Treatment for *H. pylori* Infection

**New Challenges With Antimicrobial Resistance**

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**Abstract:** The treatment of *Helicobacter pylori* infection is in a state of flux as traditional therapies fail and new therapies do not achieve the 90% eradication rates desired by clinicians. Triple therapy, which has been the mainstay of treatment in many countries over the last decade, now has suboptimal results in many parts of the world. A number of new treatments have been described with variable success in different parts of the world. In this article, the fundamentals of treatment for *H. pylori* treatment are reviewed and new treatment algorithms are proposed for regions of the world where triple therapy is failing. Sequential therapy and quadruple therapy (either bismuth-based or non–bismuth-based) are the best current options to replace initial treatment with triple therapy. When initial treatment fails, salvage treatments using rifabutin and levofloxacin are the best options. With knowledge of local resistance patterns and with meticulous confirmation of eradication with retreatment, most *H. pylori* infections can be successfully eradicated.

**Key Word:** *H. pylori* treatment, sequential therapy, quadruple therapy, triple therapy


*Helicobacter pylori* is an important pathogen worldwide. It has been associated with chronic gastritis, peptic ulcer disease, gastric cancer, gastric mucosa associated lymphoid tumor lymphoma, some patients with unexplained iron deficiency anemia, and idiopathic thrombocytopenic purpura. Eradication of *H. pylori* is an important challenge in clinical practice because of the increasing prevalence of resistant strains of *H. pylori* worldwide. A rational strategy for the management of *H. pylori* depends on knowledge of the role of individual agents in the therapeutic regimen, appropriate durations of treatment, and local resistance patterns.

**PRINCIPLES OF ANTIMICROBIAL THERAPY FOR *H. PYLORI***

**Gastric pH and Volume**

The gastric mucus layer limits the delivery of antimicrobials to *H. pylori* and penetration of antimicrobials into the mucus is important for treatment success. Drugs that dissolve mucus (eg, pronase) increase drug delivery through the gastric mucus but are not used clinically. Instead, proton pump inhibitors (PPIs) are used as an integral part of the treatment regimen to enhance drug delivery through the gastric mucus. PPIs decrease the volume of gastric juice and raise antimicrobial concentrations in the gastric juice. PPIs also decrease the viscosity of the gastric mucus layer and therefore improve its permeability. Antibiotics can be unstable at the low pH found in the stomach. Clarithromycin is very sensitive to degradation by gastric acid and has a half-life of < 1 hour at a pH of 2.2,3 Metronidazole is very stable in gastric juice regardless of pH with a half-life of over 800 hours. Amoxicillin is less stable at low pH but its half-life is 15 hours at a pH of 2.2,3 Antimicrobial agents used for *H. pylori* infections were not specifically designed for this application.

**Drug Substitutions**

The antimicrobial effect of agents used to treat *H. pylori* is primarily local, within the gastric lumen, but the formulation of the drugs is designed to enhance blood levels for the treatment of systemic infections. As a result, some drug substitutions are not effective in *H. pylori* treatment regimens, for example, ampicillin cannot be substituted for amoxicillin, clarithromycin cannot be replaced by azithromycin, and ciprofloxacin cannot replace levofloxacin.

**Adherence With Treatment Regimens**

As antimicrobial resistance rates increase and the success of therapy decreases, adherence with treatment is a very important consideration. There are a number of challenges with *H. pylori* treatment: (1) side effects are reported by approximately 50% of patients; (2) the treatment regimens are complicated and require careful attention to detail. Quadruple therapies, which require ingestion of multiple medications 4 times a day, can cause problems with adherence.4 Sequential therapy can cause confusion because the first 5 days of therapy require 2 agents and the subsequent 5 days need 3 agents. (3) Patients taking < 80% of their treatment regimen has a high rate of treatment failure; and (4) failed treatment is associated with the emergence of antimicrobial resistance. Measures to enhance compliance improve success with eradication and are meaningful in areas with a high prevalence of *H. pylori* infection where large numbers of patients are treated. At a minimum, patients should receive counseling regarding the anticipated side effects, the importance of completing the treatment regimen, and the risk of antimicrobial resistance with failed therapy. Some drugs have been specifically developed for delivery to *H. pylori*, but there has been little progress in this area in the last few years. Ranitidine bismuth citrate is an example of such an agent. It disintegrates rapidly in the stomach allowing bismuth to be delivered to *H. pylori* but is no longer available in the United States.5
Antimicrobial Resistance

There are 3 key antimicrobial agents that are used in treatment regimens for *H. pylori*. Key agents in eradication regimens for *H. pylori* are amoxicillin, clarithromycin, and metronidazole (or tinidazole). In salvage regimens, levofloxacin and rifabutin are also key agents. All successful treatment regimens for *H. pylori* contain ≥1 of these agents. Combinations of drugs that contain none of these agents have limited efficacy. Of the 3 key drugs, amoxicillin is used in many different combinations of drugs because resistance to this agent rarely develops in clinical practice. Metronidazole and clarithromycin resistance are important in clinical practice and resistance to one of these agents is often the cause of failed therapy. Antimicrobial resistance is a major cause of treatment failure and is responsible for the declining rates of *H. pylori* eradication seen in many countries. Clarithromycin works by interruption of bacterial protein synthesis and resistance is caused by a mutation in the organism that prevents binding of the antibiotic to the ribosome of *H. pylori*. A rapid efflux pathway may also develop in *H. pylori*. These efflux channels develop in the organism when exposed to clarithromycin. The drug is rapidly pumped out of the organism preventing the antimicrobial effect. It has been suggested that sequential therapy may be more effective than triple therapy because the initial treatment with a PPI and amoxicillin poisons the cell wall of the organism preventing the development of efflux channels. There is cross-reactivity between macrolides, and therefore, resistance to clarithromycin may develop with exposure to any macrolides.

A nitroimidazole such as metronidazole is a prodrug, which needs to be reduced in the cell to have an adverse effect on bacterial DNA. Frame-shift mutations in a gene called rdxA have been associated with metronidazole resistance, but mutations in other genes may also be responsible. In 1999, a systematic review of *H. pylori* therapy found that when clarithromycin was the key drug in a regimen, eradication rates fell by 56% when clarithromycin resistant strains were present. A more recent analysis of published studies found a 70% decline in eradication rates if clarithromycin resistance was present and a clarithromycin-containing regimen was used. Nitroimidazole resistance causes a 50% reduction in eradication with triple and quadruple therapies. Resistance rates in Europe have recently been reported and are summarized in Table 1. Recent data from Asia are also summarized in Table 1.

### TABLE 1. Antimicrobial Resistance Rates for *Helicobacter pylori* Around the World

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Year</th>
<th>Clarithromycin (%)</th>
<th>Metronidazole (%)</th>
<th>Amoxicillin (%)</th>
<th>Fluoroquinolones (%)</th>
<th>Tetracycline (%)</th>
<th>Rifabutin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>2004</td>
<td>12.9</td>
<td>25.1</td>
<td>0.9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>2012</td>
<td>7.7</td>
<td>28.6</td>
<td>—</td>
<td>7.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Central Western Europe</td>
<td>2012</td>
<td>18.7</td>
<td>43.8</td>
<td>—</td>
<td>18.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>2012</td>
<td>21.5</td>
<td>29.7</td>
<td>—</td>
<td>13.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Korea</td>
<td>2012</td>
<td>10.8</td>
<td>30.3</td>
<td>2.2</td>
<td>15.7</td>
<td>0.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>China</td>
<td>2011</td>
<td>84.9</td>
<td>61.6</td>
<td>—</td>
<td>13.7</td>
<td>—</td>
<td>—</td>
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</tbody>
</table>

TREATMENT FOR *H. PYLORI* INFECTION

**PPI Triple Therapy**

Triple therapy is the most widely used treatment in much of the United States (Table 2). The most recent studies performed in the United States are now several years old and have demonstrated very low eradication rates if clarithromycin resistance was present and a clarithromycin-containing regimen was used. Nitroimidazole resistance causes a 50% reduction in eradication with triple and quadruple therapies. Resistance rates in Europe have recently been reported and are summarized in Table 1. Recent data from Asia are also summarized in Table 1.
In 1 study, the intent-to-treat eradication rate was 65% with confidence interval (CI) ranging from 57% to 73%. In another, the intent-to-treat eradication rate was 78% with CI ranging from 72% to 84%. It is likely that eradication rates have declined further. The recent Maastricht guidelines recommend that triple therapy should be abandoned as a primary form of therapy when the prevalence of clarithromycin resistance rises to 15% to 20%. Unfortunately, there is no active monitoring for resistance rates in the United States and the prevalence of resistance is unclear. However, as the pattern of antibiotic use in the United States resembles practices in western Europe, high resistance rates are very likely at least in some parts of the United States. Therefore, most practitioners in the United States should be considering using sequential therapy or quadruple therapy as the initial treatment regimen.

The results of triple therapy in Latin America remain surprisingly robust. In a recent study performed in multiple Latin American countries, eradication success with triple therapy was 82-2%, which was higher than with quadruple therapy (73.6%) and sequential therapy (76.5%).

Some studies have suggested that triple therapy can still be used in clinical practice by testing for cure and selectively using second-line and third-line treatments in the event of failure. In an Irish study, 3280 patients received PPI triple therapy, which was effective in 2530 (77%) patients. Bismuth-based “quadruple” or an alternative triple therapy was successful in 56% of 270 treatment failures with the initial therapy. Subsequent eradication attempts using rifabutin-based and furazolidone-based regimens were successful in 38% and 60% patients, respectively. This trial suggested that it is possible to achieve successful eradication in the majority of patients using traditional treatments. In another trial performed in Greece, patients were initially treated with PPI triple therapy, failures were given quadruple therapy and patients failing both treatments were given levofloxacin triple therapy. Using this strategy, of the 540 patients receiving treatment, 484 had successful eradication (intent-to-treat eradication rate: 89.6%). A study from Spain with a total of 500 patients reported a high success rate of 99.5% when traditional triple therapy was used initially and salvage therapies were administered to those who failed triple therapy. A practical strategy in areas where the results of antimicrobial sensitivity testing are not available is to monitor success with whatever treatment is being used as the initial therapy. If all patients return for confirmation of eradication, the failure rate for the initial treatment regimen can be determined. The initial treatment regimen should be changed if the failure rate is ≥20%. The major points to be taken away from recent data on triple therapy are: (a) Initial treatment may fail in as many as 30% of patients; (b) test all patients after treatment to confirm eradication and use the results as a guide to success with triple therapy in your area; (c) establish a salvage plan for treatment failures; and (d) consider switching to sequential therapy or quadruple therapy as the first line of treatment.

Nonbismuth Quadruple Therapies

The combination of PPI-clarithromycin-amoxicillin-nitromidazole is referred to as nonbismuth quadruple therapy and was developed because bismuth is not available in some countries. This treatment has also been referred to as concomitant therapy, a term that implies that all the antibiotics are administered together. This is a misnomer as all treatments for H. pylori, with the exception of sequential therapy are in fact concomitant therapies. A meta-analysis of randomized trials comparing nonbismuth quadruple therapy was recently reported and showed that the eradication rate with quadruple therapy was 90% compared with 78% with triple therapy. A recent open-label study using a novel quadruple therapy comprising levofloxacin, omeprazole, nitazoxanide, and doxycycline with a PPI had a high eradication rate in a single open-label study. It needs further validation.

The main take-away points with non–bismuth-based quadruple therapy are: (a) this treatment is a good alternative to triple therapy in areas with high prevalence rates of clarithromycin resistance and (b) when clarithromycin therapy fails, bismuth quadruple therapy is the best choice for empirical treatment in the United States (Table 2).

Quadruple Therapy

Quadruple (bismuth + metronidazole + tetracycline + PPI administered for 7 to 10 d) therapy is a particularly useful treatment in areas where metronidazole resistance is low and clarithromycin resistance is high. As it is an inexpensive regimen, it is often preferred in situations where the cost of therapy is the main concern. In 2002, a large, randomized, controlled trial (RCT) compared 7-day quadruple therapy (bismuth + metronidazole + tetracycline + PPI) with 7-day triple therapy. Eradication rates were similar with PPI triple therapy (78%) and quadruple therapy (82%). In another RCT in Spain, a 7-day PPI triple therapy was similar to quadruple therapy in the eradication of H. pylori. A recent meta-analysis found 9 studies of sufficient quality to allow comparisons between quadruple therapy and triple therapy and concluded that there was no statistically significant difference between PPI triple therapy and quadruple therapy. Many of these comparative studies predate the emergence of high rates of clarithromycin resistance. Recent studies performed with a single-capsule preparation of bismuth biskalactrate with metronidazole and tetracycline provides insights into current success with quadruple and triple therapy.

Initial results were promising with an eradication rate of 93% by intent-to-treat analysis in Europe and 87.7% in the United States for 10-day therapy. A recent RCT in Europe showed that quadruple therapy using this single-capsule preparation was superior to triple therapy and with an eradication rate of 93% compared with 68% with triple therapy. In the United States, the single capsule contains (40 mg of bismuth subcitrate potassium, 125 mg of metronidazole, and 125 mg of tetracycline hydrochloride). Quadruple therapy using bismuth has a long track record and is an attractive alternative to triple therapy as an initial treatment. Bismuth is concentrated in H. pylori and as the organism does not seem to develop resistance to bismuth, the use of a bismuth quadruple therapy may offer advantages over nonbismuth quadruple therapy. The main take-away points with bismuth-based quadruple therapy are: (a) this treatment is a good alternative to triple therapy in areas with high prevalence rates of clarithromycin resistance and (b) when clarithromycin therapy fails, bismuth quadruple therapy is the best choice for empirical treatment in the United States (Table 2).
Sequential Therapy

Sequential therapy is a novel treatment method. Instead of administering the antimicrobials all at once, they are administered in sequence.32 The best-characterized sequential regimen that has been best described is a 10-day treatment consisting of a PPI and amoxicillin 1 g (both twice daily) administered for the first 5 days followed by triple therapy consisting of a PPI, clarithromycin 500 mg, and tinidazole 500 mg (all twice daily) for the remaining 5 days.33 A large RCT compared sequential therapy and standard triple therapy. A total of 300 patients with \( H.\, pylori \) infection were randomized to sequential therapy or triple therapy. Sequential therapy was significantly more effective in patients with clarithromycin resistant strains (89% vs. 29%; \( P = 0.0034 \)). A recent meta-analysis evaluated 10 RCTs included 1400 patients treated with sequential therapy were compared with 1611 patients treated with triple therapy of 7 to 10 days duration.34 The eradication rate was 91.0% (95% CI, 89.6-92.1) for sequential therapy and 75.7% (95% CI, 73.6-77.7) for triple therapy, with a difference in the eradication rate of 15.3% (95% CI, 13.1-17.4). The odds ratio (OR) for eradication of \( H.\, pylori \) with sequential therapy compared with triple therapy was 2.99 (95% CI, 2.47-3.62). In patients with clarithromycin resistance, the OR for eradication with sequential therapy was 10.21 (95% CI, 3.01-34.58) compared with triple therapy, but the numbers studied are small. The available data suggest that sequential treatment seems to maintain a high level of efficacy in patients with clarithromycin resistance. In Korea, where a high prevalence of clarithromycin resistant \( H.\, pylori \) is seen, the results of sequential therapy (79% eradication) were significantly better than triple therapy (62%).35 An RCT that compared sequential and nonbismuth quadruple therapy in Taiwan found that the both treatments were similar and had high efficacy.36 The rate of clarithromycin resistance in the population studied was low and therefore the potential advantage of sequential therapy in patients with resistant strains may not have been realized. The major take-away points about sequential therapy are: (a) the results vary depending on the prevalence of clarithromycin resistance; (b) despite the variable results, eradication rates are consistently 15% better than with triple therapy; (c) sequential therapy should be considered as a potential replacement treatment for triple therapy in areas with moderate rates of resistance to \( H.\, pylori \), for example, United States; (d) in areas with extremely high levels of clarithromycin resistance (Table 1), quadruple therapy is preferable.

Salvage Therapies

Levofloxacin and rifabutin are treatments for patients in whom standard treatments fail. There are important differences between these 2 agents. The first is that levofloxacin resistance develops rapidly in populations where this agent is used frequently (Table 1). Rifabutin resistance is generally low (Table 1). A recent meta-analysis performed a comparison of bismuth quadruple therapy (bismuth + tetracycline + metronidazole + PPI) with triple therapy using levofloxacin (levofloxacin 500 mg/d + amoxicillin 1 g twice a day + a PPI twice a day) in patients who failed eradication with standard triple therapy.37 Levofloxacin triple therapy was better tolerated than quadruple therapy and had better eradication rates (81% vs. 70%; OR,1.80; 95% CI, 0.94-3.46). Ten-day levofloxacin triple therapy was superior to 7-day therapy and the lower dose of levofloxacin (250 mg twice a day) was as effective as the higher dose (500 mg twice a day). In Korea, which has a high prevalence of levofloxacin resistance, an
RCT in patients who had failed 2 initial treatments, rifabutin triple therapy was more effective (71% eradication) and was more effective than levofloxacin triple therapy (57%). In an older randomized comparison of levofloxacin triple therapy and rifabutin triple therapy in patients who had failed 2 other treatment trials, levofloxacin triple therapy was significantly better than rifabutin triple therapy (85% vs. 45%). Side effects occurred frequently with both regimens: leukopenia with rifabutin in 25% and myalgia with levofloxacin in 30%. The leukopenia with rifabutin resolves with observation. Rifabutin has been reported to cure approximately 50% of patients with _H. pylori_ infection who have failed 3 regimens (a clarithromycin-based regimen, a metronidazole-tetracycline regimen, and a levofloxacin-based regimen).

**CONCLUSIONS**

Triple therapy is failing in many countries worldwide. Although monitoring of resistance is no longer being performed in the United States, there is no reason to believe that clarithromycin resistance is very different from western Europe. Standard triple therapy is unlikely to be an effective therapy in many areas of the United States. We have previously suggested that sequential therapy or quadruple therapy should replace triple therapy as the first-line treatment for _H. pylori_. Figure 1 shows the traditional paradigm for the treatment of _H. pylori_. We suggest that practitioners consider 2 alternate treatment paradigms (Figs. 2, 3). The paradigm shown in Figure 2 should result in a roughly 15% increase in eradication success compared with triple therapy. The paradigm shown in Figure 3 avoids the use of a clarithromycin-containing regimen as the first step making this the preferred strategy where clarithromycin-based treatment regimens fail.

**REFERENCES**


