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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. Sitaflaxacin, 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; Sitaflaxacin; Moxifloxacin; *gyrA*; 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 sitaflaxacin-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^[12]. 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^[18,19]. *gyrA* mutations in *H. pylori* strains correlate with phenotypic resistance of levofloxacin and sitafloxacin^[8,20]. Liou *et al*^[20] concluded that *gyrA* mutation in *H. pylori* strains is a better marker than phenotypic resistance in the prediction of levofloxacin-containing treatment outcomes^[20]. 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^[9]. 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^[9]. The MICs of double-mutated strains were extremely higher than those of single-mutated strains^[19].

gyrB is unlikely to mutate and is thought to have little resistance^[21,22], but some reports have reported resistance due to *gyrB*^[23,24]. Since neither *parC* nor *parE* is found in the complete gene sequences of *H. pylori*, it is thought to be not involved in resistance^[25,26].

EPIDEMIOLOGY OF RESISTANCE TO QUINOLONES IN *H. PYLORI*

The prevalence of primary resistance of *H. pylori* to levofloxacin has been reported to range from 11.0% to 62.2% in different countries (Figure 1)^[21,27-35]. 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)^[36-64]. Wong *et al*^[36] 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^[36]. In addition, Zullo *et al*^[37] and Nista *et al*^[38] 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 *et al*^[39] and Watanabe *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 *et al*^[42] 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)^[42]. As a result, 7-d metronidazole-amoxicillin-lansoprazole triple therapy was confirmed as a second-line treatment in Japan^[14]. 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^[65]. Moreover, Murakami *et al*^[58] 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^[14].

Di Caro *et al*^[47] 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)^[47]. Similarly, Tai *et al*^[57] 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

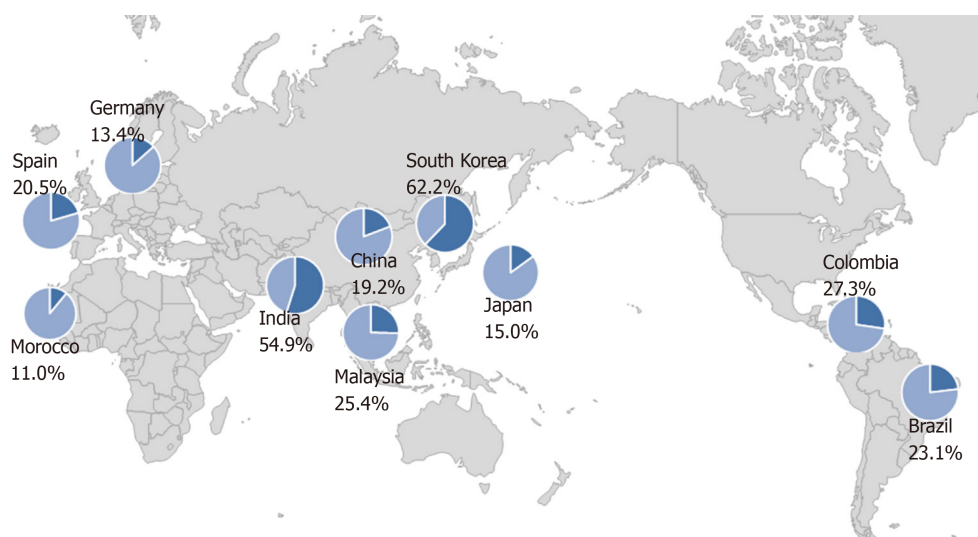


Figure 1 Primary resistance of *Helicobacter pylori* to levofloxacin in different countries.

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*^[58] 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%^[20,45], 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)	Eradica- tion rate (%)	
						ITT	PP
Wong <i>et al</i> ^[36]	China	2 nd and more	2003	LVFX 500 mg + RBT 300 mg + RPZ 40 mg	7	91.1	91.1
Zullo <i>et al</i> ^[37]	Italy	3 rd	2003	LVFX 500 mg + AMX 2000 mg + RPZ 40 mg	10	83.3	88.2
Nista <i>et al</i> ^[38]	Italy	2 nd	2003	LVFX 500 mg + AMX 2000 mg + RPZ 40 mg	10	94.3	94.3
Perri <i>et al</i> ^[39]	Italy	2 nd	2003	LVFX 500 mg + AMX 2000 mg + PPZ 80 mg	7	63.8	66.1
Watanabe <i>et al</i> ^[40]	Japan	2 nd	2003	LVFX 400 mg + AMX 2000 mg + LPZ 60 mg	7	69.7	69.7
Bilardi <i>et al</i> ^[41]	Italy	2 nd and more	2004	LVFX 500 mg + AMX 2000 mg + PPZ 80 mg	10	70.5	75.6
Matsumoto <i>et al</i> ^[42]	Japan	2 nd	2005	LVFX 600 mg + AMX 2000 mg + LPZ 60 mg	7	70.0	72.4
Wong <i>et al</i> ^[43]	China	2 nd and more	2006	LVFX 1000 mg + AMX 2000 mg + LPZ 60 mg	7	57.4	59.6
Gisbert <i>et al</i> ^[44]	Spain	3 rd	2006	LVFX 1000 mg + AMX 2000 mg + OPZ 40 mg	10	60.0	66.3
Perna <i>et al</i> ^[45]	Italy	2 nd	2007	LVFX 500 mg + AMX 2000 mg + RPZ 40 mg	10	72.7	72.7
Gisbert <i>et al</i> ^[46]	Spain	2 nd	2008	LVFX 1000 mg + AMX 2000 mg + OPZ 40 mg	10	77.3	81.4
Di Caro <i>et al</i> ^[47]	Italy	2 nd	2009	LVFX 500 mg + AMX 2000 mg + EPZ 40 mg	7	65.0	65.0
Di Caro <i>et al</i> ^[47]	Italy	2 nd	2009	LVFX 1000 mg + AMX 2000 mg + EPZ 40 mg	7	70.0	70.0
Di Caro <i>et al</i> ^[47]	Italy	2 nd	2009	LVFX 500 mg + AMX 2000 mg + EPZ 40 mg	10	90.0	90.0
Di Caro <i>et al</i> ^[47]	Italy	2 nd	2009	LVFX 1000 mg + AMX 2000 mg + EPZ 40 mg	10	85.0	85.0
Liou <i>et al</i> ^[48]	Taiwan	2 nd	2010	LVFX 750 mg + AMX 2000 mg + LPZ 60 mg	7	76.9	80.0
Liou <i>et al</i> ^[49]	Taiwan	2 nd	2011	Modified sequential regimen ¹	10	95.1	96.4
Hu <i>et al</i> ^[50]	Taiwan	2 nd	2011	LVFX 500 mg + AMX 2000 mg + EPZ 80 mg	7	68.9	75.6
Ermis <i>et al</i> ^[51]	Turkey	2 nd	2011	LVFX 1000 mg + AMX 2000 mg + LPZ 60 mg	7	37.8	41.2
Goh <i>et al</i> ^[52]	Malaysia	2 nd	2012	LVFX 1000 mg + AMX 2000 mg + RPZ 40 mg	14	90.3	90.3
Chuah <i>et al</i> ^[53]	Taiwan	2 nd	2012	LVFX 500 mg + AMX 2000 mg + EPZ 80 mg	7	78.1	80.3
Gisbert <i>et al</i> ^[54]	Spain	2 nd	2013	LVFX 1000 mg + AMX 2000 mg + OPZ 40 mg	10	73.8	75.1
Calhan <i>et al</i> ^[55]	Turkey	2 nd	2013	Modified sequential regimen ²	12	82.2	85.7
Calhan <i>et al</i> ^[55]	Turkey	2 nd	2013	LVFX 500 mg + TET 2000 mg + PPZ 80 mg + bismuth 1200 mg	10	90.6	93.1
Moon <i>et al</i> ^[56]	South Korea	2 nd	2013	LVFX 500 mg + MTZ 1500 mg + LPZ 60 mg	7	67.9	73.1
Tai <i>et al</i> ^[57]	Taiwan	2 nd	2013	LVFX 500 mg + AMX 2000 mg + EPZ 80 mg	10	68.0	75.6
Tai <i>et al</i> ^[57]	Taiwan	2 nd	2013	LVFX 500 mg + AMX 2000 mg + EPZ 80 mg	14	86.0	92.5
Murakami <i>et al</i> ^[58]	Japan	3 rd	2013	LVFX 500 mg + AMX 1500 mg + LPZ 60 mg	7	43.1	43.7
Gisbert <i>et al</i> ^[59]	Spain	2 nd	2015	LVFX 500 mg + AMX 2000 mg + EPZ 80 mg + bismuth 480 mg	14	90.0	91.1
Cao <i>et al</i> ^[60]	China	2 nd	2015	LVFX 500 mg + AMX 2000 mg + LPZ 60 mg + bismuth 480 mg	14	83.0	85.4
Paoluzi <i>et al</i> ^[61]	Italy	3 rd	2015	LVFX 1000 mg + DOXY 200 mg + EPZ 40 mg	7	46.0	49.0
Liou <i>et al</i> ^[62]	Taiwan	2 nd	2016	LVFX 500 mg + AMX 2000 mg + LPZ 60 mg	10	75.3	78.8
Liou <i>et al</i> ^[62]	Taiwan	2 nd	2016	Modified sequential regimen ³	10	84.3	86.3
Song <i>et al</i> ^[63]	China	2 nd	2016	LVFX 500 mg + AMX 2000 mg + EPZ 40 mg + bismuth 440 mg	14	73.5	78.5
Hsu <i>et al</i> ^[64]	Taiwan	2 nd	2017	LVFX 500 mg + TET 2000 mg + EPZ 80 mg + bismuth 480 mg	10	98.0	97.8
Hsu <i>et al</i> ^[64]	Taiwan	2 nd	2017	LVFX 500 mg + AMX 2000 mg + EPZ 80 mg	10	69.2	68.6

¹Esomeprazole 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.

²Pantoprazole 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.

³Lansoprazole 60 mg and amoxicillin 2 g for the first 5 d, followed by lansoprazole 60 mg, levofloxacin 500 mg and metronidazole 1000 mg for another 5 d. 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*^[69] initially showed the efficacy of moxifloxacin-based therapies as a first-line therapy at first in 2002. Cheon *et al*^[70] 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^[71-74]; from 2014 the eradication rates gradually decreased and hovered around 60%^[75-79]. 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^[27,80]. Marušić *et al*^[81] 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*^[82] 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*^[83] 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^[84]. Murakami *et al*^[85] 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^[8]. 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^[58]. 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^[9]. 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)^[9]. The 10-d regimens also could not improve eradication rates when compared with the 7-d sitafloxacin-containing regimen^[9]. Furuta *et al*^[86] 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-esomeprazole triple therapy as a third-line regimen (83.3% *vs* 57.1%, *P* = 0.04)^[87]. Vonoprazan, a first-in-class potassium-competitive acid blocker, exhibits more rapid, strong, and continuous gastric acid suppression was compared with conventional PPIs^[10]. Vonoprazan-containing regimens showed more efficacy than PPI-containing regimens in first- and second-line treatments^[10,11]. Recently, we revealed that changes in the rate of resistance to sitafloxacin were not observed from 2009 to 2015^[68].

Regarding adverse events to sitafloxacin-containing regimens, severe side effects

Table 2 Moxifloxacin-containing therapies

Ref.	Country	X-line	Publication year	Drug combination (per day)	Duration (d)	Eradication rate (%)	
						ITT	PP
Cheon <i>et al</i> ^[70]	South Korea	2 nd	2006	MOFX 400 mg + AMX 2000 mg + RPZ 40 mg	7	75.6	83.8
Kang <i>et al</i> ^[71]	South Korea	2 nd	2007	MOFX 400 mg + AMX 2000 mg + EPZ 40 mg	10	71.9	82.6
Bago <i>et al</i> ^[72]	Croatia	2 nd	2009	MOFX 400 mg + MTZ 1500 mg + OPZ 40 mg	7	73.2	78.9
Yoon <i>et al</i> ^[73]	South Korea	2 nd	2009	MOFX 400 mg + AMX 2000 mg + EPZ 40 mg	7	75.6	83.8
Yoon <i>et al</i> ^[73]	South Korea	2 nd	2009	MOFX 400 mg + AMX 2000 mg + EPZ 40 mg	10	71.9	82.6
Yoon <i>et al</i> ^[73]	South Korea	2 nd	2009	MOFX 400 mg + AMX 2000 mg + EPZ 40 mg	14	68.0	79.9
Miehlke <i>et al</i> ^[74]	Germany	2 nd and more	2011	MOFX 400 mg + AMX 2000 mg + EPZ 40 mg	7	78.9	78.9
Miehlke <i>et al</i> ^[74]	Germany	2 nd and more	2011	MOFX 400 mg + AMX 2000 mg + EPZ 40 mg	14	95.0	94.4
Kang <i>et al</i> ^[75]	South Korea	2 nd	2014	MOFX 400 mg + AMX 2000 mg + RPZ 20 mg	7	58.0	62.5
Kang <i>et al</i> ^[75]	South Korea	2 nd	2014	MOFX 400 mg + AMX 2000 mg + RPZ 20 mg	14	71.8	77.5
Chung <i>et al</i> ^[77]	South Korea	2 nd	2014	MOFX 400 mg + AMX 2000 mg + RPZ 40 mg	7	62.7	62.7
Lee <i>et al</i> ^[76]	South Korea	2 nd	2015	MOFX 400 mg + AMX 2000 mg + PPI	7	53.1	55.6
Lee <i>et al</i> ^[76]	South Korea	2 nd	2015	MOFX 400 mg + AMX 2000 mg + PPI	14	73.5	80.6
Hwang <i>et al</i> ^[78]	South Korea	2 nd	2015	MOFX 400 mg + AMX 2000 mg + RPZ 40 mg	7	70.8	77.7
Hwang <i>et al</i> ^[78]	South Korea	2 nd	2015	MOFX 400 mg + AMX 2000 mg + RPZ 40 mg	14	81.4	90.4
Lim <i>et al</i> ^[79]	South Korea	2 nd	2015	MOFX 400 mg + AMX 2000 mg + RPZ 40 mg	7	56.7	59.6
Lim <i>et al</i> ^[79]	South Korea	2 nd	2015	MOFX 400 mg + AMX 2000 mg + RPZ 40 mg	14	76.3	80.6
Marušić <i>et al</i> ^[81]	Croatia	2 nd	2017	MOFX 400 mg + MTZ 1000 mg + Bismuth 480 mg + PPZ 80 mg	14	80.6	88.0

ITT: Intention-to-treat; PP: Per protocol; MOFX: Moxifloxacin; AMX: Amoxicillin; RPZ: Rabeprazole; EPZ: Esomeprazole; OPZ: Omeprazole; PPI: Proton pump inhibitors; PPZ: Pantoprazole; MTZ: Metronidazole.

are rarely reported. Mild and transient adverse effects, such as diarrhea and soft stool, were reported by 24%-80% of patients who received treatments^[68,86,87].

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^[22]. 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 (%)	
						ITT	PP
Matsuzaki <i>et al</i> ^[8]	Japan	3 rd	2012	STFX 200 mg + AMX 2000 mg + RPZ 40 mg	7	78.2	83.6
Murakami <i>et al</i> ^[58]	Japan	3 rd	2013	STFX 200 mg + AMX 1500 mg + LPZ 60 mg	7	70.0	72.1
Furuta <i>et al</i> ^[86]	Japan	3 rd	2014	STFX 200 mg + AMX 2000 mg + RPZ 20-40 mg	7	84.1	86.4
Furuta <i>et al</i> ^[86]	Japan	3 rd	2014	STFX 200 mg + AMX 2000 mg + RPZ 20-40 mg	14	88.9	90.9
Furuta <i>et al</i> ^[86]	Japan	3 rd	2014	STFX 200 mg + MTZ 500 mg + RPZ 20-40 mg	7	90.9	90.9
Furuta <i>et al</i> ^[86]	Japan	3 rd	2014	STFX 200 mg + MTZ 500 mg + RPZ 20-40 mg	14	87.2	91.1
Mori <i>et al</i> ^[9]	Japan	3 rd	2015	STFX 200 mg + AMX 2000 mg + EPZ 40 mg	10	81.0	82.0
Mori <i>et al</i> ^[9]	Japan	3 rd	2015	STFX 200 mg + MTZ 500 mg + EPZ 40 mg	10	72.4	76.4
Sue <i>et al</i> ^[87]	Japan	3 rd	2019	STFX 200 mg + AMX 1500 mg + PPI	7	53.3	57.1
Sue <i>et al</i> ^[87]	Japan	3 rd	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.

recommended before using quinolone-containing regimen. In using levofloxacin-containing regimen, 10- or 14-d regimen or bismuth containing regimen are recommended and should be restricted to regions of low levofloxacin resistance. Seven-day sitafloxacin-amoxicillin-vonoprazan triple therapy is the best choice for third-line treatment at the current moment.

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