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Optimal treatment strategy for *Helicobacter pylori*: Era of antibiotic resistance

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Abstract

Standard triple therapy, consisting of a proton pump inhibitor, plus amoxicillin and clarithromycin, has been the most commonly used first-line treatment regimen for *Helicobacter pylori* (*H. pylori*) eradication for many years worldwide. However, as a result of increased resistance to antibiotics, *H. pylori* eradication rates with use of standard triple therapy have been declining and recently reached < 80% in many countries. Several new strategies to enhance the eradication rate of *H. pylori* have been studied. Currently, among the alternative first-line eradication regimens, concomitant and hybrid regimens have shown excellent results and could be the optimal treatment option. Although clinical usefulness of rescue therapy for patients in whom eradication of *H. pylori* with non-bismuth quadruple regimen has failed is unclear, levofloxacin-based quadruple therapy has shown promise as a rescue treatment. The choice of third-line therapy depends on factors such as the local pattern of antibiotic resistance, drug availability, and previous treatment. We hope that a simple method for detection of antibiotic susceptibility using polymerase chain reaction would be a possible alternative to administration of "tailored treatment" in the era of increasing prevalence of anti-

microbial resistance.

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Key words: *Helicobacter pylori*; Standard therapy; Bacterial eradication; Concomitant therapy; Hybrid therapy

Core tip: Currently, among the alternative first-line eradication regimens, concomitant and hybrid regimens have shown excellent results and could be the optimal treatment option. Levofloxacin-based quadruple therapy has shown promise as a rescue treatment.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is an important factor worldwide influencing progression from chronic gastritis to peptic ulcer and gastric cancer^[1]. Nowadays, the incidence of *H. pylori* infection has shown a declining trend. In Korea, in a survey of 5732 asymptomatic patients in 1998, the seropositive rate of *H. pylori* infection was reported as 66.9% in adults^[2]. However, it had declined to 59.6% in 2005^[3]. The main cause of this difference is treatment for *H. pylori* infection.

Triple therapy, consisting of a proton pump inhibitor (PPI), plus amoxicillin and clarithromycin, was accepted by the international guidelines in 1996 and has been the most commonly used first-line treatment regimen for *H. pylori* eradication in most countries for many years^[4,5]. According to Graham *et al*^[6], the treatment regimen that meets the category of Grade A [intention-to-treat (ITT)

cure rate is 95%-100%] should be prescribed as a therapeutic regimen for *H. pylori* infection. Regimens scoring as B (ITT cure rate 90%-95%) can be used if Grade A is not obtainable. Unfortunately, *H. pylori* eradication rates with standard triple therapy have been declining and recently reached < 80% in many countries^[6].

This phenomenon has been largely related to an increase in bacterial resistance to antibiotics, particularly against clarithromycin^[7]. In Japan, resistance to clarithromycin increased from 19% to 28% during 2002-2005^[8]. In Korea, a study of 652 isolates from 1994 to 1999 found that resistance to metronidazole and clarithromycin increased from 33% to 48% and 4.8% to 7.7%, respectively^[9]. Another recent survey reported that resistance to clarithromycin increased from 16.7% to 38.5% during 2003-2005 and 2007-2009 in Korea^[10].

Several strategies to enhance the eradication rate of *H. pylori* have been studied and ongoing results are anticipated. The aim of this review is to suggest timely suitable approaches to management of patients with *H. pylori* infection.

FIRST-LINE THERAPY

Triple therapy with longer duration

There was a simple question regarding whether longer duration of standard triple therapy could result in a higher rate of eradication. In a multicenter study conducted in the US, of 284 patients, the *H. pylori* eradication rate after triple therapy for 14 d was 85% (96/113), which did not differ from 84% (103/123) reported for triple therapy for 10 d^[11]. In another study comparing 3-, 7- and 10-d triple therapies with rabeprazole to a 10-d omeprazole control triple therapy, no statistically significant difference was observed between the 7-d rabeprazole-based regimen (77%) and 10-d rabeprazole-based regimen (78%) and omeprazole-based regimen (73%)^[12]. In a meta-analysis of the duration of triple therapy, relative risk for eradication was reported as 1.05 (95%CI: 1.01-1.10) for 7-d compared with 10-d triple therapy and 1.07 (95%CI: 1.02-1.12) for 7-d compared with 14-d therapy^[13]. Thus, currently, extending the duration of triple therapy beyond 7 d did not show a marked benefit. Other regimens with longer duration have shown promise and are discussed below.

Bismuth-containing quadruple therapy

Bismuth-containing quadruple therapy has been proven as a salvage therapy regimen for failure of standard triple therapy in many countries^[14,15]. The regimen consists of PPI, bismuth, tetracycline and metronidazole. However, regarding the first-line therapy, recent results have been disappointing. In a large study, bismuth-containing quadruple therapy [ITT, 82%; per-protocol (PP), 88%] did not show superior eradication rate compared with standard triple therapy (ITT, 78%; PP, 82%)^[16]. In a meta-analysis of bismuth-containing quadruple therapy with standard triple therapy [nine randomized controlled trials

(RCTs), $n = 1679$], bismuth quadruple therapy achieved an eradication rate similar to that of primary therapy for *H. pylori* infection compared with standard triple therapy (78.3% *vs* 77.0%, RR = 1.002, 95%CI: 0.936-1.073)^[17].

In a recent RCT, the new combination of bismuth containing 2 wk quadruple therapy, including bismuth, PPI, amoxicillin, and clarithromycin, achieved an eradication rate of 90.7% as a first-line treatment^[18]. In another RCT, quadruple therapy with moxifloxacin and bismuth showed an eradication rate of 92%^[19]. Although conduct of additional studies is needed to validate these results, these studies imply that another bismuth-containing regimen could be an alternative option as a first-line treatment.

Non-bismuth-containing quadruple regimen

In a meta-analysis of the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapy for *H. pylori*^[20], clarithromycin resistance had a greater effect on treatment efficacy than nitroimidazole resistance. Metronidazole resistance reduced efficacy by 26% in triple therapies containing nitroimidazole, tetracycline and bismuth, while efficacy was reduced by only 14% when a gastric acid inhibitor was added to the regimen. Quadruple therapies containing both clarithromycin and metronidazole were the most efficacious; > 80% eradication rate for *H. pylori* infection. Therefore, non-bismuth, three-antibiotic-containing quadruple therapies, consisting of PPI, amoxicillin, clarithromycin and nitroimidazole, could be the key as a new standard first-line regimen.

Sequential therapy: Sequential therapy was introduced as a novel therapeutic approach for *H. pylori* eradication by Zullo *et al*^[21,22] in 2000. Ten-day sequential therapy regimen consists of 5 d of dual treatment with a PPI plus amoxicillin, followed by 5 d of triple treatment with a PPI, clarithromycin and nitroimidazole. Zullo *et al*^[21] reported eradication rates for sequential therapy of 92% by ITT and 95% by PP analysis. Since then, many studies have reported a superior result of sequential therapy compared with standard triple therapy^[23,24]. In two meta-analyses of RCTs, sequential therapy showed an association with a higher eradication rate of *H. pylori* at 91%-93.4%, compared with standard triple regimen at 75.7%-76.9%^[25,26]. However, these RCTs were conducted before 2008. In recent studies, the success rate of the sequential regimen appeared to be lower, compared to previous trials. In 10 recent RCTs on sequential therapy during 2008-2012, the eradication rate was 80.6% (95%CI: 78.5%-82.7%) for sequential therapy compared to 75.8% (95%CI: 73.5%-78.1%) for standard triple therapy^[27]. Theoretically, the objective during the first 5 d of taking amoxicillin is to disrupt the cell wall of *H. pylori* and to prevent activation of efflux channels. Therefore, this damage to the cell wall could help to improve the efficacy of clarithromycin in the sequential phase of treatment^[28,29]. However, there is a conflicting opinion against this theory. The main role of sequential therapy

may be related to use of large numbers of antibiotics, including nitroimidazole, not the sequential administration itself^[30,31]. In addition, there is a problem with sequential therapy, which is that taking the medication is relatively complex for patients. The patient is required to switch from a dual to a triple regimen^[32], which may reduce the compliance of patients and result in a decrease in eradication rates in patients with multiple antibiotic resistance in clinical practice.

In this regard, the triple combination of antibiotics such as clarithromycin plus amoxicillin and a nitroimidazole with PPI has been highlighted or has re-emerged as a non-sequential regimen - concomitant therapy.

Concomitant therapy: In a systemic review reported by Essa *et al*^[32], which included nine studies, concomitant therapy achieved an eradication rate of 89.7% in ITT and 92.9% in PP. In a meta-analysis of 15 studies (1723 patients), a significantly higher eradication rate was achieved with concomitant therapy, compared to standard triple therapy (90%, 95%CI: 86%-93%)^[33]. A tendency towards better results with longer treatments (7-10 d *vs* 3-5 d) was observed. In our interim analysis of multicenter RCTs (six institutes, 214 patients in ITT analysis, unpublished), the eradication rate of the 10-d concomitant therapy group was significantly higher than that of the 10-d standard triple therapy group (89.3% *vs* 79.3%, $P = 0.049$).

Both sequential therapy and concomitant therapy have shown superiority over legacy triple therapy, especially in cases of clarithromycin resistance. Clarithromycin resistance is the result of different point mutations, which have a different therapeutic impact on current regimens. In a systematic review of sequential therapy, the eradication rate was reported as 75% (41/55, four studies) in clarithromycin-resistant strains^[34]. However, the effect of clarithromycin resistance on the efficacy of concomitant regimens was negligible, with 95% efficacy in the clarithromycin-sensitive arm, and 96% in the clarithromycin-resistant arm^[20]. In addition, in another study, concomitant therapy was found to be more suitable for patients with dual antibiotic resistances than sequential therapy^[35].

Hybrid therapy (sequential-concomitant therapy):

Hybrid therapy is a combination of sequential therapy and concomitant therapy. Hybrid therapy regimens consist of PPI and amoxicillin for 10-14 d, with addition of clarithromycin and metronidazole for the final 5-7 d. In a recent study, this regimen showed excellent results, with an eradication rate of 99.1% (95%CI: 97.3%-100%) by PP and 97.4% (95%CI: 94.5%-100%) by ITT analysis^[36]. This study is meaningful for achievement of Grade A treatment success for *H. pylori* infection. In another recent RCT ($n = 343$) for comparison with concomitant therapy, the rates of eradication for hybrid and concomitant therapies were 92% (95%CI: 87%-95%) and 96.1% (95%CI: 93%-99%), respectively ($P = 0.07$)^[37]. In that study, 23.5% of patients had *H. pylori* strains that were

resistant to clarithromycin, and 8.8% were resistant to clarithromycin and metronidazole. This antimicrobial resistance did not impair the efficacy of either of the non-bismuth quadruple regimens. However, larger sample size and conduct of studies in other countries is needed in order to validate the effectiveness of hybrid therapy.

Data from RCTs for the first-line non-bismuth-containing quadruple therapies are provided in Table 1^[35,37-42].

SECOND-LINE (RESCUE) THERAPY

After failure of a PPI-clarithromycin-containing regimen, bismuth-containing quadruple therapy is recommended by the Maastricht IV guidelines^[43]. In three studies of bismuth-containing quadruple therapy as second-line therapy, eradication rates of 55%-69.1% have been reported^[44-46]. In a recent study conducted in Korea, higher eradication rates were reported for 2-wk bismuth-containing quadruple therapy compared with the same regimen for 1 wk (64.3% *vs* 82.6%, ITT analysis, $P = 0.002$)^[47]. However, these data were regarding the rescue therapy after failure of standard triple therapy. Data regarding rescue therapy after failure of non-bismuth-containing quadruple therapy as a first-line treatment are insufficient^[48].

The Maastricht IV guidelines recommend levofloxacin-based triple therapy containing PPI and amoxicillin as a rescue treatment in areas of high clarithromycin resistance^[43]. The eradication rate of levofloxacin 500 mg with PPI and amoxicillin was 60%-85% after two eradication failures with key antibiotics such as amoxicillin, clarithromycin, metronidazole and tetracycline^[49,50]. However, the recommended regimen had a somewhat disappointing eradication rate as a rescue treatment after failure of sequential or concomitant treatment, below 80%^[51,52]. In addition, the rapid acquisition of resistance to levofloxacin may be a problem in future efficacy. In fact, a recent study reported a high prevalence of levofloxacin resistance (29.5%) in *H. pylori* strains isolated from Korean patients^[10]. Therefore, a new combination regimen is warranted. In a recent study conducted in Taiwan, 10-d quadruple therapy containing PPI, bismuth, tetracycline, and levofloxacin achieved an excellent result, with an eradication rate of 95.8% after failure of first-line treatment with sequential therapy^[53]. This new combination of levofloxacin-based quadruple therapy is expected as the second-line therapy and validation of other combinations with levofloxacin is needed. In addition, high dose of levofloxacin (750 mg), which achieved a better effect against infectious disease^[54], should be validated for *H. pylori* eradication. In summary, although further validation is needed, levofloxacin-based quadruple therapy is a promising rescue regimen after failure of first-line non-bismuth-containing quadruple therapy.

THIRD-LINE THERAPY

After failure of second-line treatment, antimicrobial

Table 1 Randomized-controlled trials for the first-line non-bismuth containing quadruple therapies

Author	Country	Publication year		Therapy regimen	Patients (n)	Eradication rate (ITT)
Wu <i>et al</i> ^[35]	Taiwan	2010	S	E 40 mg <i>bd</i> + AMX 1 g <i>bd</i> for 5 d followed by E 40 mg <i>bd</i> + CLA 500 mg <i>bd</i> + MET 500 mg <i>bd</i> for 5 d	115	92.3%
Huang <i>et al</i> ^[38]	Taiwan	2012	C	E 40 mg <i>bd</i> + AMX 1 g <i>bd</i> + CLA 500 mg <i>bd</i> + MET 500 mg <i>bd</i> for 10 d	117	93.0%
			S	L 30 mg <i>bd</i> + AMX 1 g <i>bd</i> for 5 d followed by L 30 mg <i>bd</i> + CLA 500 mg <i>bd</i> + MET 500 mg <i>bd</i> for 5 d	85	80.0%
McNicholl <i>et al</i> ^[39]	Spain	2013	C	L 30 mg <i>bd</i> + AMX 1 g <i>bd</i> + CLA 500 mg <i>bd</i> + MET 500 mg <i>bd</i> for 10 d	84	88.1%
			S	O 20 mg <i>bd</i> + AMX 1 g <i>bd</i> for first 5 d followed by O 20 mg <i>bd</i> + CLA 500 mg <i>bd</i> + MET 500 mg <i>bd</i> for 5 d	170	81%
Lim <i>et al</i> ^[40]	Korea	2013	C	O 20 mg <i>bd</i> + AMX 1 g <i>bd</i> + CLA 500 mg <i>bd</i> + MET 500 mg <i>bd</i> for 10 d	168	87%
			S	R 20 mg <i>bd</i> + AMX 1 g <i>bd</i> for 7 d followed by R 20 mg <i>bd</i> + CLA 500 mg <i>bd</i> + MET 500 mg <i>bd</i> for 7 d	86	75.6%
Zullo <i>et al</i> ^[41]	Italy	2013	C	R 20 mg <i>bd</i> + AMX 1 g <i>bd</i> + CLA 500 mg <i>bd</i> + MET 500 mg <i>bd</i> for 14 d	78	80.8%
			S	O 20 mg <i>qd</i> + AMX 1 g <i>qd</i> 5d followed by O 20 mg <i>qd</i> + CLA 500 mg <i>qd</i> + TIN 500 mg <i>qd</i> for 5 d	90	91.1%
			C	O 20 mg <i>qd</i> + AMX 1 g <i>qd</i> + CLA 500 mg <i>qd</i> + TIN 500 mg <i>qd</i> for 5 d	90	85.5%
Sardarian <i>et al</i> ^[42]	Iran	2013	H	O 20 mg <i>qd</i> + AMX 1 g <i>qd</i> for 14 d plus CLA 500 mg <i>qd</i> + TIN 500 mg <i>qd</i> for last 7 d	90	80.0%
			S	P 40 mg <i>bd</i> + AMX 1 g <i>bd</i> for 5 d followed by P 40 mg <i>bd</i> + CLA 500 mg <i>bd</i> + TIN 500 mg <i>bd</i> for 5 d	210	76.7%
			H	P 40 mg <i>bd</i> + AMX 1 g <i>bd</i> for 14 d plus CLA 500 mg <i>bd</i> + TIN 500 mg <i>bd</i> for last 7 d	210	89.5%
Molina-Infante <i>et al</i> ^[37]	Spain, Italy	2013	C	O 40 mg <i>bd</i> + AMX 1 g <i>bd</i> + CLA 500 mg <i>bd</i> + NIT 500 mg <i>bd</i> for 14 d	172	91.7%
			H	O 40 mg <i>bd</i> + AMX 1 g <i>bd</i> for 14 d plus CLA 500 mg <i>bd</i> + TIN 500 mg <i>bd</i> for last 7 d	171	90.0%

ITT: Intention-to-treat; S: Sequential therapy; C: Concomitant therapy; H: Hybrid therapy; AMX: Amoxicillin; CLA: Clarithromycin; MET: Metronidazole; TIN: Tinidazole; E: Esomeprazole; L: Lansoprazole; P: Pantoprazole; O: Omeprazole; R: Rabeprazole; *bd*: Two times a day; *qd*: Once a day.

susceptibility testing is needed by obtaining gastric biopsy specimens for culture. In general, the method of agar dilution is needed for *H. pylori* susceptibility testing. However, culture and susceptibility testing require specific equipment, which is not available in most medical centers. In a recent study, *Helicobacter* genotype and the *CYP2C19* polymorphism were examined for detection of antimicrobial resistance^[55]. In addition, a new method using polymerase chain reaction (PCR) has been validated for detection of resistance of *H. pylori* to clarithromycin^[56]. It is a simple method and requires a shorter time than culture. However, further validation and study for use of a PCR method in real treatment are needed. In the near future, a new tailored regimen for individual patients would be the answer to antibiotic resistance.

CONCLUSION

As a result of increased resistance to antibiotics, conventional triple therapy is no longer standard therapy for naïve *H. pylori* infection. Currently, among the alternative first-line eradication regimens, concomitant and hybrid regimens have shown excellent results and could be the optimal treatment option. After failure of new first-line non-bismuth quadruple treatment, levofloxacin-based quadruple regimens could be an option for rescue treatment. In addition, we hope that development of a simple method for detection of antimicrobial resistance before *H. pylori* eradication and a new tailored treatment for *H. pylori* will be possible in the near future.

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