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TOPIC HIGHLIGHT

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Eradication of *Helicobacter pylori* infection: Which regimen first?

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Abstract

Helicobacter pylori (*H. pylori*) is a well-known human pathogen that plays an essential role in the pathogenesis of chronic gastritis, peptic ulcer disease, and gastric malignancies. Although *H. pylori* is susceptible to several antimicrobials, this infection has proven challenging to cure because of the increasing prevalence of bacterial strains that are resistant to the most commonly used antimicrobials, particularly clarithromycin. An effective (*i.e.*, > 90%) first-line therapy is mandatory for avoiding supplementary treatments and testing, and more importantly for preventing the development of secondary resistance. This study reviews the recent literature on first-line therapies for *H. pylori*. The eradication rates following standard triple therapy (a proton pump inhibitor plus amoxicillin and clarithromycin) for *H. pylori* infection are declining worldwide. Several first-line strategies have been proposed to increase the eradication rate, including extending the treatment duration to 14 d, the use of a four-drug regimen (bismuth-containing quadruple, sequential, and concomitant treatments), and the use of novel antibiotics, such as fluoroquinolones. However, the efficacy of these regimens is controversial. A first-line eradication regimen should be based on what works best in a defined geographical area and must take into account the prevalence of antimicrobial resistance in that region.

Key words: *Helicobacter pylori*; Sequential therapy; Hybrid therapy; Concomitant therapy; Clarithromycin; Levofloxacin

Core tip: First-line therapy for *Helicobacter pylori* infection should have an efficacy higher than 90% to prevent the need for additional treatment and the emergence of secondary antimicrobial resistance. The first-line eradication regimen should be based on what works best in a defined geographical area and must take into account the prevalence of antimicrobial resistance in that region. Non-bismuth quadruple (*i.e.*, concomitant) therapy appears to have high efficacy and, in our opinion, is the first choice of treatment for eradicating the infection.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a global human pathogen that plays a key role in the development of prevalent diseases, including peptic ulcer disease and gastric malignancy[1,2]. Therefore, this infection should be cured whenever it is

diagnosed[3].

Seven- to ten-day triple therapy consisting of a proton-pump inhibitor (PPI) plus amoxicillin and clarithromycin is the standard first-line treatment option for *H. pylori* eradication since its first acceptance in the international guidelines in 1996[4-6]. The efficacy of this treatment is strongly affected by clarithromycin resistance, and we have been witnessing a progressive decline in the eradication rate over the last decade, both in the United States and Europe, to below the acceptability threshold of 80%[7-11]. In some European countries, the success rates are disappointingly low, with values of only 25%-60%[12,13].

Several strategies have been proposed to increase the eradication rate, including the extension of the treatment duration to 14 d, the use of a four-drug regimen (bismuth-containing quadruple, sequential, and concomitant treatments), and the use of novel antibiotics, such as levofloxacin[14-21]. As with other infectious diseases, the treatment results are best when reliably excellent regimens are used to treat patients infected with organisms that are susceptible to the chosen antimicrobials[22,23]. Pretreatment susceptibility testing can be performed directly (by culture of the organism) or indirectly [by molecular testing of the stools of infected patients or by fluorescent in-situ hybridization using paraffin-embedded gastric biopsy samples] and allows the selection of a regimen that is tailored based on antimicrobial susceptibility[7]. However, in many instances, therapy must be chosen empirically, and in this case, the best approach is to use regimens that have proven to be reliable and to perform well locally[24]. This approach should take advantage of knowledge of resistance patterns obtained from local or regional antimicrobial surveillance programs and/or should be based on local clinical experience with regard to which regimens are effective in a given area.

The present article aims to critically assess, through a systematic review of the literature and pooled-data analysis, the current options for *H. pylori* eradication. To this end, we analyzed and compared recent evidence regarding the efficacy of several therapeutic regimens. The advantages and disadvantages of the proposed anti-*H. pylori* regimens, as well as the existing evidence for their clinical validation and widespread use in routine practice, are provided. This article will focus on first-line treatment; therefore, second-line or rescue therapies will not be discussed.

STANDARD TRIPLE THERAPY

Standard triple therapy consists of a 7-10-d regimen with a PPI [standard dose, twice a day (*bid*)], amoxicillin (1 g, *bid*), and clarithromycin (500 mg, *bid*). Clarithromycin resistance is the major cause of eradication failure for standard triple therapy[25]. Pooled data from 20 studies involving 1975 patients treated with standard triple therapy showed an eradication rate of 88% in clarithromycin-sensitive strains *vs* 18% in clarithromycin-resistant strains[26]. Therefore, the background rate of clarithromycin resistance is critically important, as it negatively impacts the efficacy of standard triple therapy. A systematic review showed that the rate of clarithromycin-resistant strains ranged from 49% (Spain) to 1% (The Netherlands) worldwide[27]. In areas with clarithromycin resistance of < 10% [*i.e.*, The Netherlands, Sweden, Ireland, Germany, Malaysia, and Taiwan (South)], it is still possible to employ a standard triple therapy to achieve a per-protocol (PP) eradication rate > 90%. The obsolescence of standard therapies for high clarithromycin resistance areas is now clearly stated in the 2012 Maastricht Ⅳ/Florence consensus report: a threshold of 20% is used to separate the regions of high/low clarithromycin resistance, with clarithromycin-containing regimens maintaining their role as standard therapies only if local resistance to this agent does not exceed 20%[28]. However, standard triple therapy should be abandoned in areas with clarithromycin resistance ⩾ 20% [*i.e.*, Spain, Turkey, Italy (Central), Alaska, China, Japan, and Cameroon] because the PP eradication rates of standard therapy are often less than 85%, and the intention-to-treat (ITT) eradication rates are usually less than 80%[7,26,29].

The use of probiotics has attracted attention as an alternative approach for increasing eradication rates and decreasing treatment-related side effects. The exact role of probiotics in the eradication of *H. pylori* remains largely unknown. However, evidence for an encouraging increase in the eradication rates achieved with standard triple therapy by including *Saccharomyces boulardii*[30] or *Lactobacillus* spp.[31] supplementation has been provided by recent meta-analytical data.

MODIFIED TRIPLE THERAPY

Based on a large body of published clinical trials, a quinolone-containing triple therapy has proven to be effective as a first-line therapy for *H. pylori* infection. The eradication rates of levofloxacin-containing triple therapy ranged from 72% to 96%[30].

This regimen might be considered in populations with clarithromycin resistance greater than 15%-20% and quinolone resistance less than 10%[32]. However, quinolone-containing triple therapy is not generally recommended as a first-line therapy at the moment due to concerns about the rising prevalence of quinolone-resistant *H. pylori* strains. Furthermore, greater use of quinolones would likely result in the development of more quinolone-resistant pathogens responsible for respiratory and urogenital tract infections.

STANDARD SEQUENTIAL THERAPY

The standard sequential therapy regimen consists of a 5-d dual therapy with a PPI (standard dose, *bid*) and amoxicillin (1 g, *bid*) followed by a 5-d triple therapy with a PPI (standard dose, *bid*), clarithromycin (500 mg, *bid*), and metronidazole/tinidazole (500 mg, *bid*). Recently, several studies have shown that a 10-d sequential therapy

can achieve a promising success rate of 85%-90%[19,33,34]. In a recent rigorous systematic review of 46 randomized clinical trials evaluating 5666 previously untreated patients, Gatta *et al*[35] showed that the overall eradication rate of sequential therapy was 84.3% (95%CI: 82.1%-86.4%) and that sequential therapy was able to eradicate 72.8% (95%CI: 61.6%-82.8%) of the strains resistant to clarithromycin.

This superiority is attributed to the capability of the sequential regimen to overcome clarithromycin resistance. In this regard, a randomized, double-blind, placebo-controlled trial demonstrated that the PP eradication rates of sequential therapy and standard triple therapy for clarithromycin-resistant strains were 89% and 29%, respectively[19].

The mechanism by which sequential administration of antimicrobials is effective despite clarithromycin resistance remains to be fully elucidated. It has been hypothesized that the initial administration of amoxicillin may cause disruption of the bacterial cell wall, thereby preventing the development of clarithromycin efflux channels, which are known to rapidly transport the drug out of the bacterial cell[36]. Alternatively, the improved efficacy of the sequential regimen may be attributed to the larger number of antibiotics (*e.g.*, 3) to which the microorganism is exposed compared with standard triple therapy.

However, more recent studies have questioned both the optimal performance rates and the superiority of sequential therapy compared to legacy triple therapy[37,38]. Indeed, a recent multicenter South American randomized trial demonstrated that 14-d standard triple therapy was more efficacious than the 10-d sequential regimen[17]. Additionally, Choi *et al*[39] showed that, in South Korea, the PP eradication rates of sequential therapy and standard triple therapy were 86% and 77%, respectively, with no statistically significant difference between the two. More recently, a multicenter randomized trial was published comparing high-dose PPI 14-d triple, 14-d sequential, and 10-d sequential therapies in Taiwan[40]. This study showed that 10-d sequential therapy was a nonoptimized regimen, achieving an efficacy of less than 90% in a setting with 9% clarithromycin resistance. As such, the failure of sequential therapy might be expected in settings with high rates of clarithromycin and metronidazole resistance.

MODIFIED SEQUENTIAL THERAPY

Over the past several years, numerous studies have evaluated the use of a modified (*i.e.*, non-clarithromycin-containing) sequential therapy[41].

In 6 studies, the efficacy of a tetracycline-containing sequential therapy was investigated[41]. The eradication rate at ITT analysis varied widely from 50.0% to 87.9%. The eradication rate did not appear to increase when quadruple, rather than triple, therapy was administered for 5 d in the second sequential therapy phase, the cure rate being 78.5%[42]. In 3 studies, a 14-d tetracycline-containing sequential therapy was compared with the 14-d triple therapy. The *H. pylori* eradication rate was higher with the sequential than with the triple regimen, the infection being cured in 77.2% and 63.6% of cases, respectively[43-45]. In 9 studies, the efficacy of a levofloxacin-containing sequential therapy was investigated[41]. The eradication rates at ITT analysis ranged from 65.4% to 96.8%. One study, conducted in an area with > 20% clarithromycin resistance and relatively low (*i.e.*, < 6%) levofloxacin resistance, demonstrated that levofloxacin-containing sequential regimens (at 250 mg *bid* or 500 mg *bid*) were significantly superior to a clarithromycin-containing sequential regimen, achieving eradication rates higher than 90%[46]. This result was confirmed by another study that used high-dose PPI (*i.e.*, esomeprazole 40 mg, *bid*) and high-dose levofloxacin (*i.e.*, 500 mg, *bid*) and demonstrated an eradication rate of 93% at ITT and 95 PP[47]. Levofloxacin-containing sequential regimens have also been demonstrated to achieve cure rates higher than 90% by Molina-Infante *et al*[48], who used levofloxacin 250 mg *bid*, and by Ozdil *et al*[49], who used levofloxacin 500 mg *bid*.

Extending the duration of levofloxacin-containing sequential treatment from 10-d to 14-d does not appear to increase the efficacy, although the 14-d therapy achieved a distinctly higher eradication rate compared with standard 14-d triple therapy (86.6% *vs* 45.3%)[50]. The efficacy of a tinidazole-free sequential therapy was tested in 1 study, in which clarithromycin (500 mg, *bid*) was added to a PPI and amoxicillin (*i.e.*, amoxicillin was not substituted with tinidazole) in the second 5-d segment of the treatment[51]. Following this sequential therapy, the eradication rate did not differ compared to that of a 10-d triple therapy at ITT analysis (73.0% *vs* 72.2%, respectively).

Another study tested the efficacy of two 10-d modified bismuth-containing sequential therapies consisting of a PPI, amoxicillin, bismuth, and metronidazole or clarithromycin for the first 5-d followed by a PPI, amoxicillin, bismuth, and furazolidone for 5 additional days[52]. The infection was cured in 78.5% of cases treated with the metronidazole-containing regimen and in 82% of cases treated with the clarithromycin-containing regimen, the success rates being similar to that of a standard 10-d triple therapy (81.1%).

In conclusion, the value of sequential regimens as first-line therapies for *H. pylori* infection appears to be decreasing, and these regimens will require a thorough re-evaluation.

CONCOMITANT THERAPY

Concomitant therapy is another novel regimen that proved to be successful in the presence of clarithromycin resistance[25]. This 4-drug regimen includes a PPI (standard dose, *bid*), clarithromycin (500 mg, *bid*), amoxicillin (1 g, *bid*), and metronidazole (500 mg, *bid*), all of which are

given for the entire duration of therapy. This therapy is superior to standard triple therapy for *H. pylori* eradication[52] and is also less complex than sequential therapy, as this regimen does not involve changing drugs halfway through. A head-to-head non-inferiority trial of 10-d sequential and 10-d concomitant therapy showed that these therapies were equivalent (93.1% *vs* 93.0% by PP analysis)[53]. Further advantages of concomitant therapy include its simplicity (addition of a nitroimidazole to standard treatment) and its wider geographical validation (including Japan, Colombia, Taiwan, Spain, and Greece) compared with sequential therapy.

Recently, Kim *et al*[54] compared concomitant quadruple therapy with standard triple therapy for first-line *H. pylori* eradication, showing that 5-d quadruple concomitant therapy eradicated *H. pylori* in over 90% of patients. In particular, the eradication rates were 86.1% with the triple therapy and 91.4% with the concomitant therapy (PP); however, the difference was not statistically significant. Georgopoulos *et al*[55,56] recently evaluated the efficacy and tolerability of a 10-d concomitant regimen in Greece. This country has high resistance rates to both clarithromycin (nearly 25%) and metronidazole (approximately 40%)[57,58]; thus, it is a setting in which sequential therapy is reportedly more likely to fail[51]. This was an open-label, single arm trial[55], and thereafter, a randomized controlled trial was performed to compare legacy triple therapy of the same duration (10 d)[57]. The performance of the concomitant regimen at ITT analysis was 90% in the former study and 90.2% (*vs* 73.8% for standard triple therapy) in the latter study.

In a recent comparative study, patients with dual antibiotic resistance had significantly lower eradication rates (*i.e.*, 33.3%) compared with patients without dual resistance (*i.e.*, 95.1%) after sequential therapy, whereas concomitant therapy led to eradication of the infection in 75% of patients with dual resistance compared with 92.4% of patients without dual resistance[53]. However, this study was conducted in a low-clarithromycin-resistance setting where even standard regimens can still yield excellent eradication. In a report from Spain, a country with high rates of antibiotic resistance, a 10-d concomitant therapy successfully eradicated 100% of clarithromycin-resistant and 75% of dual-resistant strains (*vs* 75% and 60%, respectively, with sequential therapy), although the small number of clarithromycin- and dual-resistant strains (5 and 4, respectively), does not allow firm conclusions to be drawn[59]. Recently, our group performed a non-inferiority randomized trial[47] to determine whether a 5-d levofloxacin-containing quadruple concomitant regimen was as safe and effective as the 10-d levofloxacin-containing sequential regimen for eradicating *H. pylori* infection in patients naïve to treatment. ITT analysis showed similar eradication rates for concomitant (92.2%) and sequential therapies (93.3%). The PP eradication results were 96.5% for concomitant therapy and 95.5% for sequential therapy. The differences between the sequential and concomitant treatments were 1.1% in ITT analysis and -1.0% in the PP analysis, confirming that 5-d levofloxacin-containing quadruple concomitant therapy is similarly effective and safe for eradicating *H. pylori* infection compared with 10-d levofloxacin-containing sequential therapy. Additionally, 5-d levofloxacin-containing quadruple concomitant therapy is less expensive than 10-d levofloxacin-containing sequential therapy.

Bismuth-containing quadruple therapy (omeprazole, bismuth, metronidazole, and tetracycline) has been recommended by the Second Asia-Pacific Consensus Guidelines for *H. pylori* Infection[60] and by the Maastricht Ⅳ Consensus Report[28] as an alternative first choice regimen to standard triple therapy in areas with a low clarithromycin resistance, and it is recommended as the first-line therapeutic option in areas with a high prevalence of clarithromycin resistance. Bismuth-containing quadruple therapy has the advantage of utilizing compounds for which resistance has rarely been reported, with the exception of metronidazole; however, metronidazole resistance can be at least partially overcome by increasing the dose and duration of therapy[61]. Two studies, each with more than 100 patients, have demonstrated eradication rates of > 90% when this combination was given for 10 d[44,62]. Recently, a novel bismuth-containing quadruple therapy using a single 3-in-1 capsule containing bismuth subcitrate, metronidazole, and tetracycline has been proposed to decrease the pill burden and improve patient compliance. In a randomized clinical trial, this single-capsule bismuth-containing 10-d treatment showed an ITT cure rate of 80% and a PP cure rate of 94%[18].

In a 2010 meta-analysis evaluating first-line use of 10-d bismuth-containing quadruple therapy or standard therapy, 78.3% of the patients who received quadruple therapy and 77% of those who received standard therapy achieved ITT eradication, indicating similar (and suboptimal) therapeutic effectiveness for both regimens[63]. Recently, Malfertheiner *et al*[18] compared the efficacy of a 10-d bismuth-containing quadruple therapy and a 7-d triple therapy. In this study, quadruple therapy resulted in a PP eradication rate of 94%, whereas triple therapy achieved a rate of only 70%.

Currently, the optimal treatment duration of bismuth-containing quadruple therapy remains unclear; however, a 10-14 d course is most commonly employed in clinics[64].

HYBRID THERAPY

Hsu *et al*[65] reported a hybrid (sequential-concomitant) therapy consisting of a dual therapy with a PPI (standard dose, *bid*) and amoxicillin (1 g, *bid*) for 7 d followed by a concomitant quadruple therapy with a PPI (standard dose, *bid*), amoxicillin (1 g, *bid*), clarithromycin (500 mg, *bid*), and metronidazole (500 mg, *bid*) for 7 d. The new therapy extends the duration of amoxicillin treatment to 14 d and concomitantly employs three antibiotics

Table 1 Recommended first-line therapies for *Helicobacter pylori* infections

	Treatment	Days	No. of patients	Methods of evaluating eradication	Eradication rate % (ITT)	Eradication rate % (PP)	Adverse effects %	Ref.	Type of study
Low clarithromycin resistance area (< 20%)	PPI (standard dose, *bid*) + amoxicillin (1 g, *bid*) + clarithromycin (500 mg, *bid*)	7-10	1975	UBT or H or R	Overall 77.3-100		0-33	Mégraud *et al*[26]	Meta-analysis
	PPI (standard dose, *bid*) + amoxicillin (1 g, *bid*) followed by a triple therapy with a PPI (standard dose, *bid*) + clarithromycin (500 mg, *bid*) + metronidazole/tinidazole (500 mg, *bid*)	5 + 5	5666	UBT or H or R	Overall 84.3		0-44	Gatta *et al*[35]	Meta-analysis
High clarithromycin resistance area (≥ 20%)	PPI (standard dose, *bid*) + amoxicillin (1 g, *bid*) + levofloxacin (250 mg, *bid*)	7-10	900	UBT or H or R	Overall 72-96		0-52	Berning *et al*[32]	Meta-analysis
	PPI (standard dose, *bid*) + amoxicillin (1 g, *bid*) followed by a triple therapy with a PPI (standard dose, *bid*) + levofloxacin (250/500 mg, *bid*) + tinidazole (500 mg, *bid*).	5 + 5	250	UBT	96/96.8	98.3/98.4	22.1-23.5	Romano *et al*[46]	RCT
	PPI (standard dose, *bid*) + amoxicillin (1 g, *bid*) + clarithromycin (500 mg, *bid*) + metronidazole (500 mg, *bid*)	5	135	UBT	91.4	91.4	35.6	Kim *et al*[54]	RCT
	PPI (high dose, *bid*) + amoxicillin (1 g, *bid*) + levofloxacin (500 mg, *bid*) + tinidazole (500 mg, *bid*)	5	90	UBT	92.2	96.5	27.8	Federico *et al*[47]	RCT
	PPI (standard dose, *bid*) + metronidazole (500 mg, *bid*) + bismuth (120 mg, q.i.d.) + tetracycline (500 mg, q.i.d.)	10	218	UBT	92	94	47	Malfertheiner *et al*[18]	RCT
	PPI (high dose, *bid*) + amoxicillin (1 g, *bid*) followed by a quadruple therapy with a PPI (high dose, *bid*) + amoxicillin (1 g, *bid*) + clarithromycin (500 mg, *bid*) + metronidazole (500 mg, *bid*)	7 + 7	171	UBT	90	92	47	Molina-Infante *et al*[66]	RCT

PPI: Proton pump inhibitor; UBT: Urea breath test; H: Histology; R: Rapid urease test; RCT: Randomized controlled trial; PP: Per-protocol; ITT: Intention-to-treat.

in the last 7 d of the treatment course. In 117 *H. pylori* -infected subjects, the novel therapy provided excellent eradication rates of 99% and 97% according to PP and ITT analysis, respectively[65]. It is important to note that the new therapy has a high efficacy for the treatment of *H. pylori* strains harboring dual resistance to clarithromycin and metronidazole. The extension of the amoxicillin treatment duration to 14 d in the hybrid therapy might account for the higher eradication rate of *H. pylori* strains with dual resistance to clarithromycin and metronidazole. Recently, in a randomized clinical trial, Molina-Infante *et al*[66] compared hybrid therapy (omeprazole 40 mg *bid* and amoxicillin 1 g *bid* for 14 d with clarithromycin 500 mg *bid* and nitroimidazole 500 mg *bid* for the final 7 d) with concomitant therapy (the same 4 drugs taken concurrently twice daily for 14 d) in 343 consecutive individuals with *H. pylori* infection who were naïve to treatment and resided in areas of high clarithromycin and metronidazole resistance (Spain and Italy). In PP analysis, the rates of eradication for hybrid and concomitant therapies were 92% and 96.1%, respectively. In ITT analysis, the rates were 90% and 91.7%, respectively, showing that optimized non-bismuth quadruple hybrid and concomitant therapies cured more than 90% of patients with *H. pylori* infections in areas of high clarithromycin and metronidazole resistance. However, further studies comparing bismuth and non-bismuth quadruple regimens in this setting are warranted. Table 1 shows the recommended first-line therapies for *Helicobacter pylori* infections.

CONCLUSION

Ideally, the treatment for an infectious disease should be chosen based on culture and susceptibility testing using biological material (*e.g.*, urine, sputum) obtained from each patient. This is not always feasible in *H. pylori*-infected patients because it requires an invasive procedure

(*i.e.*, esophago-gastro-duodenoscopy), which is not indicated in dyspeptic patients younger than 45 years of age without "alarm" symptoms. To ensure a higher chance of eradicating the infection during the first attempt, an empirical first-line therapy should be chosen based on the pattern of local antimicrobial resistance[67]. We suggest in vitro antimicrobial sensitivity testing for cases in which two different eradication regimens fail to eradicate the infection.

It is important to keep in mind that clarithromycin-containing triple therapy loses efficacy when resistance is between 7% and 10%. Moreover, clarithromycin-containing sequential and concomitant regimens lose efficacy in the face of clarithromycin resistance between 15% and 20% and when metronidazole resistance approaches 40%, thus increasing the likelihood of dual (*i.e.*, clarithromycin + metronidazole) resistance. A valid alternative to concomitant therapy is represented by hybrid (*i.e.*, sequential + concomitant) therapy, which has proven to be effective in more than 90% of *H. pylori*-infected patients in the setting of high clarithromycin and metronidazole resistance[66]. Bismuth-containing quadruple therapy is also a valid alternative; however, in our opinion, the duration should be extended to 14 d to overcome metronidazole resistance.

Compliance is an important issue, and significant effort should be directed toward identifying a regimen that is short and easy for the patient to follow. In this regard, the recently reported 5-d levofloxacin concomitant regimen[47] might represent an easy regimen to follow, although its use as an empirical first-line therapy should be limited to patients living in areas where fluoroquinolone resistance is rare and resistance to both clarithromycin and metronidazole is high. Additionally, the 5-d levofloxacin concomitant regimen might be regarded to as a good alternative to rescue therapy, provided the patient has no history of prior fluoroquinolone resistance[68].

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