Update on quinolone-containing rescue therapies for *Helicobacter pylori* infection

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Abstract

Third generation of quinolones, such as levofloxacin and moxifloxacin, -containing regimens are often used in second-line or rescue treatment of *Helicobacter pylori* infection. However, the increasing antibiotic resistance to quinolones affects the efficacies of quinolones-containing therapies in recent years. Therefore, there is a need to enhance the effectiveness of quinolones-containing therapies. Sitafloxacin, a fourth-generation quinolone, and vonoprazan, a novel potassium-competitive acid blocker, are now available as more effective treatment options. The aim of this paper is to summarize the current evidence of quinolone-containing therapies in rescue treatments, and to discuss the importance of drug sensitivity tests or analysis of *gyrA* mutation before treatments.

Key words: *Helicobacter pylori*; Levofloxacin; Moxifloxacin; Vonoprazan

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Core tip: The efficacies of 7-d levofloxacin or moxifloxacin, -containing regimens are becoming less effective in recent years due to the increasing antibiotic resistance, which necessitates 10-d or 14-d regimens or bismuth containing regimen are needed to achieve sufficient eradication rates. *gyrA* mutation is the most sensitive marker for predicting successful eradication in using quinolone-containing therapies. Thus, analysis of *gyrA* mutation before treatments is recommended. Seven-day sitafloxacin-amoxicillin-vonoprazan triple therapy is the best choice for third-line treatment at present.

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INTRODUCTION

Helicobacter pylori (H. pylori) is closely related to gastric cancer, gastric ulcer, atrophic gastritis, mucosa-associated lymphoid tissue lymphoma, and H. pylori-associated dyspepsia. Thus, eradication of H. pylori is useful for treatment and prevention of these diseases[1-6]. In recent years, eradication of H. pylori has become difficult due to an increase in antibiotic resistance, thereafter selection of an efficient regimen has become increasingly important[1,7].

Levofloxacin-containing regimens are used as rescue therapy in many countries. However, in recent times, levofloxacin-amoxicillin-proton pump inhibitor (PPI) regimens were shown to be insufficient for gyrA mutation positive H. pylori strains. Moreover, prevalence of quinolone resistance combined with increased gyrA mutation positive strains have reduced the effectiveness of levofloxacin-amoxicillin-PPI regimen.

In recent years, the high effectiveness of sitafloxacin, a fourth-generation quinolone, containing regimens to gyrA mutation positive H. pylori strains, has been demonstrated[8,9]. At this time, this article only reported the use of sitafloxacin-containing regimen in Japan. However, sitafloxacin will likely be the main quinolone-containing treatment in the future.

Vonoprazan, a novel potassium-competitive acid blocker which has a strong acid secretion inhibitory effect, has been available since 2015. The high efficacy of vonoprazan as first- and second-line H. pylori eradication therapy treatment has already been shown[10,11]. Thus, vonoprazan is expected to play a role in quinolone-containing rescue therapies.

In this article, we describe the current status of quinolone-containing rescue therapies.

STATUS OF QUINOLONE-CONTAINING RESCUE THERAPIES IN THE WORLD’S GUIDELINES

We reviewed guidelines from the United States (2017), Europe (2016), Canada (2016), China (2016) and Japan (2016)[7,12-14]. Only the guideline from America suggested levofloxacin-containing triple therapy consisting of a PPI, levofloxacin, and amoxicillin as a first-line treatment option[14]. The basis of this recommendation was a network meta-analysis that showed levofloxacin-containing triple therapy for 10-14 d proved superior to clarithromycin-containing triple therapy for 7 d (90%, 95%CI: 84%-94% vs 73%, 95%CI: 71%-75%; RR 1.23, 95%CI: 1.16–1.29)[15]. The guidelines in the United States, Europe, Canada and China recommended levofloxacin-containing triple regimen as a rescue therapy[1,7,12,13]. The guidelines in Canada and China stated that increasing resistance rate of quinolones might affect the eradication rate, hence it did not recommend levofloxacin-containing regimen to be used as an initial treatment. The Japanese guideline of 2009 suggested levofloxacin-containing triple therapy as a third-line treatment option[16]. However, the 2016 guideline for Japan suggested sitafloxacin-containing triple therapy consisting of a PPI, sitafloxacin, and amoxicillin as a third-line treatment option[14]. Levofloxacin triple therapy was no longer recommended in Japan.

IMPORTANT ROLE OF GYRA MUTATION FOR RESISTANCE TO QUINOLONES

The most common mechanism of high-level fluoroquinolone resistance is due to mutation in one or more of the genes that encode the primary and secondary targets of these drugs, the type II topoisomerases (gyrA, gyrB, parC and parE)[17].

Mutations of gyrA within the quinolone resistance-determining regions have been found to be the main mechanism for quinolone resistance in H. pylori. The position of the gyrA mutation is usually limited to N87 or D91, both of which are in the DNA-
binding region on the N-terminal domain of the gyrA protein, which includes fluoroquinolone-binding sites\(^{16,19}\). Gyra mutations in \textit{H. pylori} strains correlate with phenotypic resistance of levofloxacin and sitafloxacin\(^{8,20}\). Liou \textit{et al.}\(^{20}\) concluded that gyrA mutation in \textit{H. pylori} strains is a better marker than phenotypic resistance in the prediction of levofloxacin-containing treatment outcomes\(^{39}\). We also showed that the presence of gyrA mutation is a more sensitive marker of eradication failure compared to minimum inhibitory concentrations (MICs) of sitafloxacin in using sitafloxacin-containing regimen\(^{9}\). In fact, the eradication rates of gyrA mutation-positive strains were around 70% with sitafloxacin-containing regimen, whereas most of all strains without gyrA mutation can be eradicated\(^{40}\). In meta-analysis, we found that the relative risk of the eradication failure is significantly lower in gyrA mutation at D91 compared to gyrA mutation at N87\(^{70}\). The MICs of double-mutated strains were extremely higher than those of single-mutated strains\(^{40}\).

\textit{gyrB} is unlikely to mutate and is thought to have little resistance\(^{21,22}\), but some reports have reported resistance due to \textit{gyrB}\(^{25,26}\). Since neither \textit{parC} nor \textit{parE} is found in the complete gene sequences of \textit{H. pylori}, it is thought to be not involved in resistance\(^{37-39}\).

### EPIDEMIOLOGY OF RESISTANCE TO QUINOLONES IN \textit{H. PYLORI}

The prevalence of primary resistance of \textit{H. pylori} to levofloxacin has been reported to range from 11.0% to 62.2% in different countries (Figure 1)\(^{21,23-25}\). There is no relationship between geographic factor and the resistance to levofloxacin. These data suggested that acquisition of resistance is related to high consumption rate of quinolones. Thus, the prevalence of resistance rates should be taken into consideration in selecting quinolone-containing treatments as a rescue therapy.

### LEVOFLOXACIN-CONTAINING THERAPIES

Levofloxacin, one of the third-generation fluoroquinolones, is available worldwide. There is abundant evidence of levofloxacin-containing rescue regimens (Table 1)\(^{8,20}\). Wong \textit{et al.}\(^{8}\) showed the efficacy of levofloxacin-rifabutin-rabeprazole triple therapy as a rescue therapy in 2003. However, in this study, one patient developed drug-related neutropenia and thrombocytopenia, thus they concluded that rifabutin should be reserved only for resistant cases or even as a third-line therapy\(^{40}\). In addition, Zullo \textit{et al.}\(^{8}\) and Nista \textit{et al.}\(^{20}\) reported the efficacy of 10-d levofloxacin-amoxicillin-rabeprazole triple therapy as a third- and second-line rescue therapy, respectively, and the eradication rates seem to be sufficient (88.2% and 94.3%, respectively)\(^{37,38}\). On the other hand, Perri \textit{et al.}\(^{8}\) and Watanabe \textit{et al.}\(^{40}\) revealed that the efficacy of 7-d levofloxacin-amoxicillin-rabeprazole triple therapy as a second-line regimen is insufficient (66.1% and 69.7%, respectively)\(^{39,40}\). Matsumoto \textit{et al.}\(^{40}\) showed that 7-d metronidazole-amoxicillin-lansoprazole triple therapy is significantly more effective than 7-d levofloxacin-amoxicillin-lansoprazole triple therapy as a second-line therapy in a prospective randomized trial in Japan (100.0% vs 72.4%, respectively)\(^{40}\). As a result, 7-d metronidazole-amoxicillin-lansoprazole triple therapy was confirmed as a second-line treatment in Japan\(^{41}\). The remarkable efficacy of 7-d metronidazole-amoxicillin-lansoprazole triple therapy is definitely due to the low rate of metronidazole-resistant strains in Japan, which seems to be an exceptional situation\(^{41}\). Moreover, Murakami \textit{et al.}\(^{41}\) revealed that 7-d sitafloxacin-amoxicillin-lansoprazole triple therapy is significantly more effective than 7-d levofloxacin-amoxicillin-lansoprazole triple therapy as a third-line therapy in a prospective randomized trial in Japan (70.0% vs 43.1%, respectively). At present, levofloxacin containing triple therapy is no longer used in Japan\(^{41}\).

Di Caro \textit{et al.}\(^{41}\) conducted a randomized study to determine dosage and length of levofloxacin-containing regimens as a second-line rescue treatment. In this study, patients were randomized into 4 groups to receive 7-d or 10-d levofloxacin 500 mg, amoxicillin 2000 mg and esomeprazole 40 mg per day or 7-d or 10-d levofloxacin 1000 mg, amoxicillin 2000 mg and esomeprazole 40 mg per day. Interestingly, based upon duration of treatment, eradication rates in the 10-d groups were significantly higher than those in the 7-d groups (87.5% vs 67.5 %, respectively); however, dosage of levofloxacin did not affect the eradication rates (77.5% vs 77.5%, respectively)\(^{41}\). Similarly, Tai \textit{et al.}\(^{41}\) showed that the eradication rate of 14-d levofloxacin-amoxicillin-lansoprazole triple therapy was higher than that of 10-d levofloxacin-amoxicillin-lansoprazole triple therapy (92.5% vs 75.6%, respectively). A meta-analysis showed...
that the eradication rates of 10-d levofloxacin-containing regimens were significantly higher than those of 7-d levofloxacin-containing regimens (81.0% vs 73.0%, respectively)[66]. One other meta-analysis also showed 14-d levofloxacin-containing regimens seemed to be more effective compared to 7-d levofloxacin-containing regimens (83.4% vs 74.6%, respectively)[67]. These data suggested the dose and duration of levofloxacin-containing regimens of 500 mg per day for 10-14 d should be sufficient.

From 2013, levofloxacin and bismuth-containing regimens were reported as rescue treatments[55]. Gisbert et al[59] achieved 91.1% of eradication with 14-d levofloxacin-amoxicillin-esomeprazole-bismuth regimen as a second-line therapy. Hsu et al[64] showed 10-d levofloxacin-tetracycline-esomeprazole-bismuth regimen was more effective than levofloxacin-amoxicillin-esomeprazole triple regimen as a second-line therapy (97.8% vs 68.6%, respectively). On the other hand, Cao et al[60] revealed that 14-d levofloxacin-amoxicillin-lansoprazole-bismuth regimen was less effective compared to 14-d classical metronidazole-tetracycline-lansoprazole-bismuth quadruple therapy in areas of high quinolones resistance such as China (85.4% vs 90.6%, respectively).

Some reports showed the efficacies of modified sequential therapy containing levofloxacin[49,55,62]. Liou et al[62] revealed modified sequential therapy containing levofloxacin was more effective than 10-d levofloxacin-amoxicillin-lansoprazole triple regimen in the second-Line treatment (86.3% vs 78.8%, respectively). On the other hand, Calhan et al[55] showed that modified sequential therapy containing levofloxacin was less effective than 10-d levofloxacin-tetracyclin-pantoprazole-bismuth quadruple regimen (85.7% vs 93.1%, respectively).

Eradication rates of levofloxacin-containing regimens against levofloxacin-resistant strains or gyrA mutation-positive strains were reported to be 33.3% to 41.7%[20,68], while those of sitafloxacin-containing regimens were 68.4% to 74.4%[8,9,68]. Moreover, 7-d or 10-d sitafloxacin-containing regimens, achieved almost perfect eradication of gyrA mutation-negative strains, whereas the eradication rate of a 7-d levofloxacin-containing triple regimen was only 82.7%[9,20].

Regarding adverse effects, levofloxacin-containing triple therapies are more tolerable compared to bismuth-containing quadruple therapy[66]. 10- and 14-d levofloxacin-containing triple therapies are equally safe compared to 7-d levofloxacin-containing triple therapy[57,66].

From these data, when levofloxacin-containing regimens are used as a rescue therapy, a drug sensitivity test or an analysis of gyrA mutation should be performed before treatment. In areas of high quinolones resistance, classical bismuth-containing quadruple therapy or fourth-generation fluoroquinolone, such as sitafloxacin, -containing regimen seems to be better choices. Modified sequential therapy containing levofloxacin or 10-d levofloxacin-tetracyclin-PPI-bismuth quadruple regimen could be an option as a third-line regimen.
Table 1  Levofloxacin-containing therapies

| Ref.          | Country/Region | X-line | Publication year | Drug combination (per day)                                      | Duration (d) | Eradication rate (%) |
|---------------|----------------|--------|------------------|---------------------------------------------------------------|--------------|----------------------|
| Wong et al[3] | China          | 2nd and more | 2003        | LVFX 500 mg + RBT 300 mg + RPZ 40 mg                          | 7            | 91.1 91.1            |
| Zullo et al[8] | Italy          | 3rd    | 2003            | LVFX 500 mg + AMX 2000 mg + RPZ 40 mg                        | 10           | 83.3 88.2             |
| Nista et al[9] | Italy          | 2nd    | 2003            | LVFX 500 mg + AMX 2000 mg + RPZ 40 mg                        | 10           | 94.3 94.3             |
| Perri et al[10]| Italy          | 2nd    | 2003            | LVFX 500 mg + AMX 2000 mg + PPZ 80 mg                        | 7            | 63.8 66.1             |
| Watanabe et al[11] | Japan     | 2003     | LVFX 400 mg + AMX 2000 mg + LPZ 60 mg                        | 7            | 67.9 69.7             |
| Bilardi et al[12] | Italy     | 2nd and more | 2004    | LVFX 500 mg + AMX 2000 mg + PPZ 80 mg                        | 10           | 70.5 75.6             |
| Matsumoto et al[13] | Japan     | 2nd    | 2005            | LVFX 600 mg + AMX 2000 mg + LPZ 60 mg                        | 7            | 70.0 72.4             |
| Wong et al[14] | China          | 2nd and more | 2006    | LVFX 1000 mg + AMX 2000 mg + LPZ 60 mg                        | 7            | 57.4 59.6             |
| Gisbert et al[15] | Spain       | 3rd    | 2006            | LVFX 1000 mg + AMX 2000 mg + OPZ 40 mg                        | 10           | 60.0 66.3             |
| Perna et al[16] | Italy          | 2nd    | 2007            | LVFX 500 mg + AMX 2000 mg + RPZ 40 mg                        | 10           | 72.7 72.7             |
| Gisbert et al[17] | Spain       | 2nd    | 2008            | LVFX 1000 mg + AMX 2000 mg + OPZ 40 mg                        | 10           | 77.3 81.4             |
| Di Caro et al[18] | Italy        | 2nd    | 2009            | LVFX 500 mg + AMX 2000 mg + EPZ 40 mg                        | 7            | 65.0 65.0             |
| Di Caro et al[19] | Italy        | 2nd    | 2009            | LVFX 1000 mg + AMX 2000 mg + EPZ 40 mg                        | 7            | 70.0 70.0             |
| Di Caro et al[20] | Italy        | 2nd    | 2009            | LVFX 500 mg + AMX 2000 mg + EPZ 40 mg                        | 10           | 90.0 90.0             |
| Liou et al[21] | Taiwan        | 2nd    | 2009            | LVFX 1000 mg + AMX 2000 mg + EPZ 40 mg                        | 10           | 85.0 85.0             |
| Liou et al[22] | Taiwan        | 2nd    | 2011            | LVFX 750 mg + AMX 2000 mg + LPZ 60 mg                        | 7            | 76.9 80.0             |
| Hu et al[23]   | Taiwan        | 2011   | LVFX 500 mg + AMX 2000 mg + EPZ 40 mg                        | 10           | 95.1 96.4             |
| Ermis et al[24] | Turkey        | 2nd    | 2011            | LVFX 1000 mg + AMX 2000 mg + EPZ 80 mg                        | 7            | 68.9 75.6             |
| Goh et al[25]  | Malaysia      | 2nd    | 2012            | LVFX 500 mg + AMX 2000 mg + EPZ 80 mg                        | 7            | 37.8 41.2             |
| Chua et al[26] | Taiwan        | 2nd    | 2012            | LVFX 500 mg + AMX 2000 mg + OPZ 40 mg                        | 14           | 90.3 90.3             |
| Gisbert et al[27] | Spain       | 2nd    | 2013            | LVFX 1000 mg + AMX 2000 mg + OPZ 40 mg                        | 10           | 78.1 80.3             |
| Calhan et al[28] | Turkey      | 2nd    | 2013            | LVFX 1000 mg + AMX 2000 mg + OPZ 40 mg                        | 10           | 73.8 75.1             |
| Calhan et al[29] | Turkey      | 2nd    | 2013            | LVFX 1000 mg + AMX 2000 mg + OPZ 40 mg                        | 12           | 82.2 85.7             |
| Moon et al[30] | South Korea   | 2nd    | 2013            | LVFX 500 mg + MTZ 1500 mg + LPZ 60 mg                        | 7            | 67.9 73.1             |
| Tai et al[31]  | Taiwan        | 2nd    | 2013            | LVFX 500 mg + AMX 2000 mg + EPZ 80 mg                        | 10           | 68.0 75.6             |
| Tai et al[32]  | Taiwan        | 2nd    | 2013            | LVFX 500 mg + AMX 2000 mg + EPZ 80 mg                        | 14           | 86.0 92.5             |
| Murakami et al[33] | Japan     | 3rd    | 2013            | LVFX 500 mg + AMX 1500 mg + LPZ 60 mg                        | 7            | 43.1 43.7             |
| Gisbert et al[34] | Spain       | 2nd    | 2015            | LVFX 500 mg + AMX 2000 mg + EPZ 80 mg + bismuth 480 mg        | 14           | 90.0 91.1             |
| Cao et al[35]  | China         | 2nd    | 2015            | LVFX 500 mg + AMX 2000 mg + LPZ 60 mg + bismuth 480 mg        | 14           | 83.0 85.4             |
| Paoluzi et al[36] | Italy       | 3rd    | 2015            | LVFX 1000 mg + DOXY 200 mg + EPZ 40 mg                        | 7            | 46.0 49.0             |
| Liou et al[37] | Taiwan        | 2nd    | 2016            | LVFX 500 mg + AMX 2000 mg + LPZ 60 mg                        | 10           | 75.3 78.8             |
| Liou et al[38] | Taiwan        | 2nd    | 2016            | LVFX 500 mg + AMX 2000 mg + LPZ 60 mg                        | 10           | 84.3 86.3             |
| Song et al[39] | China         | 2016   | LVFX 500 mg + AMX 2000 mg + EPZ 40 mg + bismuth 440 mg        | 14           | 73.5 78.5             |
| Hsu et al[40]  | Taiwan        | 2nd    | 2017            | LVFX 500 mg + TET 2000 mg + EPZ 80 mg + bismuth 480 mg        | 10           | 98.0 97.8             |
| Hsu et al[41]  | Taiwan        | 2nd    | 2017            | LVFX 500 mg + AMX 2000 mg + EPZ 80 mg                        | 10           | 69.2 68.6             |

1. Esomeprazole 80 mg and amoxicillin 2 g for the first 5 d, followed by esomeprazole 80 mg, levofloxacin 500 mg and metronidazole 1000 mg for another 5 d.
2. Pantoprazole 80 mg and amoxicillin 2 g for the first 5 d, followed by pantoprazole 80 mg, metronidazole 1500 mg and levofloxacin 500 mg for another 7 d.
3. Lansoprazole 60 mg and amoxicillin 2 g for the first 5 d, followed by lanosaprazole 60 mg, levofloxacin 500 mg and metronidazole 1000 mg for another 5 d.
4. ITT: Intention-to-treat; PP: Per Protocol; LVFX: Levofloxacin; RBT: Rifabutin; AMX: Amoxicillin; RPZ: Rabeprazole; PPZ: Pantoprazole; LPZ: Lansoprazole; OPZ: Omeprazole; EPZ: Esomeprazole; TET: Tetracycline; MTZ: Metronidazole; DOXY: Doxycycline.

MOXIFLOXACIN-CONTAINING THERAPIES

Moxifloxacin, one of the third-generation fluoroquinolones, is available worldwide.
Di Caro et al[8] initially showed the efficacy of moxifloxacin-based therapies as a first-line therapy at first in 2002. Cheon et al[9] reported moxifloxacin-amoxicillin-esomeprazole triple therapy achieved 83.8% successful eradication, and significant superiority to bismuth-containing regimen in Korea. The reports of moxifloxacin-containing therapies were shown in Table 2. Most of the reports were published from South Korea. Interestingly, 7-d moxifloxacin-amoxicillin-PPI triple therapy achieved over 78% in PP before 2011[57-60]; from 2014 the eradication rates gradually decreased and hovered around 60%-70%. On the other hand, 14-d moxifloxacin-amoxicillin-PPI triple therapy is more effective than 7-d regimen, and maintains the efficacy over 80% in PP. These data suggested that 7-d moxifloxacin-amoxicillin-PPI triple therapy should not be used as a second-line regimen in Korea any longer. It is believed that the diminished effectiveness of 7-d moxifloxacin-amoxicillin-PPI triple therapy was attributed to increasing antimicrobial resistance of H. pylori to quinolones, especially in Korea[61,62]. Marušić et al[63] showed that 14-d bismuth-based quadruple therapy modified with moxifloxacin achieved 88.0% of eradication in Croatia as a second-line treatment, thus this regimen might be useful in regions of low metronidazole resistance.

Few reports are available on whether levofloxacin- or moxifloxacin-containing therapy is a better rescue therapy. As a first-line treatment, Rakici et al[64] performed randomized trial between levofloxacin-amoxicillin-lansoprazole triple therapy and moxifloxacin-amoxicillin-lansoprazole triple therapy, and there was no significant difference (92.0% vs 91.8%, respectively). The side effects observed in the two groups were similar.

In conclusion, levofloxacin- or moxifloxacin-containing therapies seem to be equally effective as second-line treatments; thus, either regimens can be used at present. In regions of high quinolones resistance, 14-d moxifloxacin-amoxicillin-PPI triple therapy is better choice than 7-d regimen. Few data are available on 10-d regimen, thus future research is needed to confirm its efficacy as a second-line therapy.

### SITAFLOXACIN-CONTAINING THERAPIES

Sitafloxacin, one of the fourth-generation fluoroquinolones, is only available in Japan and Thailand. The reports of sitafloxacin-containing therapies were shown in Table 3. Sánchez et al[85] initially showed that sitafloxacin was the most active fluoroquinolone compared with ciprofloxacin and moxifloxacin in vitro. Moreover, we reported that sitafloxacin exhibited the most potent activity against gyrA mutation-positive strains compared with gatifloxacin and garenoxacin, two other fourth-generation fluoroquinolones[8,86]. Murakami et al[87] also showed that sitafloxacin had a strong activity compared with garenoxacin and levofloxacin in vitro. Based on these in vitro data, we revealed that sitafloxacin-amoxicillin-rabeprazole triple therapy achieved 83.6% success in eradicating H. pylori as a third-line rescue treatment[88]. Moreover, even among patients with gyrA mutation-positive H. pylori, the eradication rates reached to be 74.4%. Multi-center randomized controlled study showed that sitafloxacin-amoxicillin-lansoprazole triple therapy achieved 70.0% of successful eradication as a third-line rescue treatment, whereas the eradication rates of levofloxacin-amoxicillin-lansoprazole triple therapy and high dose amoxicillin-lansoprazole dual therapy were 43.1% and 54.3%, respectively[88]. We examined randomized controlled study to assess the efficacy with extension of the duration of regimens from 7 to 10 d and the efficacy of sitafloxacin-metronidazole-esomeprazole triple therapy as a third-line rescue treatment[89]. However, there was no significant difference in the eradication rates between 10-d sitafloxacin-amoxicillin-esomeprazole triple therapy and 10-d sitafloxacin-metronidazole-esomeprazole triple therapy (82.0% vs 76.4%, P = 0.50)[89]. The 10-d regimens also could not improve eradication rates when compared with the 7-d sitafloxacin-containing regimen[89]. Furuta et al[90] compared sitafloxacin-amoxicillin-rabeprazole for 7 or 14 d or sitafloxacin-metronidazole-rabeprazole for 7 or 14 d; however, there were no significant difference between them. Recently, a randomized trial showed that 7-d sitafloxacin-amoxicillin-vonoprazan triple therapy is more effective than 7-d sitafloxacin-amoxicillin-vonoprazan triple therapy as a third-line regimen (83.3% vs 57.1%, P = 0.04)[91]. Vonoprazan, a first-in-class potassium-competitive acid blocker, exhibits more rapid, strong, and continuous gastric acid suppression was compared with conventional PPIs[92]. Vonoprazan-containing regimens showed more efficacy than PPI-containing regimens in first- and second-line treatments[93,94]. Recently, we revealed that changes in the rate of resistance to sitafloxacin were not observed from 2009 to 2015[95].

Regarding adverse events to sitafloxacin-containing regimens, severe side effects...
are rarely reported. Mild and transient adverse effects, such as diarrhea and soft stool, were reported by 24%-80% of patients who received treatments[22,26,27]. These data suggested that 7-d sitafloxacin-amoxicillin-vonoprazan triple therapy is the best choice for third-line treatment at the current moment. However, the efficacy of 7-d sitafloxacin-amoxicillin-vonoprazan triple therapy to gyrA mutation-positive *H. pylori* should be evaluated in the future.

ANTIBIOTIC RESISTANCE INFLUENCES DUE TO ERADICATION FAILURE WITH QUINOLONE-CONTAINING RESCUE THERAPIES

Wueppenhorst et al[88] showed that the levofloxacin/ciprofloxacin resistance occurred significantly more often in patients who had received quinolones-containing regimen when compared with patients who had not (44.5% vs 23.1%). We found that 20.8% of strains obtained double mutations in gyrA after eradication failure with sitafloxacin-containing third-line treatment, which exhibited seven-fold increased MICs of sitafloxacin compared with pre-treatment. On the other hand, the MICs of sitafloxacin did not increase, when the location of the gyrA mutations did not change after treatment. Double mutations in gyrA also cause higher resistance to other fluoroquinolones[25]. If strains obtain new mutation in gyrA, quinolone-containing regimen will be less effective. Therefore, we recommend a more powerful regimen to be used, e.g., sitafloxacin-containing or extension of duration, and stronger inhibition of gastric acid secretion, when quinolone-containing regimen is used as a rescue treatment.

CONCLUSION

Quinolone-containing regimen is effective as a rescue treatment. The drug susceptibility test to quinolones and the identification of gyrA mutation are
### Table 3  Sitafloxacin-containing therapies

| Ref.          | Country | X-line | Publication year | Drug combination (per day) | Duration (d) | Eradication rate (%) |
|---------------|---------|--------|------------------|---------------------------|--------------|----------------------|
| Matsuzaki et al[8] | Japan | 3rd | 2012            | STFX 200 mg + AMX 2000 mg + RPZ 40 mg | 7            | 78.2 83.6 |
| Murakami et al[9] | Japan | 3rd | 2013            | STFX 200 mg + AMX 1500 mg + LPZ 60 mg | 7            | 70.0 72.1 |
| Furuta et al[10]  | Japan | 3rd | 2014            | STFX 200 mg + AMX 2000 mg + RPZ 20-40 mg | 14           | 84.1 86.4 |
| Furuta et al[10]  | Japan | 3rd | 2014            | STFX 200 mg + AMX 2000 mg + RPZ 20-40 mg | 14           | 88.9 90.9 |
| Furuta et al[10]  | Japan | 3rd | 2014            | STFX 200 mg + MTZ 500 mg + RPZ 20-40 mg | 7            | 90.9 90.9 |
| Furuta et al[10]  | Japan | 3rd | 2014            | STFX 200 mg + MTZ 500 mg + RPZ 20-40 mg | 14           | 87.2 91.1 |
| Mori et al[4]    | Japan | 3rd | 2015            | STFX 200 mg + AMX 2000 mg + EPZ 40 mg | 10           | 81.0 82.0 |
| Mori et al[4]    | Japan | 3rd | 2015            | STFX 200 mg + MTZ 500 mg + EPZ 40 mg | 10           | 72.4 76.4 |
| Sue et al[11]    | Japan | 3rd | 2019            | STFX 200 mg + AMX 1500 mg + PPI  | 7            | 53.3 57.1 |
| Sue et al[11]    | Japan | 3rd | 2019            | STFX 200 mg + AMX 1500 mg + VPZ 40 mg | 7            | 75.8 83.3 |

ITT: Intention-to-treat; PP: Per Protocol; STFX: Sitafloxacin; AMX: Amoxicillin; RPZ: Rabeprazole; LPZ: Lansoprazole; EPZ: Esomeprazole; MTZ: Metronidazole; PPI: Proton pump inhibitors; VPZ: Vonoprazan.

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