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Editorial board member of *World Journal of Gastroenterology*, Mortada HF El-Shabrawi, MD, Professor, Department of Pediatrics, Cairo University, Cairo 11559, Egypt

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Andrzej S Tarnawski, MD, PhD, DSc (Med),
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World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
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E-mail: editorialoffice@wjgnet.com
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Second-line rescue treatment of *Helicobacter pylori* infection: Where are we now?

Te-Fu Lin, Ping-I Hsu

Te-Fu Lin, Ping-I Hsu, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan

ORCID number: Te-Fu Lin (0000-0003-1996-5008); Ping-I Hsu (0000-0003-3905-4674).

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Correspondence to: Ping-I Hsu, MD, Attending Doctor, Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, No. 386, Ta-Chung 1st Rd, Kaohsiung 813, Taiwan. williamhsup@yahoo.com.tw
Telephone: +886-7-3468233
Fax: +886-7-3468237

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Abstract

At present, the best rescue therapy for *Helicobacter*

pylori (*H. pylori*) infection following failure of first-line eradication remains unclear. The Maastricht V/Florence Consensus Report recommends bismuth quadruple therapy, or fluoroquinolone-amoxicillin triple/quadruple therapy as the second-line therapy for *H. pylori* infection. Meta-analyses have shown that bismuth quadruple therapy and levofloxacin-amoxicillin triple therapy have comparable eradication rates, while the former has more adverse effects than the latter. There are no significant differences between the eradication rates of levofloxacin-amoxicillin triple and quadruple therapies. However, the eradication rates of both levofloxacin-containing treatments are suboptimal. An important caveat of levofloxacin-amoxicillin triple or quadruple therapy is poor eradication efficacy in the presence of fluoroquinolone resistance. High-dose dual therapy is an emerging second-line therapy and has an eradication efficacy comparable with levofloxacin-amoxicillin triple therapy. Recently, a 10-d tetracycline-levofloxacin (TL) quadruple therapy comprised of a proton pump inhibitor, bismuth, tetracycline and levofloxacin has been developed, which achieves a markedly higher eradication rate compared with levofloxacin-amoxicillin triple therapy (98% vs 69%) in patients with failure of standard triple, bismuth quadruple or non-bismuth quadruple therapy. The present article reviews current second-line anti-*H. pylori* regimens and treatment algorithms. In conclusion, bismuth quadruple therapy, levofloxacin-amoxicillin triple/quadruple therapy, high-dose dual therapy and TL quadruple therapy can be used as second-line treatment for *H. pylori* infection. Current evidence suggests that 10-d TL quadruple therapy is a simple and effective regimen, and has the potential to become a universal rescue treatment following eradication failure by all first-line eradication regimens for *H. pylori* infection.

Key words: *Helicobacter pylori*; Rescue treatment; Levofloxacin-amoxicillin triple therapy; Bismuth quadruple therapy; Tetracycline-levofloxacin quadruple therapy; High-dose dual therapy

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Core tip: The present article reviews current second-line anti-*Helicobacter pylori* (*H. pylori*) regimens. Bismuth quadruple therapy and levofloxacin-amoxicillin triple therapy have comparable eradication rates in the rescue treatment of *H. pylori* infection, while the former has more adverse effects than the latter. High-dose dual therapy has an eradication rate comparable with levofloxacin-amoxicillin triple therapy. Ten-day tetracycline-levofloxacin quadruple therapy achieves a markedly higher eradication rate compared with levofloxacin-amoxicillin triple therapy (98% *vs* 69%) in patients with failure of standard triple, bismuth quadruple or non-bismuth quadruple therapy. In conclusion, tetracycline-levofloxacin quadruple therapy has the potential to become a universal second-line treatment for *H. pylori* infection.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infects > 50% of humans globally. It is a major cause of chronic gastritis, peptic ulcer disease, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma^[1,2]. With the rising prevalence of global antibiotic resistance, the eradication rate of *H. pylori* with standard triple therapy has decreased to < 80% worldwide^[3]. Although there are other emerging 1st-line therapies, including bismuth quadruple therapy and non-bismuth quadruple (sequential, concomitant or hybrid) therapy, which can increase the eradication rate, *H. pylori* eradication still fails in 3%-24% of infected patients^[4-7]. At present, the optimal choice for second-line anti-*H. pylori* therapy has not been well established. The present article aims to review and update the current options for second-line therapy against *H. pylori* infections.

ANTIBIOTIC RESISTANCE IN ANTI-*H. PYLORI* THERAPY

Causes of treatment failure of anti-*H. pylori* therapies include antibiotic resistant bacteria, poor patient compliance, low gastric pH and a high bacterial load. Among these reasons, antibiotic resistance is the main factor which determines the efficacy of an eradication therapy^[8]. Primary resistance to amoxicillin is either null or < 1% in most countries^[9]. In contrast, the rate of primary clarithromycin-resistance ranges from 49% (Spain) to 1% (the Netherlands) worldwide^[10]. High

primary resistance to clarithromycin and low resistance to metronidazole have been observed in Japan; moderate resistance to clarithromycin and high resistance to metronidazole were reported in South Korea; and high primary resistance to both clarithromycin and metronidazole was observed in China^[11]. High primary resistance to both clarithromycin and metronidazole has also been reported in some other countries, such as Italy, Spain, Mexico and Vietnam. Low clarithromycin resistance is generally observed in northern Europe, including the Netherlands, Sweden and Ireland^[10,11].

In patients who experience eradication failure following standard triple therapy, the rates of drug resistance to clarithromycin, metronidazole, levofloxacin, amoxicillin and tetracycline are 65%-75%, 30%-56%, 26%-37%, 0%-6.1% and 0%-10%, respectively^[12-16]. Whereas for patients who experience failure of non-bismuth quadruple therapy, the rates of drug resistance to clarithromycin, metronidazole, levofloxacin, amoxicillin and tetracycline are 75%, 75%, 25%, 0%, and 0%, respectively^[17,18]. This data implies that amoxicillin, tetracycline and levofloxacin are good choices of antibiotics for rescue treatment of *H. pylori* infection.

Point mutations play a primary role in the antimicrobial resistance of *H. pylori*, and different mutations involving the *rdxA* gene have been identified in metronidazole resistant strains^[19]. Resistance to clarithromycin in *H. pylori* is commonly caused by point mutations in the *rrl* gene encoding two 23S rRNA nucleotides, namely 2142 and 2143^[20]. Another mechanism associated with the development of clarithromycin resistance is the efflux pump system^[21,22]. Fluoroquinolone acts on the site of the type A DNA gyrase enzyme, which is encoded by the *gyrA* gene, to inhibit DNA cleavage and rejoining^[23]. Gene mutations in *gyrA* are associated with fluoroquinolone resistance. In particular double mutations at both N87 and D91 in *gyrA* have been reported to increase fluoroquinolone resistance^[24].

UPDATED SECOND-LINE THERAPIES

Current updated second-line therapies include bismuth quadruple therapy, fluoroquinolone-amoxicillin triple therapy, fluoroquinolone-amoxicillin quadruple therapy, tetracycline-levofloxacin (TL) quadruple therapy and high-dose dual therapy.

Bismuth quadruple therapy

Bismuth quadruple therapy consists of a proton pump inhibitor (PPI), bismuth, metronidazole and tetracycline (Table 1). The standard regimen comprises PPI twice daily, colloidal bismuth subcitrate 120 mg four times daily, tetracycline 500 mg four times daily and metronidazole 500 mg three times daily for 10 to 14 d. A pool analysis demonstrated that bismuth quadruple therapy fails in 5%-63% of patients as a second-line therapy and achieves a mean 76% eradication rate^[25-27]. Its efficacy is related to metronidazole resistance in

Table 1 Regimens for second-line anti-*Helicobacter pylori* therapy

Regimen	Drug						Duration of therapy
	PPI	Bismuth	Levo	Amox	Tetra	Metro	
Bismuth-containing quadruple therapy	SD, <i>b.i.d.</i>	120 mg, <i>q.i.d.</i>			500 mg, <i>q.i.d.</i>	500 mg, <i>t.i.d.</i>	10-14 d
Levofloxacin-containing triple therapy	SD, <i>b.i.d.</i>		500 mg, <i>q.d.</i>	1 g, <i>b.i.d.</i>			10-14 d
Levofloxacin-amoxicillin quadruple therapy	SD, <i>b.i.d.</i>	120 mg, <i>q.i.d.</i>	500 mg, <i>q.d.</i>	1 g, <i>b.i.d.</i>			10-14 d
Tetracycline-levofloxacin quadruple therapy	SD, <i>b.i.d.</i>	120 mg, <i>q.i.d.</i>	500 mg, <i>q.d.</i>		500 mg, <i>q.i.d.</i>		10 d
High-dose dual therapy	SD, <i>q.i.d.</i>			750 mg, <i>b.i.d.</i>			14 d

PPI: Proton pump inhibitor; Levo: Levofloxacin; Amox: Amoxicillin; Tetra: Tetracycline; Metro: Metronidazole.

H. pylori strains and the duration of the regimens^[28]. Meta-analysis of randomized controlled trials of bismuth quadruple therapy as a rescue treatment after failure of clarithromycin triple therapy revealed a significantly higher eradication rate for the 14-d regimen compared with the 7-d regimen^[29]. Therefore, it is reasonable to encourage a 14-d regimen duration for bismuth quadruple therapy when used as a second-line treatment for *H. pylori* infection.

Fluoroquinolone-based triple/quadruple therapy

The most commonly used fluoroquinolone-based triple therapy is composed of levofloxacin 500 mg daily, amoxicillin 1 g twice daily and a PPI (standard dose) twice daily for 10 to 14 d (Table 1). Meta-analyses revealed that levofloxacin-amoxicillin triple therapy and bismuth quadruple therapy had comparable eradication rates, whereas the former had fewer adverse effects than the latter^[30]. A systemic review and meta-analysis revealed that levofloxacin-amoxicillin triple therapy achieved an overall eradication rate of 78% after failure of a non-bismuth quadruple therapy^[31]. It was similarly effective after failure of sequential and concomitant therapies (81% vs 78%, respectively), and the cure rate of levofloxacin-amoxicillin triple therapy following hybrid therapy was 50%.

An important drawback of levofloxacin-amoxicillin triple therapy is poor eradication efficacy in the presence of fluoroquinolone resistance. Bismuth salts have a synergistic effect on antibiotics and have been used to increase eradication rates^[32]. The Maastricht V/Florence Consensus Report also recommended the application of fluoroquinolone-amoxicillin quadruple therapy as a second-line therapy for *H. pylori* infection^[31]. Levofloxacin-amoxicillin quadruple therapy is composed of levofloxacin 500 mg daily, amoxicillin 1 g twice daily, PPI (standard dose) twice daily and bismuth 240 mg twice daily for 10 to 14 d (Table 1). A randomized controlled trial showed there were no significant differences between the eradication rates of second-line 14-d levofloxacin-amoxicillin quadruple therapy and 14-d levofloxacin-amoxicillin triple therapy (87% vs 83%, respectively)^[33]. However, the former had a higher eradication rate for levofloxacin-resistant strains than the latter (71% vs 37%)^[33].

TL quadruple therapy

Recently, Hsu *et al*^[17] developed a novel TL quadruple

therapy as a rescue treatment for *H. pylori* infection. It consists of esomeprazole 40 mg twice daily, tripotassium dicitrate bismuthate 120 mg four times daily, tetracycline 500 mg four times daily, and levofloxacin 500 mg once daily for 10 d (Table 1). The simple regimen maintains a high eradication rate for *H. pylori* strains with levofloxacin resistance^[17]. A randomized control study showed that as a second-line anti-*H. pylori* treatment, 10-d of TL quadruple therapy achieved a much higher eradication rate compared with 10-d levofloxacin triple therapy containing esomeprazole, amoxicillin and levofloxacin (98% vs 68%, respectively)^[34]. Subgroup analysis revealed that the former was superior to the latter in patients with failure of either standard triple therapy (100% vs 75%) or non-bismuth quadruple therapy (95% vs 53%). There were only 7 patients recruited into the study with eradication failure by bismuth quadruple therapy as a first-line treatment, and both TL quadruple and levofloxacin-amoxicillin triple therapies had a 100% eradication rate in this subgroup of patients. The data suggests that 10-d TL quadruple therapy is a good option for second-line treatment after failure of standard triple, concomitant and bismuth quadruple therapies.

High-dose dual therapy

High-dose dual therapy is another emerging second-line treatment for *H. pylori* infection^[35]. The new therapy consists of high-dose PPI and amoxicillin (Table 1), which keep the intragastric pH higher than 6.5 regardless of *CYP2C19* genotype^[36], and maintain a steady plasma concentration of amoxicillin above the minimal inhibitory concentration for *H. pylori*^[37]. A randomized control trial from Taiwan revealed that 14-d high-dose dual therapy achieved a higher eradication rate than 10-d sequential therapy as a second-line treatment for *H. pylori* infection (89% vs 52%), and had an eradication rate comparable with 7-d levofloxacin-amoxicillin triple therapy (79%)^[35]. Another randomized controlled trial from Germany demonstrated that 14-d high-dose dual therapy and 14-d bismuth quadruple therapy had comparable efficacies as a rescue treatment for *H. pylori* infection (76% vs 81%, respectively)^[38].

TREATMENT ALGORITHM

After a first failure of *H. pylori* treatment, if an endoscopy is arranged, the Maastricht V/Florence Consensus Report recommends antimicrobial susceptibility testing

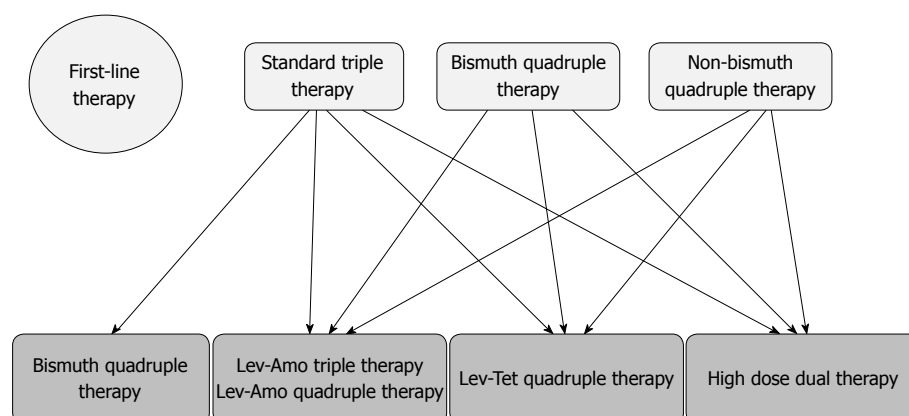


Figure 1 Algorithm for second-line therapy of *Helicobacter pylori* infection. Lev: Levofloxacin; Amo: Amoxicillin; Tet: Tetracycline.

(AST)^[31] to enable tailoring of the rescue eradication therapy. However, AST is not routinely performed in clinical practice due to the invasiveness of the endoscopy procedure, the availability of laboratory culture facilities and cost considerations. If AST data are not available, 10-d TL quadruple therapy can be used as a rescue treatment since it achieves an eradication rate of > 90% following failure of standard triple, concomitant and bismuth quadruple therapies. In addition, the novel 10-d TL quadruple regimen can maintain a high eradication rate (> 90%) for *H. pylori* strains with levofloxacin resistance^[34]. However, the choice of second line rescue regimen also depends on regional factors. In Japan, PPI-containing triple therapy with metronidazole and amoxicillin is the standard second line regimen and is covered under Japan's national health insurance. This second-line therapy can also achieve an eradication rate of around 90% because metronidazole resistance rate is relatively low in Japan.

After failure of a standard triple therapy

According to the Maastricht V/Florence Consensus Report^[31], bismuth-containing quadruple therapy, fluoroquinolone-containing triple therapy or fluoroquinolone-amoxicillin quadruple therapy are recommended following failure of standard triple therapy. As TL quadruple therapy achieves a higher eradication rate than levofloxacin triple therapy, and high-dose dual therapy has a comparable eradication rate with levofloxacin-amoxicillin triple therapy in patients with failure of standard triple therapy^[34,35], both TL quadruple and high-dose dual therapies can be recommended as a rescue regimen following failure of standard triple therapy (Figure 1).

After failure of a non-bismuth quadruple therapy

The Maastricht V/Florence Consensus Report recommends bismuth quadruple therapy, levofloxacin-amoxicillin triple therapy and levofloxacin-amoxicillin quadruple therapy as rescue treatments after failure of a non-bismuth quadruple therapy^[31]. As 10-d TL quadruple therapy is superior to 10-d levofloxacin-amoxicillin triple therapy, it is reasonable to recommend TL-quadruple therapy as the

rescue treatment for patients with eradication failure by non-bismuth quadruple therapy (Figure 1).

After failure of a bismuth quadruple therapy

According to the Maastricht V/Florence Consensus Report^[31], fluoroquinolone-containing triple or fluoroquinolone-amoxicillin quadruple therapy can be recommended for patients with eradication failure by bismuth quadruple therapy for *H. pylori* infection. As both TL quadruple and levofloxacin-amoxicillin triple therapies achieved a 100% cure rate in this setting. TL quadruple therapy may also be considered as an option for the rescue treatment of bismuth quadruple therapy (Figure 1).

CONCLUSION

The current updated second-line therapies include bismuth quadruple therapy, fluoroquinolone-amoxicillin triple therapy, fluoroquinolone-amoxicillin quadruple therapy, TL quadruple therapy and high-dose dual therapy. Ten-day TL quadruple therapy has great potential to become a universal rescue treatment following eradication failure by all first-line eradication regimens for *H. pylori* infection, and warrants further investigation.

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