

# Update on triple therapy for eradication of *Helicobacter pylori*: current status of the art

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**Abstract:** With the rising prevalence of antimicrobial resistance, the treatment success of standard triple therapy has recently declined to unacceptable levels (ie, 80% or less). Following the failure of conventional triple therapy, novel eradication regimens have been developed including sequential therapy, concomitant quadruple therapy, hybrid (dual-concomitant) therapy, bismuth-containing quadruple therapy, and a therapy with administration of N-acetylcysteine before a culture-guided antibiotic regimen. This article reviews the literature published on *Helicobacter pylori* eradication in the last year, focusing on the development of alternative strategies for first-, second-, and third-line rescue therapy for the eradication of *H. pylori*.

**Keywords:** sequential therapy, quadruple therapy, concomitant therapy, hybrid therapy, N-acetylcysteine

## Introduction

*Helicobacter pylori* infection is the main cause of gastritis, gastroduodenal ulcers, gastric adenocarcinoma, and mucosa-associated tissue lymphoma. Many patients attribute symptoms of dyspepsia to ulcers and believe that ulcers are caused by diet, stress, and lifestyle factors, but it is now clear that eradication of *H. pylori* is central to the management of this illness. Several large clinical trials and meta-analyses have shown that the eradication rate of the standard triple therapy has generally declined to unacceptable levels (ie, 80% or less)<sup>1,2</sup> and in some European countries the success rates are only 25%–60%.<sup>3,4</sup> It is unclear why this fall in efficacy has occurred, but it may be related to the increasing incidence of clarithromycin-resistant strains of *H. pylori*.<sup>1,2,5,6</sup>

This article reviews the literature on special populations of *H. pylori* and their eradication using short-duration treatment regimens.

## First-line therapy: triple therapy

The duration of treatment and adverse effects should be considered when selecting a therapy to eradicate *H. pylori*. The recommended duration of therapy for *H. pylori* eradication ranges from 7 to 14 days. The most widely recommended regimens are summarized in Table 1.

Over the past decade, it has been widely reported that *H. pylori* eradication treatment success rates are falling. A steady decline was observed in the number of patients achieving eradication with standard first-line triple therapy of two antibiotics and a proton pump inhibitor (PPI).<sup>7–9</sup> It now appears that the first-line eradication

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**Table 1** Regimens for *Helicobacter pylori* therapy

<b>First-line therapy</b>	
Standard triple therapy	PPI (standard dose, bid), clarithromycin (500 mg, bid) and amoxicillin (1 g, bid) for 7–14 days
Concomitant therapy	PPI (standard dose, bid), clarithromycin (500 mg, bid), amoxicillin (1 g, bid) and metronidazole (500 mg, bid) for 7–10 days
Hybrid therapy	7-day dual therapy with a PPI (standard dose, bid) and amoxicillin (1 g, bid) followed by a 7-day quadruple therapy with a PPI (standard dose, bid), amoxicillin (1 g, bid), clarithromycin (500 mg, bid), and metronidazole (500 mg, bid)
Bismuth-containing quadruple therapy	PPI (standard dose, bid), bismuth (standard dose, qid), tetracycline (500 mg, qid), and metronidazole (250 mg, qid) for 10–14 days
<b>Second-line therapy</b>	
Levofloxacin-based triple therapy	PPI (standard dose, bid), levofloxacin (500 mg, qd), and amoxicillin (1 g, bid) for 10 days
Bismuth-containing quadruple therapy	PPI (standard dose, bid), bismuth (standard dose, qid), tetracycline (500 mg, qid), and metronidazole (500 mg, tid) for 10–14 days
<b>Sequential therapy</b>	
Sequential therapy	5-day dual therapy with a PPI (standard dose, bid) and amoxicillin (1 g, bid) followed by a 5-day triple therapy with a PPI (standard dose, bid), clarithromycin (500 mg, bid), and metronidazole (500 mg, bid)
<b>Third-line therapy</b>	
Culture-guided therapy	10-day quadruple therapy comprising a PPI (standard dose, bid), bismuth (standard dose, qid), and two antibiotics selected by antimicrobial sensitivity tests
Levofloxacin-based quadruple therapy	PPI (standard dose, bid), bismuth (standard dose, qid), levofloxacin (500 mg, qd), and amoxicillin (500 mg, qid) for 10 days

**Abbreviations:** bid, twice daily; PPI, proton pump inhibitor; qd, once daily; qid, four times daily; tid, three times daily.

therapies most commonly used in everyday clinical practice (omeprazole-clarithromycin-amoxicillin) fall considerably short of the 80% intention-to-treat (ITT) eradication rates that are considered the minimal acceptable levels recommended in the Maastricht guidelines.<sup>10</sup>

The main reasons for eradication failure seem to be rapid metabolism of PPIs, antibiotic resistance, and poor patient compliance.<sup>1</sup> However, the major cause of eradication failure appears to be clarithromycin resistance,<sup>6</sup> with a systemic review showing that the rate of clarithromycin-resistant strains worldwide ranged from 49% in Spain to 1% in The Netherlands.<sup>11</sup> In areas where clarithromycin resistance is <10%, it is still possible to employ a standard triple therapy to achieve a per-protocol eradication rate of >90%. However, standard triple therapies should be abandoned in areas with clarithromycin resistance  $\geq 20\%$  (ie, Spain, Turkey, Alaska,

China, and Japan) because the per-protocol eradication rates of standard therapies are often <85% and the ITT eradication rates are usually <80%.<sup>6,12,13</sup>

Based on a large body of published clinical trials,<sup>14–17</sup> it appears that a quinolone-based triple therapy can be effective in the first-line therapy of *H. pylori* infection. Levofloxacin-based triple therapy comprised of levofloxacin (500 mg, once daily), amoxicillin (1 g, twice daily [bid]), and a PPI (standard dose, bid). Levofloxacin may be used as a substitute for clarithromycin in either a standard triple or sequential regimen. A large study comparing the antibiotics in either regimen shows a clear advantage to levofloxacin in both combinations. Per-protocol cure rates for triple therapy were 66% for omeprazole-clarithromycin-amoxicillin compared with 83% for omeprazole-levofloxacin-amoxicillin, 81% for omeprazole-amoxicillin-clarithromycin-metronidazole, and 85% for omeprazole-amoxicillin-levofloxacin-metronidazole, with no difference in compliance rates or adverse events.<sup>14</sup>

Another study showed that the eradication rates of levofloxacin-based triple therapy ranged from 72% to 96%, a regimen that might be considered in populations with clarithromycin resistance > 15%–20%.<sup>15</sup> However, a quinolone-based triple therapy is not generally recommended as first-line therapy at present due to concerns about the rising prevalence of quinolone-resistant strains in the first- and second-line anti-*H. pylori* therapies.<sup>16</sup> The literature from Asia also seems to support levofloxacin as a good alternative first-line therapy. A study examining a triple regimen showed per-protocol eradication rates of 78% for standard clarithromycin-containing therapies compared with 83% for a levofloxacin-based regimen.<sup>16</sup> Another study looked at whether combining clarithromycin and levofloxacin in the same regimen could be effective and found a 90% eradication rate for a combined clarithromycin-levofloxacin-esomeprazole regimen, compared with 85% for levofloxacin-amoxicillin-esomeprazole, and 79% for clarithromycin-amoxicillin-esomeprazole, with no difference in the incidence or severity of adverse events.<sup>17</sup>

The question remains, however, as to whether levofloxacin's best place is as first- or second-line therapy. A crossover study published in 2010 indicates that a clarithromycin-amoxicillin-lansoprazole regimen performs better than a levofloxacin-amoxicillin-lansoprazole regimen as first-line therapy (84% vs 74%), but this is reversed in second-line therapy (77% vs 60%).<sup>18</sup> The eradication rate was significantly lower in the presence of levofloxacin resistance in the levofloxacin-amoxicillin-lansoprazole group (50% vs 84%).

Another role of levofloxacin may be in the treatment of patients with penicillin allergies. In a study of a levofloxacin-based regimen used in penicillin-allergic patients after omeprazole-clarithromycin-metronidazole had been unsuccessful, eradication rates of 73% were noted.<sup>19</sup>

## Second-line therapy: quadruple versus triple therapy

The second-line therapy for patients for whom new first-line therapies fail to eradicate *H. pylori* remains unclear. The Maastricht III Consensus Report<sup>10</sup> and the Second Asia-Pacific Consensus Guidelines<sup>20</sup> for *H. pylori* infection recommended a bismuth-containing quadruple therapy regimen comprising a PPI, bismuth, metronidazole, and tetracycline as second-line therapy. As in the case of clarithromycin, the prevalence of metronidazole-resistant strains, dose, and duration of rescue therapy seem to be important variables for the efficacy of this treatment.<sup>7,20</sup> This rescue regimen fails in 5%–63% of patients, with an average eradication rate of 76% on the basis of a pooled analysis.<sup>21,22</sup> In bismuth-containing quadruple regimens, the PPI should be prescribed in the usual dose twice per day, colloidal bismuth subcitrate 120 mg four times per day, tetracycline 500 mg four times per day, and metronidazole 500 mg three times per day.<sup>23</sup> A report from Korea showed that the 2-week bismuth-containing quadruple therapy was more effective than the 1-week treatment (83% vs 64% by ITT analysis).<sup>23</sup>

Two other studies with more than 100 patients have shown eradication rates of >90% with this combination given for 10 days.<sup>24,25</sup> A study has compared the efficacy of a 10-day bismuth-containing quadruple therapy (omeprazole-bismuth-metronidazole-tetracycline) with a 7-day conventional triple therapy (omeprazole-clarithromycin-amoxicillin).<sup>26</sup> The data indicated that the former had a higher eradication rate than the latter (93% vs 70% by per-protocol analysis). The optimal treatment duration of bismuth-containing quadruple therapy remains unclear, but a 10–14 day treatment is most commonly employed in clinical practice.<sup>27</sup> A meta-analysis compared the effectiveness of a 10-day regimen of levofloxacin-based triple therapy versus a 7-day bismuth-based quadruple therapy and demonstrated the superiority of the former.<sup>28</sup> Another meta-analysis demonstrated a borderline significance of higher *H. pylori* cure rates with levofloxacin-based triple regimens compared with quadruple therapies (81% vs 70%). Additionally, the study revealed fewer adverse effects with levofloxacin than with quadruple regimens (19% vs 44%).<sup>29</sup>

In another study, the efficacy and safety of a 10-day novel, single-capsule, bismuth-based quadruple therapy

(bismuth-metronidazole-tetracycline-omeprazole) as first-line therapy was assessed. This multicenter study showed an eradication rate of 80% in the quadruple therapy group versus 55% for the standard 7-day triple-therapy group. Two randomized controlled trials from Taiwan and Hong Kong have shown that levofloxacin-based triple therapy was comparable to quadruple therapy in eradication efficacy as second-line therapy and a recent study has shown that a levofloxacin-based triple therapy with lansoprazole (30 mg, bid), levofloxacin (250 mg, bid), and amoxicillin (1 g, bid) achieved a high eradication rate in patients who failed to clear *H. pylori* with sequential therapy.<sup>30–32</sup>

## Sequential therapy: between first and second line?

The primary goal of the sequential regimen is to overcome clarithromycin resistance. Several studies have shown that a novel 10-day sequential therapy can achieve success rates of 90%–94%.<sup>33,34</sup> The regimen consists of a 5-day dual therapy with a PPI (standard dose, bid) and amoxicillin (1 g, bid), followed by a 5-day triple therapy with a PPI (standard dose, bid), clarithromycin (500 mg, bid), and metronidazole (500 mg, bid). One study from Thailand reported a 95% eradication rate for a 10-day sequential therapy,<sup>35</sup> while a study from Turkey, where eradication rates are low, showed 78% eradication for sequential therapy versus 53% for standard triple therapy based on a per-protocol analysis.<sup>36</sup> In China, a comparative study showed eradication rates of 83% for bismuth-based quadruple therapy and 81% for standard triple therapy, with an eradication rate of 89% for sequential therapy.<sup>37</sup>

A systematic review that identified 13 trials evaluating 3271 patients showed that sequential therapy achieved a 12% better absolute eradication rate than the standard triple therapy.<sup>38</sup> A randomized, double-blind, placebo-controlled trial demonstrated that the per-protocol eradication rates of sequential therapy and standard triple therapy for clarithromycin-resistant strains were 89% and 29%, respectively.<sup>33</sup> Another study has shown that the eradication rate in naive patients treated with sequential therapy was significantly higher than in those treated with conventional triple therapy (92.5% vs 73.7%,  $P=0.0015$ , odds ratio = 4.39, [95% confidence interval (CI) 1.66 to 11.58]).<sup>39</sup> A recent trial in Korea found that the per-protocol eradication rates of sequential therapy versus standard triple therapy were 86% and 77%, respectively.<sup>40</sup> It should be noted, however, that most of the studies concerning sequential therapies were conducted in Italy and there is a clear need for well-designed

randomized trials from other countries to confirm the real advantages of this regimen.

### Third-line therapy

The Maastricht III Consensus Report recommended the use of bacterial culture with antimicrobial sensitivity tests to select antibiotics for third-line regimens, but it has been reported that the sensitivity of culture is <60%.<sup>7,41</sup> Additionally, in vitro antimicrobial sensitivity does not necessarily lead to eradication in vivo, or vice versa. Cammarota et al treated 94 patients with a culture-guided third-line regimen: 89 patients received a 1-week quadruple regimen including omeprazole, bismuth, doxycycline, and amoxicillin, and five patients received a 1-week triple regimen containing omeprazole, amoxicillin, and levofloxacin or clarithromycin. Overall, *H. pylori* eradication was obtained in 90% of subjects treated with the culture-guided therapy.<sup>42</sup>

Another proposed alternative therapy in the multiresistant and clarithromycin-resistant forms is a quadruple therapy called “concomitant” therapy.<sup>43</sup> This is a four-drug regimen containing a PPI (standard dose, bid), clarithromycin (500 mg, bid), amoxicillin (1 g, bid), and metronidazole (500 mg, bid), which are all given for the entire duration of therapy. This regimen is intended to reduce the complexity associated with sequential therapy, as the patient takes all three antibiotics for the entire 10-day duration. When compared with standard triple therapy in a meta-analysis, concomitant therapy had an ITT eradication rate of 90%, superior to standard triple therapy, with a pooled odds ratio of 2.86.<sup>43</sup> When compared with the sequential regimen, concomitant administration of the same drugs provides similar results in terms of efficacy and safety. A head-to-head noninferiority trial of 10-day sequential and 10-day concomitant therapy showed that they were equivalent (93.1% vs 93.0% by per-protocol analysis).<sup>44</sup>

Hsu et al reported a “hybrid (dual-concomitant) therapy” consisting of a dual therapy with a PPI (standard dose, bid) and amoxicillin (1 g, bid) for 7 days followed by a concomitant quadruple therapy with a PPI (bid), amoxicillin (1 g, bid), clarithromycin (500 mg, bid), and metronidazole (500 mg, bid) for 7 days.<sup>45</sup> This regimen extends the duration of amoxicillin treatment to 14 days and concomitantly employs three antibiotics in the last 7 days of the treatment course. In 117 treated subjects, the therapy provided excellent eradication rates of 99% and 97% according to per-protocol and ITT analysis, respectively. It is important to note that the new therapy has a high efficacy in the treatment of *H. pylori* strains harboring dual resistance to clarithromycin

and metronidazole. Further studies in populations with different levels of prevalence of clarithromycin and metronidazole resistance are needed to assess the efficacy of the new regimen.

A novel regimen has been proposed in an open-label, randomized controlled trial<sup>46</sup> involving 40 subjects with a history of at least four *H. pylori* eradication failures. Subjects were randomly assigned to receive (group A) or not (group B) N-acetylcysteine before a culture-guided antibiotic regimen. *H. pylori* was eradicated in 13/20 (both per-protocol and ITT analyses, 65%; 95% CI: 44%–86%) group A participants and 4/20 (both per-protocol and ITT analyses, 20%; 95% CI: 3%–37%) group B participants ( $P < 0.01$ ). Biofilms persisted only in participants unsuccessfully treated. *H. pylori* genotypes did not influence treatment outcome.

N-acetylcysteine pretreatment before a culture-guided antibiotic regimen is effective in overcoming *H. pylori* antibiotic resistance.<sup>46</sup> Two other therapeutic regimens involving a proposed use of rifabutin (150 mg, bid), amoxicillin (1 g, bid), and omeprazole (20 mg, bid) for 14 days and the other the use of lansoprazole (30 mg, bid), tripotassium dicitrato-bismuthate (240 mg, bid), furazolidone (200 mg, bid), and tetracycline (1 g, bid) for 7 days.<sup>47,48</sup> In the first regime, the per-protocol and ITT eradication was achieved in 11/14 patients (79%), while in the second regime the eradication rate was 90% by both ITT and per-protocol analysis.

Table 2 lists the recommended regimens in countries with clarithromycin resistance.

### A role for probiotics?

Some studies have recently evaluated the role of the *Saccharomyces boulardii* as a coadjutant in the eradication of *H. pylori* and in the prevention of the secondary effects of antibiotic therapy. A meta-analysis showed that supplementation with *S. boulardii* significantly increased the *H. pylori* eradication rate and reduced the risk of overall *H. pylori* therapy-related adverse effects.<sup>49</sup> In a cohort of patients in Korea who received *S. boulardii* for 4 weeks during and after a 1-week course of standard triple therapy, eradication rates were 10% higher than for those who did not receive the supplement.<sup>50</sup> Other studies in which *Bifidobacterium* spp. and *Lactobacillus acidophilus* have been administered revealed no significant difference in eradication rates in patients who were infected with strains susceptible to both antibiotics and who were treated with standard triple therapy.<sup>51,52</sup> Further studies will be necessary to clarify the exact role of the probiotics in the eradication treatment.

**Table 2** Recommended regimens in countries with clarithromycin resistance

Regimen	Country	ITT			% clarithromycin resistance
		Eradication rate 14 days	Eradication rate 7 days	Eradication rate 10 days	
PAC	Italy	57%–80%	82%	70%	≥20%
PAM	Italy	52%	–	56%	≥20%
PAC	Spain	86%	–	–	≥20%
PAC	Korea	71%	–	76%	≤20%
PCL	Italy	87%	–	–	≥20%
BAL	Spain	–	84%	–	≥20%
PAC	China	81%	–	–	≥20%
PBMT	Italy	–	91%	–	≥20%
PBMT	Spain	89%	–	–	≥20%
PBMT	China	83%	–	–	≥20%
PAMC	Taiwan	–	93%	–	≥20%
SeTrT	Italy	–	92%–94%	–	≥20%
SeTrT	China	–	89%	–	≥20%
SeTrT	Thailand	–	95%	–	≤20%
SeTrT	Korea	–	86%	–	≤20%

**Abbreviations:** P, proton pump inhibitor; A, amoxicillin; C, clarithromycin; M, metronidazole; L, levofloxacin; B, ranitidine bismuth citrate; M, metronidazole; T, tetracycline; ITT, intention to treat; SeTrT, sequential triple therapy.

## Conclusion

The constant development of new antibiotic resistances suggests that future treatment will need to be individualized on the basis of host polymorphisms, antibiotic resistance, demographic factors, and, occasionally, comorbidity. Sequential therapy could be an alternative to the conventional triple therapy as first-line therapy. If the standard triple therapy or sequential therapy should fail, a levofloxacin-based triple therapy or a bismuth-containing quadruple therapy can be employed as rescue treatment. A levofloxacin-based triple therapy is an acceptable salvage treatment and an alternative to metronidazole. A culture-guided third-line therapy has been recommended, but if antimicrobial sensitivity data are unavailable, an empirical triple or quadruple therapy can be employed.

While there are a large number of emerging therapies, no consensus has been reached on these, and no “magic bullet” has emerged for *H. pylori* eradication. The authors of this review believe that, at present, the optimal approach in the treatment of patients with *H. pylori* infection is to use whichever protocol the literature indicates has the highest eradication rates and shorter duration. The type of regimen chosen will vary depending on the level of clarithromycin resistance in the country concerned, so each country should periodically publish data on the outcomes of eradication regimens and the antibiotic resistance rates to facilitate the appropriate therapeutic choice.

## Disclosure

The authors report no conflicts of interest in this work.

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