be broadly divided into bismuth, clarithromycin, and levofloxacin containing regimens ( table 1 and algorithm 1).

**Bismuth quadruple therapy** — Bismuth quadruple therapy consists of bismuth subsalicylate, metronidazole, tetracycline, and a PPI given for 14 days [19]. A combination capsule containing bismuth subcitrate, metronidazole, and tetracycline (Pylera) has been approved by the United States Food and Drug Administration. A regimen using the combination capsule (three capsules four times daily plus PPI twice daily) is somewhat simpler than standard quadruple therapy (four to eight pills four times daily and a PPI twice daily). For details, refer to bismuth subcitrate-metronidazole-tetracycline in Lexicomp. If tetracycline is not available, doxycycline (100 mg twice daily) may be substituted [20,21].

In North American trials, the mean eradication rate with bismuth quadruple therapy administered for 10 days was 91 percent [12,22,23]. A 2013 meta-analysis of 12 randomized trials reported comparable eradication rates with bismuth quadruple therapy and clarithromycin triple therapy (78 and 69 percent, respectively) [24]. However, there was significant heterogeneity in treatment duration, drug dosing, and the meta-analysis included trials performed in North America, Europe, and Asia. No significant differences in efficacy were noted when both regimens were administered for 10 to 14 days. Metronidazole resistance has a limited impact on eradication success rate in patients treated with bismuth quadruple therapy and can be overcome by increasing the dose, duration, or frequency of therapy [25]. (See 'Factors associated with antibiotic treatment failure' below.)

### Clarithromycin-based therapy

**Triple therapy** — Clarithromycin triple therapy consists of clarithromycin, amoxicillin, and a PPI, all given twice daily ( table 1). We suggest treatment for 14 days, as longer duration of treatment may be more effective in curing infection [7,8,26]. Metronidazole can be used instead of amoxicillin in penicillin-allergic individuals. PPI-clarithromycin-metronidazole and PPI-clarithromycin-amoxicillin regimens are equivalent [9,27].

Eradication rates for clarithromycin triple therapy in the United States are below 80 percent [7]. The eradication rates of clarithromycin triple therapy is significantly impacted by the presence of clarithromycin resistance [18,24]. In a meta-analysis of two trials in which patients were treated with clarithromycin triple therapy, eradication rates for clarithromycin-sensitive *H. pylori* strains and clarithromycin-resistant strains were 90 and 22 percent respectively [18]. Addition of bismuth to 14-day clarithromycin-based triple therapy may improve eradication rates in areas with high antimicrobial resistance [28]. However, further studies are needed.

**Concomitant therapy** — Concomitant therapy consists of a clarithromycin, amoxicillin, a nitroimidazole (tinidazole or metronidazole), and a PPI administered together ( table 1). If concomitant therapy is used to treat *H. pylori,* the regimen should be continued for 10 to 14 days.

While efficacy data from the North America are lacking, in a meta-analysis of 19 randomized trials that included 2070 individuals in Europe, Asia and Latin America, eradication rates were significantly higher with concomitant quadruple therapy as compared with clarithromycin triple therapy (90 and 78 percent, respectively) [29]. The efficacy of concomitant therapy was decreased in patients with clarithromycin-resistant *H. pylori* infection but to a smaller degree as compared with clarithromycin triple therapy. In this meta-analysis, longer durations of therapy (7 to 10 versus 3 to 5) were associated with a trend toward higher cure rates. However,

additional studies are needed to assess whether extending the duration of concomitant therapy to 14 days results in improved eradication rates.

**Hybrid therapy** — Hybrid therapy consists of amoxicillin and a PPI for seven days followed by amoxicillin, clarithromycin, a nitroimidazole, and a PPI for seven days ( table 1). Hybrid therapy has been suggested as an alternative to clarithromycin triple therapy. However, the complexity of the treatment regimen has limited its use as a first-line regimen in the treatment of *H. pylori.*

In a meta-analysis that included six randomized trials, which compared hybrid therapy with sequential and/or concomitant therapy, the eradication rate with hybrid therapy was 89 percent [30]. The efficacy and tolerability of hybrid therapy is comparable to concomitant and sequential regimens [31]. Hybrid therapy has not been directly compared with clarithromycin-based triple therapy. However, in one randomized trial in which 440 patients were assigned to 12 days of triple therapy or reverse hybrid therapy (amoxicillin and pantoprazole for 12 days and clarithromycin plus metronidazole for the initial seven days), eradication rates were significantly higher with reverse hybrid therapy (96 versus 89 percent) [32]. In contrast to patients who received clarithromycin triple therapy, clarithromycin resistance did not significantly impact eradication rates in patients treated with reverse hybrid therapy.

**Sequential therapy** — The 10-day clarithromycin-containing sequential therapy regimen consists of amoxicillin and a PPI for five days, followed by clarithromycin and nitroimidazole (eg, metronidazole) plus a PPI for five days ( table 1) [33]. Given the complexity of the sequential therapy regimen and the lack of superiority to 14 day clarithromycin triple therapy in North America, clarithromycin-containing sequential therapy has not been uniformly endorsed by guidelines as a first-line therapy [8]. (See 'Patients without risk factors for macrolide resistance' above.)

In a 2013 meta-analysis of 46 randomized trials that included 13,532 patients who were assigned to sequential therapy or other regimens, the overall eradication rate for sequential therapy was 84 percent [34]. Eradication rates with sequential therapy were significantly higher as compared with clarithromycin triple therapy administered for 7 or 10 days. However, there was no significant difference in eradication rates between sequential therapy and 14 days of clarithromycin-based triple therapy or 10 to 14 days of bismuth quadruple therapy. The efficacy of sequential therapy varies widely by region [7]. Randomized trials in Latin America and Asia have also demonstrated lower eradication rates with sequential therapy as compared with clarithromycin triple therapy; however, the efficacy of sequential therapy may be higher in Europe [35-39].

**Levofloxacin based therapy** — Due to rising rates of levofloxacin resistance, levofloxacin should not be used for treatment unless the *H. pylori* strain is known to be sensitive to it or if the population levofloxacin resistance rates are known to be less than 15 percent [7,11,40,41]. Studies evaluating the efficacy of levofloxacin containing regimens in North America are lacking. Limited data suggest that fluoroquinolone resistance rates in North America are high [11]. Levofloxacin resistance decreases the eradication success rate of levofloxacin containing regimens by 20 to 40 percent [7]. (See 'Approach to selecting an antibiotic regimen' above and 'Salvage regimens' below.)

- Levofloxacin **triple therapy** – Levofloxacin triple therapy consists of levofloxacin, amoxicillin, and a PPI for 10 to 14 days. In a network meta-analysis eradication rates with levofloxacin triple therapy for 10 to 14 days were significantly higher than clarithromycin triple therapy for seven days (90 versus 73 percent) [31]. Although not directly compared, the pooled eradication rate of levofloxacin triple therapy was also higher than clarithromycin triple therapy for 10 to 14 days (81 percent, 95% CI, 78 to 84 percent). Metronidazole can be substituted for amoxicillin in penicillin-allergic individuals.

- Levofloxacin **quadruple therapy** – Limited data support the use of quadruple therapy with levofloxacin, omeprazole, nitazoxanide, and doxycycline (LOAD). In an open label prospective trial, *H. pylori* treatment-naïve patients randomized to LOAD for 7 or 10 days had significantly higher eradication rates as compared with clarithromycin triple therapy for 10 days (89, 90, and 73 percent, respectively) [42]. However, additional studies are needed to confirm these results and determine whether this more expensive regimen is cost-effective. Other levofloxacin-based quadruple therapy regimens that have been used as salvage therapy include PBLA (PPI, bismuth, levofloxacin, amoxicillin), PBLT (PPI, bismuth, levofloxacin, tetracycline), and PBLM (PPI, bismuth, levofloxacin, metronidazole) [41].

- Levofloxacin **sequential therapy** – Levofloxacin sequential therapy consists of amoxicillin and a PPI for five to seven days followed by levofloxacin, amoxicillin, a nitroimidazole and a PPI for five to seven days. A meta-analysis of six international trials compared the efficacy of fluoroquinolone sequential therapy for 10 to 14 days and either clarithromycin triple therapy for 7 to 14 days or standard sequential therapy for 10 days [43]. The pooled eradication rate with fluoroquinolone sequential therapy was significantly higher as compared with clarithromycin triple or standard sequential therapies combined (88 versus 71 percent).

**PCAB containing regimens** — Regimens containing vonoprazan, an oral potassium-competitive acid blocker (PCAB) as triple therapy with amoxicillin and clarithromycin

(vonoprazan-amoxicillin-clarithromycin) or as dual therapy with high-dose amoxicillin (vonoprazan-amoxicillin), are associated with high *H. pylori* eradication rates [44-47]. Vonoprazan triple therapy may be an option for initial treatment in areas of low clarithromycin resistance rates. However, in areas with high or unknown clarithromycin resistance, further studies are needed to compare eradication rates with bismuth quadruple therapy [47]. (See "Antiulcer medications: Mechanism of action, pharmacology, and side effects", section on 'Potassium-competitive acid inhibitors'.)

## CONFIRM ERADICATION IN ALL PATIENTS

Tests to confirm eradication should be performed in all patients treated for *H. pylori*. Eradication may be confirmed by a urea breath test, fecal antigen test, or upper endoscopy performed four weeks or more after completion of antibiotic therapy. PPI therapy should be withheld for one to two weeks prior to testing [12,40,48]. Endoscopy with biopsy for culture and sensitivity should be performed in patients with persistent *H. pylori* infection after two courses of antibiotic treatment [41]. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Confirm eradication in all patients'.)

## TREATMENT FAILURE

Approximately 20 percent of patients fail an initial attempt at *H. pylori* eradication [49]. Such patients require salvage therapy ( algorithm 2 and table 2).

**Factors associated with antibiotic treatment failure** — Factors associated with treatment failure include poor patient compliance and resistance of the patient's *H. pylori* strain to prescribed antibiotics. *H. pylori* is naturally resistant to several commonly used antibiotics, including vancomycin, trimethoprim, and sulfonamides [50]. A specific mutation leading to clarithromycin resistance appears to be associated with a reduced likelihood of eradication [51]. Prior use of macrolide antibiotics, and levofloxacin increases the risk of *H. pylori* resistance to these antibiotics [52]. Clarithromycin resistance has a greater effect on treatment efficacy as compared with metronidazole resistance [25]. Resistance rates to amoxicillin, tetracycline, and rifabutin are low (<5 percent), and these can be considered for subsequent therapies in refractory *H. pylori* infection [41]. Inadequate acid suppression is also associated with *H. pylori* eradication failure.

**Salvage therapy for persistent H. pylori infection**

**Suggested approach** — In patients with persistent *H. pylori* infection, the choice of antibiotic therapy should be guided by the patient's initial treatment regimen, the use of other antibiotics, and the presence of relevant antibiotic allergies [41]. Antibiotics included in the initial regimen should generally be avoided [53]. However, amoxicillin can be reused as resistance rarely develops. Patients with a reported history of penicillin allergy should be referred to an allergist to determine if they have a true penicillin allergy. A suggested approach to the selection of antibiotics for persistent *H. pylori* infection is outlined in the algorithm ( algorithm 2 and table 2). (See "An approach to the patient with drug allergy".)

Culture with antibiotic sensitivity testing should be performed to guide antibiotic treatment in patients who have failed two prior treatment regimens. Compliance with medications should also be reinforced. We reserve the use of rifabutin-containing regimens for patients with ≥3 previous antibiotic failures. However, other experts have suggested its use as a second-line agent [41]. The impact of metronidazole resistance can be overcome by increasing the dose (1.5 to 2 g daily in divided doses), duration, or frequency of administration of metronidazole [41]. Resistance rates to amoxicillin, tetracycline, and rifabutin are low (<5 percent), and these can be considered for subsequent therapies in refractory *H. pylori* infection even if previously used [41].

The use of high-dose PPIs (double the standard dose), use of more potent PPIs and those less dependent on metabolism by CYP2C19 (eg, esomeprazole or rabeprazole), or potassium-competitive acid blockers where available, can lower intragastric acidity in patients with refractory *H. pylori* infection [41,54]. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Bacterial culture and sensitivity testing'.)

**Salvage regimens** — Salvage regimens in patients who have failed initial antibiotic therapy include ( table 2):

- **Bismuth quadruple therapy** – Bismuth quadruple therapy should be used for 14 days when used as salvage regimen. In randomized trials performed in Europe, United States, and Asia eradication rates with 14-day salvage bismuth quadruple therapy were approximately 80 percent [12]. Eradication rates were significantly higher in studies performed in Asia as compared with Europe and the United States (82 versus 74 percent) [55-57]. The overall eradication rate for 14-day bismuth quadruple therapy in these trials was higher in patients who had previously failed clarithromycin-based regimens without bismuth as compared with bismuth quadruple treatment (100 versus 53 percent).

- **Levofloxacin-based therapy** – Levofloxacin-based triple therapy has demonstrated efficacy as a salvage regimen in patients who have failed initial clarithromycin triple therapy or bismuth quadruple therapy. Levofloxacin triple therapy has also demonstrated

efficacy in patients who have failed two prior attempts at treatment. In a pooled analysis from six European cohort studies, when used as a salvage regimen in patients who had failed two previous eradication attempts, levofloxacin triple therapy administered for 10 days has a pooled eradication rate of 73 percent [58]. Most patients in these studies were treated with clarithromycin triple therapy followed by bismuth quadruple therapy.

Other levofloxacin-based quadruple therapy regimens that have been used as salvage therapy include PBLA (PPI, bismuth, levofloxacin, amoxicillin), PBLT (PPI, bismuth, levofloxacin, tetracycline), and PBLM (PPI, bismuth, levofloxacin, metronidazole) [41].

- **High-dose dual therapy** – High-dose dual therapy with amoxicillin (at least 2 g divided three or four times per day to avoid low trough levels) and proton pump inhibitor (PPI) for 14 days is a salvage treatment option, particularly in patients in whom dual metronidazole/clarithromycin resistance or levofloxacin resistance is suspected [41]. The pooled eradication rate of high-dose dual therapy with amoxicillin and PPI as a salvage regimen in three randomized trials performed in Europe and Asia was 78 percent [12].

  The role of high-dose dual therapy as first-line treatment is unclear, as studies evaluating the efficacy of this regimen have been conflicting. In studies conducted in the United States and Korea, eradication rates in treatment-naive patients were low (72 and 79 percent, respectively) [59,60]. However, in a randomized trial in China in which 232 treatment-naive patients were assigned to high-dose dual therapy or bismuth quadruple therapy, there was no significant difference in eradication rates between the two groups [61]. While high-dose dual therapy had lower treatment-related adverse effects as compared with bismuth quadruple therapy, it is important to note that there may have been reporting bias due to the open-label study design.

- Rifabutin **triple therapy** – Rifabutin triple therapy has demonstrated efficacy as a salvage regimen. The rifabutin-based triple regimen consists of rifabutin, amoxicillin, and a PPI twice daily for 14 days. In randomized trial, in which 364 subjects with *H. pylori* who had failed at least two prior treatments were randomly assigned to rifabutin triple therapy for 14 days or bismuth quadruple therapy, there was no significant difference in *H. pylori* eradication rates [62]. However, compliance rates were higher in patients treated with rifabutin-based triple therapy as compared with the bismuth quadruple therapy (96 versus 85 percent), and the rates of adverse effects were significantly lower (26 versus 54 percent). The most frequent adverse effects of rifabutin triple therapy were fever and skin rash (12 and 8 percent, respectively). Five subjects with fever experienced transient leukopenia. Limitations of this study include the potential risk of bias and lack of blinding.

The role of rifabutin-based triple therapy as a first-line treatment option is unclear. In a randomized trial, in which *455 H. pylori* treatment-naïve patients were assigned to treatment with rifabutin-based triple therapy or high-dose dual therapy with amoxicillin and omeprazole, eradication rates with the rifabutin-containing regimen were significantly higher (84 versus 58 percent) [63]. Eradication rates were unaffected by resistance to clarithromycin or metronidazole. However, the study was conducted in the United States and excluded persons of Asian descent due to a higher prevalence of poor CYP2C19 metabolizers. Rifabutin-based triple therapy is expensive and can cause reversible myelotoxicity. It also has the potential to increase the prevalence of rifabutin-resistant mycobacteria.

- **Clarithromycin-based therapy** – Clarithromycin-based therapy (eg, PPI, bismuth, clarithromycin, tetracycline), can be used as a salvage regimen in patients with no risk factors for macrolide resistance (no prior macrolide exposure and local clarithromycin resistance known to be <15 percent) [41,64,65]. (See 'Clarithromycin-based therapy' above.)

## ADJUVANT THERAPIES WITH UNCLEAR ROLE

A number of potential adjuvant therapies for *H. pylori* have been evaluated, but additional studies are needed to support their use.

- **Statins** – Addition of statin therapy as an adjuvant to triple therapy has been associated with a reduction in *H. pylori* mediated inflammation and an increase in *H. pylori* eradication rates [66-68]. However, large trials are needed to confirm these findings.

- **Probiotics** – Probiotics may have an inhibitory effect on *H. pylori.* In addition, they may improve compliance with treatment by reducing antibiotic side effects. A meta-analysis that included 10 clinical trials of adjuvant probiotics in patients with *H. pylori* infection demonstrated higher cure rates and a reduction in the incidence of side effects in patients who received probiotic supplementation (pooled OR 2.1 and 0.3, respectively). However, studies included in this meta-analysis were at high risk of bias due to lack of blinding and inadequate allocation concealment. In addition, there was significant variability in the probiotics used and antibiotic treatment regimens to eradicate *H. pylori*. (See "Probiotics for gastrointestinal diseases".)

## TREATMENT DURING PREGNANCY AND LACTATION

When peptic ulcer disease is diagnosed in a woman who is pregnant, the mainstay of treatment is typically acid suppression [69]. If *H. pylori* is present, treatment is typically deferred until after delivery. However, with the exception of bismuth, fluoroquinolones, and tetracycline, the other medications used for *H. pylori* eradication are low risk in pregnancy, especially after 14 weeks. This includes clarithromycin, amoxicillin, and probably metronidazole. Moreover, there is some evidence that *H. pylori* can cause severe nausea and vomiting in pregnancy, including hyperemesis gravidarum [70,71]. Thus, if indicated, *H. pylori* treatment should be considered in pregnancy.

Some of the medications typically used for the treatment of *H. pylori* are possibly unsafe for nursing infants (eg, bismuth, metronidazole, levofloxacin). (See "Medical management of gastroesophageal reflux disease in adults", section on 'Pregnancy and lactation' and "Prenatal care: Patient education, health promotion, and safety of commonly used drugs", section on 'Antibiotics'.)

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: *Helicobacter pylori*".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5$^{th}$ to 6$^{th}$ grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10$^{th}$ to 12$^{th}$ grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: H. pylori infection (The Basics)" and "Patient education: Gastritis (The Basics)")

- Beyond the Basics topic (see "Patient education: Helicobacter pylori infection and treatment (Beyond the Basics)")

## SUMMARY AND RECOMMENDATIONS

- **Choice of initial antibiotic** – All patients with evidence of active infection with *Helicobacter pylori* (*H. pylori*) should be offered treatment. The choice of initial antibiotic regimen to treat *H. pylori* should be guided by the presence of risk factors for macrolide resistance and the presence of a penicillin allergy.

  Risk factors for macrolide resistance include:

  - Prior exposure to macrolide therapy at any time for any reason.
  - High local clarithromycin resistance rates ≥15 percent or eradication rates with clarithromycin-based triple therapy ≤85 percent.

  In the United States, given the limited information on antimicrobial resistance rates, we generally assume clarithromycin resistance rates are greater than 15 percent unless local resistance data indicate otherwise. (See 'Approach to selecting an antibiotic regimen' above.)

- **Patients with risk factors for macrolide resistance** – We suggest bismuth quadruple therapy as initial treatment in patients with risk factors for macrolide resistance (**Grade 2B**) ( algorithm 1 and table 1). Quadruple therapy consists of a proton pump inhibitor (PPI), bismuth subsalicylate, and two antibiotics (metronidazole and tetracycline) given four times daily for 14 days. Alternatively, a commercially available combination capsule containing bismuth subsalicylate, metronidazole, and tetracycline may be used in conjunction with a PPI. In patients with risk factors for macrolide resistance, clarithromycin-based therapy should be avoided ( algorithm 1 and table 1). (See 'Patients with risk factors for macrolide resistance' above and 'Bismuth quadruple therapy' above.)

- **Patients without risk factors for macrolide resistance** – For initial therapy in patients without risk factors for macrolide resistance, we suggest triple therapy with a PPI, amoxicillin (1 g twice daily), and clarithromycin (500 mg twice daily) for 14 days (**Grade 2B**). Only in penicillin-allergic individuals, we suggest substitution of amoxicillin with metronidazole since metronidazole resistance is common and can reduce the efficacy of treatment (**Grade 2B**). (See 'Clarithromycin-based therapy' above.)

- **Confirmation of eradication** – Tests to confirm eradication should be performed in all patients treated for *H. pylori*. Eradication may be confirmed by a urea breath test, fecal antigen test, or upper endoscopy performed four weeks or more after completion of antibiotic therapy. PPI therapy should be withheld for one to two weeks prior to testing. (See 'Confirm eradication in all patients' above and "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Diagnostic tests'.)

- **Management of antibiotic treatment failure** – In patients with persistent *H. pylori* infection, the choice of antibiotic therapy should be guided by the patient's initial treatment regimen and the presence of relevant antibiotic allergies ( algorithm 2 and table 2). For patients failing a course of *H. pylori* treatment, we suggest an alternate regimen using a different combination of medications (**Grade 2B**). In general, clarithromycin and antibiotics used previously should be avoided if possible. (See 'Salvage therapy for persistent H. pylori infection' above.)

- **Additional evaluation in patients with two antibiotic failures** – Culture with antibiotic sensitivity testing should be performed to guide antibiotic treatment in patients who have failed two prior treatment regimens. Compliance with medications should also be reinforced. We reserve the use of rifabutin-containing regimens for patients with ≥3 prior antibiotic failures. (See 'Salvage therapy for persistent H. pylori infection' above.)

## ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Sheila E Crowe, MD, FRCPC, FACP, FACG, AGAF who contributed to an earlier version of this topic review.



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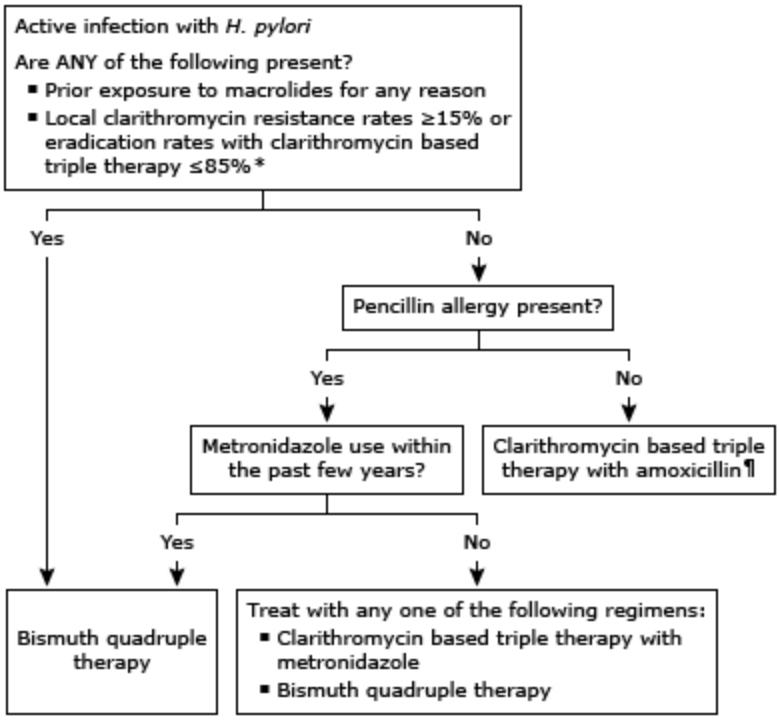
Topic 7 Version 61.0

## GRAPHICS

### Initial approach to antibiotic treatment for *Helicobacter pylori* infection




- Bismuth quadruple therapy consists of bismuth, metronidazole, tetracycline, and a PPI.
- Clarithromycin based triple therapy with amoxicillin consists of clarithromycin, amoxicillin, and a PPI.
- Clarithromycin based triple therapy with metronidazole consists of clarithromycin, metronidazole, and a PPI.

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* In the United States, given the limited information on antimicrobial resistance rates, we generally assume clarithromycin resistance rates are ≥15% unless local data indicate otherwise.

¶ Alternative first-line antibiotic regimens include bismuth quadruple therapy and clarithromycin based concomitant therapy. Other potential treatment regimens include clarithromycin based sequential or hybrid therapy. However, hybrid therapy has not been universally endorsed as an option for first-line therapy and some North American guidelines do not support the use of sequential therapy. Refer to UpToDate topic on treatment regimens for *H. pylori* for additional details.

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Graphic 112678 Version 2.0

## First-line therapies for *H. pylori* infection

| Regimen | Drugs (doses) | Dosing frequency | Duration (days) | FDA approval |
|---|---|---|---|---|
| Bismuth quadruple | PPI (standard dose[¶]) | Twice daily | 10 to 14[◇] | No[§] |
| | Bismuth subcitrate (120 to 300 mg [not available in US] or 420 mg [available in North America and elsewhere as part of Pylera combination pill])[1]<br>**or**<br>Bismuth subsalicylate (300 or 524 mg)[1] | Four times daily | | |
| | Tetracycline (500 mg) | Four times daily | | |
| | Metronidazole (250 to 500 mg) | Four times daily (250 mg) | | |
| | | Three to four times daily (500 mg) | | |
| Clarithromycin triple* | PPI (standard[¶] or double the standard dose) | Twice daily | 14 | Yes[Δ] |
| | Clarithromycin (500 mg) | Twice daily | | |
| | Amoxicillin (1 gram)<br>**or**<br>Metronidazole (500 mg) | Twice daily (amoxicillin)<br>Three times daily (metronidazole) | | |
| Clarithromycin-based concomitant* | PPI (standard dose[¶]) | Twice daily | 10 to 14 | No |
| | Clarithromycin (500 mg) | Twice daily | | |
| | Amoxicillin (1 gram) | Twice daily | | |
| | Metronidazole or tinidazole (500 mg) | Twice daily | | |
| Clarithromycin-based sequential[¥]* | PPI (standard dose[¶]) plus amoxicillin (1 gram) for 5 days followed by: | Twice daily | 10 (total) | No |
| | PPI, clarithromycin (500 mg) plus either metronidazole or | Twice daily | | |

| | | | | |
|---|---|---|---|---|
| | tinidazole (500 mg) for an additional 5 days | | | |
| Clarithromycin-based hybrid‡* | PPI (standard dose¶) plus amoxicillin (1 gram) for 7 days followed by: | Twice daily | 14 (total) | No |
| | PPI, amoxicillin, clarithromycin (500 mg), plus either metronidazole or tinidazole (500 mg) for an additional 7 days | Twice daily | | |

FDA: United States Food and Drug Administration; PPI: proton pump inhibitor.

* In patients with risk factors for macrolide resistance, clarithromycin-based therapy should be avoided.

¶ Standard doses of orally administered proton pump inhibitors include: Lansoprazole 30 mg daily, omeprazole 20 mg daily, pantoprazole 40 mg daily, rabeprazole 20 mg daily, or esomeprazole 20 mg daily.

Δ Several PPI, clarithromycin, and amoxicillin combinations have achieved FDA approval. PPI, clarithromycin, and metronidazole is not an FDA-approved treatment regimen.

◇ 14 days is recommended. Refer to UpToDate topic on treatment for *H. pylori* infection.

§ PPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera (a fixed-dose capsule containing bismuth subcitrate, tetracycline, and metronidazole) combined with a PPI for 10 days, and Helidac (a copackaged product containing bismuth subsalicylate, tetracycline, and metronidazole) combined with a PPI for 14 days, are FDA-approved treatment regimens. For additional information, refer to the Lexicomp drug monographs included within UpToDate.

¥ Some North American guidelines do not support the use of sequential therapy.

‡ Hybrid therapy has not been universally endorsed as an option for first-line therapy.

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*Reference:*

1. *Fallone CA, Chiba N, Van Zanteri et al. The Toronto Consensus for Treatment of Helicobacter pylori infection in Adults. Gastro 2016; 15:51.*



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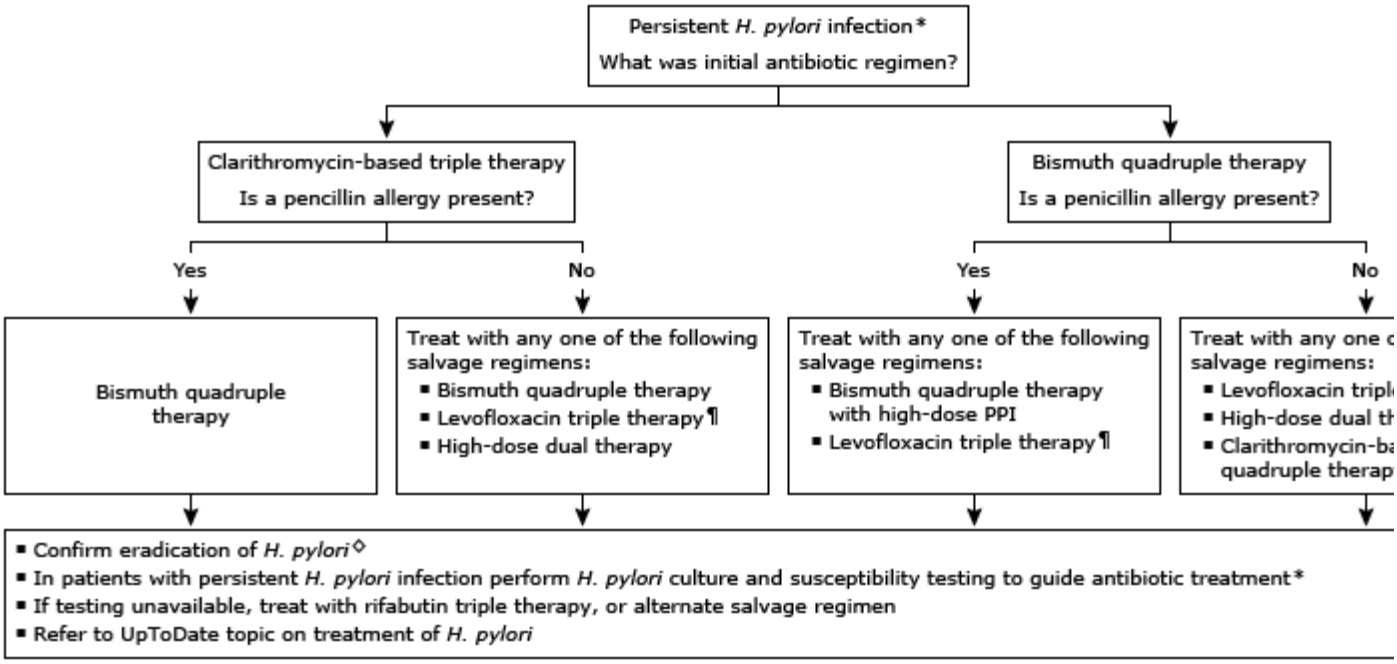
Graphic 112171 Version 9.0

## Approach to antibiotic treatment in patients with persistent *Helicobacter pylori*




- Clarithromycin-based triple therapy consists of clarithromycin, amoxicillin/metronidazole, and a PPI.
- Bismuth quadruple therapy consists of bismuth subsalicylate or bismuth subcitrate, metronidazole, tetra and a PPI.
- Levofloxacin triple therapy consists of levofloxacin, amoxicillin/metronidazole, and a PPI.
- High-dose dual therapy consists of amoxicillin and a PPI.
- Rifabutin triple therapy consists of rifabutin, amoxicillin, and a PPI.
- Clarithromycin-based concomitant therapy consists of clarithromycin, amoxicillin, nitroimidazole (eg, metronidazole), and a PPI.

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* Eradication of *H. pylori* after antibiotic treatment may be confirmed by a urea breath test, stool antigen tes endoscopy-based testing. A positive result on one of these tests is indicative of a persistent *H. pylori* infectio

¶ If known levofloxacin sensitive strain or the population levofloxacin resistance rates are known to be less t

Δ Only in patients with no risk factors for macrolide resistance (no prior macrolide exposure and local clarith resistance known to be <15%). This regimen should be avoided if local clarithromycin resistance is unknown

◇ Eradication of *H. pylori* infection can be confirmed with a urea breath test, stool antigen testing, or upper based testing. The choice of test depends on the need for an upper endoscopy (eg, follow-up of bleeding pe and local availability. *H. pylori* serology should not be used to confirm eradication of *H. pylori*. Refer to UpToD on diagnostic tests for *H. pylori*.

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Graphic 112679 Version 2.0

## Salvage therapies for *H. pylori* infection

| Regimen | Drugs (doses)* | Dosing frequency | Duration (days) |
|---|---|---|---|
| Bismuth quadruple | PPI (standard dose¶) | Twice daily | 14 |
| | Bismuth subcitrate (120 to 300 mg [not available in US] or 420 mg [available in North America and elsewhere as part of Pylera combination pill])[1]<br>**or**<br>Bismuth subsalicylate (300 or 524 mg)[1] | Four times daily | |
| | Tetracycline (500 mg) | Four times daily | |
| | Metronidazole (500 mg) | Three to four times daily | |
| Levofloxacin triple | PPI (high dose or high potency¶) | Twice daily | 14 |
| | Levofloxacin (500 mg) | Once daily | |
| | Amoxicillin (750 mg) | Three times daily | |
| Clarithromycin quadruple[2] | PPI (standard dose¶) | Twice daily | 14 |
| | Clarithromycin (500 mg) | Twice daily | |
| | Bismuth subsalicylate (300 or 524 mg)[1] | Four times daily | |
| | Tetracycline (500 mg) | Four times daily | |
| Rifabutin triple◇ | PPI (high dose or high potency¶) | Twice daily | 14 |
| | Rifabutin (300 mg) | Once daily | |
| | Amoxicillin (750 mg) | Three times daily | |
| Rifabutin triple◇ (commercially available combination capsules) | Four (4) omeprazole-amoxicillin-rifabutin combination capsules (each capsule contains 10/250/12.5 mg) | Three times daily | 14 |
| High-dose dual | PPI (high dose¶) | Twice daily | 14 |

| | | | |
|---|---|---|---|
| | Amoxicillin (1 gram three times daily or 750 mg four times daily) | Three to four times daily | |

FDA: United States Food and Drug Administration; PPI: proton pump inhibitor.

* Doses are for adults with normal kidney function. Dose adjustment is warranted in patients with kidney function impairment for certain antibiotics (eg, levofloxacin, rifabutin, clarithromycin if end-stage disease).

¶ Standard dose of orally administered proton pump inhibitors include: Lansoprazole 30 mg daily, omeprazole 20 mg daily, pantoprazole 40 mg daily, rabeprazole 20 mg daily, esomeprazole 20 mg daily, or dexlansoprazole 30 mg daily.

High-dose proton pump inhibitors are double the standard dose. High-potency proton pump inhibitors include esomeprazole or rabeprazole.

◇ Rifabutin-containing regimens should be reserved for patients with ≥3 previous eradication failures. Rifabutin is an inducer of cytochrome P450 drug metabolism (ie, accelerates drug metabolism); assess potential drug interactions before use.

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*Reference:*

1. *Fallone CA, Chiba N, van Zanten SV, et al. The Toronto Consensus for the Treatment of Helicobacter pylori Infection in Adults. Gastro 2016; 151:51.*
2. *Shah SC, Iyer PG, Moss, SF. AGA Clinical Practice Update on the Management of Refractory Helicobacter pylori Infection: Expert Review. Gastroenterology 2021; 160:1831.*



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Graphic 112172 Version 8.0

## Contributor Disclosures

**J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Mark Feldman, MD, MACP, AGAF, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

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