Sitafloxacin for Third-Line *Helicobacter pylori* Eradication: A Systematic Review

Toshihiro Nishizawa 1,2, Munkhbayar Munkjargal 1, Hirotoshi Ebinuma 1, Osamu Toyoshima 2 and Hidekazu Suzuki 3,*

1 Department of Gastroenterology and Hepatology, International University of Health and Welfare, Narita Hospital, Narita 286-8520, Japan; nisizawa@kf7.so-net.ne.jp (T.N.); mb99md@gmail.com (M.M.); ebinuma@me.com (H.E.)
2 Gastroenterology, Toyoshima Endoscopy Clinic, Tokyo 157-0066, Japan; t@iichou.com
3 Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine, Isehara 259-1193, Japan

* Correspondence: hsuzuki@tokai.ac.jp; Tel.: +81-463-93-1121 (ext. 2251)

Abstract: Background and Aim: Sitafloxacin-based therapy is a potent candidate for third-line *Helicobacter pylori* eradication treatment. In this systematic review, we summarise current reports with sitafloxacin-based therapy as a third-line treatment. Methods: Clinical studies were systematically searched using PubMed, Cochrane library, Web of Science, and the Igaku-Chuo-Zasshi database. We combined data from clinical studies using a random-effects model and calculated pooled event rates, 95% confidence intervals (CIs), and the pooled odds ratio (OR). Results: We included twelve clinical studies in the present systematic review. The mean eradication rate for 7-day regimens of either PPI (proton pump inhibitor) or vonoprazan–sitafloxacin–amoxicillin was 80.6% (95% CI, 75.2–85.0). The vonoprazan–sitafloxacin–amoxicillin regimen was significantly superior to the PPI–sitafloxacin–amoxicillin regimen (pooled OR of successful eradication: 6.00; 95% CI: 2.25–15.98, \( p < 0.001 \)). The PPI–sitafloxacin–amoxicillin regimen was comparable with PPI–sitafloxacin–metronidazole regimens (pooled OR: 1.06; 95% CI: 0.55–2.07, \( p = 0.86 \)). Conclusions: Although the 7-day regimen composed of vonoprazan, sitafloxacin, and amoxicillin is a good option as the third-line *Helicobacter pylori* eradication treatment in Japan, the extension of treatment duration should be considered to further improve the eradication rate. Considering the safety concern of fluoroquinolones, sitafloxacin should be used after confirming drug susceptibility.

Keywords: sitafloxacin; vonoprazan; *H. pylori*

1. Introduction

*Helicobacter pylori* (*H. pylori*) is associated with gastric cancer, mucosa-associated lymphoid tissue lymphoma, atrophic gastritis, and peptic ulcer [1–3]. Accordingly, *H. pylori* eradication can effectively prevent and treat these diseases [4,5]. However, a recent increase in antibiotic resistance has complicated *H. pylori* eradication [6–9]. Some patients necessitate the use of third-line treatment [10]. Available options for third-line treatment include fluoroquinolones and rifabutin [11–13]. In terms of fluoroquinolones, sitafloxacin has demonstrated excellent in vitro efficacy against *H. pylori* when compared with levofloxacin and garenoxacin [14,15]. Murakami et al. compared sitafloxacin-based therapy, levofloxacin-based therapy, and high dose proton pump inhibitor (PPI)–amoxicillin therapy in a randomised controlled trial (RCT) [16] and observed superior results with sitafloxacin-based therapy. In 2016, a Japanese guideline recommended sitafloxacin-based triple therapy instead of levofloxacin-based triple therapy [17]. Several studies have evaluated sitafloxacin-based triple therapy as third-line treatment [18–27]. A novel potassium-competitive acid blocker (vonoprazan), deemed superior to PPIs, has also been introduced [28,29]. Several
variations of sitafloxacin-based triple therapy in terms of combinations, doses, and treatment durations have been employed. In the present systematic review, we summarise up-to-date reports with sitafloxacin-based therapy as third-line treatment.

2. Methods

2.1. Search Strategy

Relevant reports were systematically searched using PubMed, Cochrane library, Web of Science, and Igaku-Chuo-Zasshi database in Japan (up to May 2021) [30]. The search words used were as follows: (sitafloxacin OR DU-6859a OR Gracevit) AND (Helicobacter pylori OR H. pylori OR Helicobacter infection) AND (eradication OR treatment OR therapy). There was no language limitation applied.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) study design: clinical study; (2) participants: patients who failed first-line and second-line eradication treatments; (3) intervention: third-line eradication treatment using sitafloxacin; (4) outcome: confirmation of H. pylori eradication at least 4 weeks after therapy. The exclusion criteria were as follows: (1) meeting abstracts; (2) review articles; (3) duplication.

2.3. Data Extraction

The following data were extracted from all included studies: principal author, publishing year, study type, drugs and doses for H. pylori eradication regimens, duration of treatment, the number of enrolled subjects, diagnostic methods employed for testing H. pylori infection after eradication, and key outcome data such as eradication rates, as well as the occurrence of diarrhoea and severe adverse events. The eligibility of all articles was independently examined by two reviewers (T.N. and M.M.). Disagreements were resolved by consulting a third reviewer (O.T.).

2.4. Assessment of Methodological Quality

We evaluated the quality of enrolled studies using the Jadad scale [31] for RCTs or by the Quality Assessment Tool for Case Series Studies (QATCSS) of the National Institutes of Health for nonrandomised, open label studies (National Heart, Lung, and Blood Institute. Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series, accessed on 1 May 2021) for nonrandomised studies. Two reviewers (T.N. and H.E.) assessed the quality of the included studies.

2.5. Statistical Analysis

Statistical analysis was performed using Comprehensive Meta-Analysis (CMA) software (version 3, Biostat, Inc., Englewood, NJ, USA) and Review Manager (RevMan; The Cochrane Collaboration, 2008; The Nordic Cochrane Centre, Copenhagen, Denmark) [32]. Pooled event rates and 95% confidence intervals (CIs) were calculated using a random-effects model. The odds ratio (OR) for successful eradication was calculated using the random-effects model and the Mantel–Haenszel method [33]. Heterogeneity between studies was assessed by Cochran’s Q and I² tests [7]. p-value < 0.1 was considered as significant heterogeneity, as the power of the Q test is low. An I² score ≥ 50% was considered a moderate level of heterogeneity [34].

3. Results

3.1. Search Results

The systematic review process identified 248 potential reports (Figure 1). Based on the exclusion criteria, we then excluded 230 studies (32 duplications, 25 unrelated topics, 63 review articles, 18 protocols for clinical trials, 90 meeting abstracts, and 2 case reports). The remaining 18 studies were scrutinised, and six additional studies were rejected. In
four studies, the sitafloxacin-containing regimen was used as first-line or second-line treatment for subjects with penicillin allergy [35–38]. One study combined the eradication rates of levofloxacin-based and sitafloxacin-based therapy [39]. One study combined the eradication rates of first, second, and third-line therapy [9]. Finally, we included 12 clinical studies in the present systematic review [16,18–27,40]. The included studies were all performed in Japan. In Sugimoto et al.’s, Saito et al.’s and Sue et al.’s studies, the first-line therapy was the 7-day regimen with vonoprazan or PPI, clarithromycin 200 mg or 400 mg b.i.d., and amoxicillin 750 mg b.i.d., and the second-line therapy was the 7-day regimen with vonoprazan or PPI, metronidazole 250 mg b.i.d., and amoxicillin 750 mg b.i.d. In another eight studies, the first-line therapy was the 7-day regimen with PPI, clarithromycin, and amoxicillin, and the second-line therapy was the 7-day regimen with PPI, metronidazole, and amoxicillin. In all included studies, the sitafloxacin dose was 100 mg b.i.d.

Table 1 summarises the efficacy of PPI–sitafloxacin–amoxicillin, which is sorted in the order of treatment duration and amoxicillin dose employed. The 1500 mg/day amoxicillin dose was administered as 750 mg b.i.d., while the 2000 mg/day was administered as 500 mg q.i.d. Prolonged treatment durations appeared to improve eradication rates. However, in an RCT comparing 7-day and 14-days regimens, Furuta et al. found no significant difference [23]. Furthermore, Mori et al. compared 7-day and 10-days regimens and observed was no significant difference [25].

Three studies evaluated the efficacy of the vonoprazan–sitafloxacin–amoxicillin regimen (Table 2) and reported eradication rates ranging between 83.3% and 93.0% in the per-protocol analysis.

Figure 2 shows the forest plot of eradication rates for 7-day regimens of either PPI or vonoprazan–sitafloxacin–amoxicillin. The mean eradication rate for 7-day regimens of either PPI or vonoprazan–sitafloxacin–amoxicillin was 80.6% (95% CI, 75.2–85.0). In the subgroup analyses, the mean eradication rates were 70.1% (95% CI, 59.0–79.2%) for PPI–sitafloxacin–amoxicillin 1500 mg/day, 84.4% (95% CI, 76.7–90.0%) for PPI–sitafloxacin–amoxicillin 2000 mg/day, and 88.9% (95% CI, 75.5–95.4%) for vonoprazan–sitafloxacin–amoxicillin.
1500 mg/day, and 87.5% (95% CI, 73.3–94.7%) vonoprazan–sitafloxacin–amoxicillin 2000 mg/day.

**Table 1.** Efficacy of PPI–sitafloxacin (STFX)–amoxicillin (AMX).

| Author     | Year | Drug Combination | Days | Eradication Rate | STFX Rate |
|------------|------|------------------|------|------------------|-----------|
| Hirata     | 2012 | RPZ 20 mg        | 1500 mg | 7 | 25.0 |
| Murakami   | 2013 | LPZ 60 mg        | 1500 mg | 7 | 21.7 |
| Hirata     | 2016 | EPZ 40 mg        | 1500 mg | 7 | 50.0 |
| Sue        | 2019 | PPI              | 1500 mg | 7 | — |
| Saito      | 2019 | PPI              | 1500 mg | 7 | — |
| Matsuzaki  | 2012 | RPZ 40 mg        | 2000 mg | 7 | 42.5 |
| Furuta     | 2014 | RPZ 20–40 mg     | 2000 mg | 7 | — |
| Tokunaga   | 2014 | RPZ 30 mg        | 1500 mg | 10 | — |
| Mori       | 2016 | EPZ 40 mg        | 2000 mg | 10 | — |
| Mori       | 2020 | EPZ 40 mg        | 2000 mg | 10 | 50.0 |
| Furuta     | 2014 | RPZ 20–40 mg     | 2000 mg | 14 | — |

Sitafloxacin resistant rate: minimum inhibitory concentration \( \geq 0.12 \mu g/mL \). PPI: proton pump inhibitor; RPZ: rabeprazole; LPZ: lansoprazole; EPZ: esomeprazole; ITT: intention-to-treat; PP: per-protocol.

**Figure 2.** Eradication rates of 7 days regimen with PPI (proton pump inhibitor) or vonoprazan. (VPZ)–sitafloxacin (STFX)–amoxicillin (AMX). RPZ: rabeprazole; EPZ: esomeprazole.

Two clinical studies compared PPI–sitafloxacin–amoxicillin and vonoprazan–sitafloxacin–amoxicillin regimens [20,22] and revealed that the vonoprazan–sitafloxacin–amoxicillin regimen was significantly superior to the PPI–sitafloxacin–amoxicillin regimen in the per-protocol analysis (pooled OR of successful eradication 6.00; 95% CI: 2.25–15.98, \( p < 0.001 \)) (Figure 3A). The intention-to-treat analysis had similar results (Figure 3B).
Table 2. Efficacy of vonoprazan (VPZ)–sitafoxacin (STFX)–amoxicillin (AMX).

| Author  | Year | Drug Combination | Days | Eradication Rate | STFX |
|---------|------|------------------|------|------------------|------|
| Sue     | 2016 | VPZ 40 mg        | 14   | 91.1             | 90.9 |
| Sue     | 2019 | VPZ 40 mg        | 10   | 76.4             | 72.4 |
| Sugimoto| 2020 | VPZ 40 mg        | 15   | 88.3             | 87.5 |

Sitafloxacin resistant rate: minimum inhibitory concentration ≥ 0.12 µg/mL.

Figure 2. Forest plot of the pooled odds ratio (OR) with 95% confidence intervals (CI) of successful eradication when using regimens of vonoprazan–sitafoxacin–amoxicillin and PPI–sitafoxacin–amoxicillin. (A) Per-protocol analysis. (B) Intention-to-treat analysis.

3.3. Efficacy of PPI–Sitafoxacin–Metronidazole

Several studies evaluated the efficacy of the PPI–sitafoxacin–metronidazole regimen. Table 3 summarises these results and is organised in the order of treatment duration.

Table 3. Efficacy of PPI–sitafoxacin (STFX)–metronidazole (MNZ).

| Author   | Year | Drug Combination | Days | Eradication Rate | STFX |
|----------|------|------------------|------|------------------|------|
| Furuta   | 2014 | RPZ 20–40 mg     | 7    | 90.9             | 90.9 |
| Sugimoto | 2015 | RPZ 40 mg        | 7    | 88.3             | 87.2 |
| Mori     | 2016 | EPZ 40 mg        | 14   | 56.9             | 76.4 |
| Furuta   | 2014 | RPZ 20–40 mg     | 10   | 88.3             | 87.2 |

Sitafloxacin resistant rate: minimum inhibitory concentration ≥ 0.12 µg/mL.
3.4. PPI–Amoxicillin–Sitafloxacin versus PPI–Metronidazole–Sitafloxacin

Three sets of RCTs compared PPI–sitafloxacin–amoxicillin and PPI–sitafloxacin–metronidazole regimens [23,24]. In each of these studies, the amoxicillin dose employed was 2000 mg/day (500 mg q.i.d.), and the metronidazole dose was 500 mg/day (250 mg b.i.d.). The treatment durations were 7, 10, and 14, respectively. Owing to the limited number of studies, RCTs that employed different criteria were included in this meta-analysis. No significant difference in eradication rates was observed between PPI–sitafloxacin–amoxicillin and PPI–sitafloxacin–metronidazole regimens in the per-protocol analysis (pooled OR: 1.06, 95% CI: 0.55–2.07, \( p = 0.86 \), Figure 4A). Additionally, no heterogeneity was detected between RCTs (\( p = 0.60, I^2 = 0% \)). The intention-to-treat analysis had similar results (Figure 4B).

| Author | Year | Drug Combination | Days | Eradication Rate | STFX | PPI | STFX | MNZ | ITT | PP | Resistant Rate |
|--------|------|------------------|------|------------------|------|-----|------|-----|-----|----|---------------|
| Furuta | 2014 | RPZ 20–40 mg      | 200 mg | 500 mg | 7    | 90.9| 90.9| 72.4| 76.4| 56.9|               |
| Sugimoto | 2015 | RPZ 40 mg       | 200 mg | 500 mg | 7    | 88.3| 88.3| 72.4| 76.4| 56.9|               |
| Mori   | 2016 | EPZ 40 mg       | 200 mg | 500 mg | 10   | 72.4| 72.4| 72.4| 72.4| 72.4|               |
| Furuta | 2014 | RPZ 20–40 mg      | 200 mg | 500 mg | 14   | 87.2| 87.2| 87.2| 87.2| 87.2|               |

Sitafloxacin resistant rate: minimum inhibitory concentration \( \geq 0.12 \mu g/mL \).

3.5. Adverse Events

Figure 5 shows the forest plot of adverse event (diarrhoea) associated with 7-day regimens composed of PPIs or vonoprazan–sitafloxacin–amoxicillin. The pooled adverse event (diarrhoea) rate was 24.4% (95% CI: 16.7–34.3%). The frequency of diarrhoea ranged between 12.5% and 50.0%. Sue et al. reported two cases (6.1%) presenting severe allergy. Other studies did not report any severe adverse events.

3.6. Quality Assessment

Quality assessment is reported in Table 4. A maximum score of 5 was obtained using the Jadad scale, whereas a maximum score of 9 was attained with QATCSS. In general, the quality of the included studies was good, apart from the study by Tokunaga et al.
3.5. Adverse Events

Figure 5 shows the forest plot of adverse event (diarrhoea) associated with 7-day regimens composed of PPIs or vonoprazan–sitafloxacin–amoxicillin. The pooled adverse event (diarrhoea) rate was 24.4% (95% CI: 16.7–34.3%). The frequency of diarrhoea ranged between 12.5% and 50.0%. Sue et al. reported two cases (6.1%) presenting severe allergy. Other studies did not report any severe adverse events.

![Figure 5. Adverse event (diarrhoea) of 7 days regimen with PPI or vonoprazan (VPZ)–sitafloxacin (STFX)–amoxicillin (AMX). Murakami et al.’s study included other adverse events. RPZ: rabeprazole; LPZ lansoprazole; EPZ: esomeprazole.]

3.6. Quality Assessment

Quality assessment is reported in Table 4. A maximum score of 5 was obtained using the Jadad scale, whereas a maximum score of 9 was attained with QATCSS. In general, the quality of the included studies was good, apart from the study by Tokunaga et al.

| Author          | Year | Type of Study                        | Quality Assessment |
|-----------------|------|--------------------------------------|--------------------|
| Murakami        | 2013 | Randomised controlled study: open label | 3                  |
| Furuta          | 2014 | Randomised controlled study: open label | 3                  |
| Sue             | 2019 | Randomised controlled study: open label | 3                  |
| Matsuzaki       | 2012 | Prospective single centre open label study | 9                  |
| Hirata          | 2012 | Prospective single center open label study | 9                  |
| Tokunaga        | 2014 | Single center open label study        | 6                  |
| Mori            | 2015 | Prospective single center open label study | 9                  |
| Sugimoto        | 2015 | Single center open label study        | 8                  |
| Hirata          | 2016 | Prospective multi-center open label study | 9                  |
| Saito           | 2019 | Single center open label study        | 8                  |
| Mori            | 2020 | Prospective single center open label study | 9                  |
| Sugimoto        | 2020 | Single center open label study        | 8                  |

*: Jadad scale reached a maximum score of 5. †: Quality assessment tool for case series studies (QATCSS) reaches a maximum score of 9.

4. Discussion

The 7-day regimen composed of vonoprazan, sitafloxacin, and amoxicillin is considered as a good option for the third-line *H. pylori* eradication treatment in Japan.

An in vitro study has reported that sitafloxacin and metronidazole exhibit a synergistic antimicrobial activity, while sitafloxacin and amoxicillin failed to demonstrate such activity [41]. Several RCTs have compared PPI–sitafloxacin–metronidazole with PPI–sitafloxacin–amoxicillin [23,24]. This meta-analysis confirmed that the efficacy of PPI–
sitafloxacin–amoxicillin was comparable with that of PPI–sitafloxacin–metronidazole. The PPI–sitafloxacin–metronidazole regimen is a good option in patients presenting penicillin allergy [36,38].

In PPI–sitafloxacin–amoxicillin, amoxicillin is administered at quantities of 1500 mg/day (750 mg b.i.d.), or 2000 mg/day (500 mg q.i.d.). The bactericidal effect of amoxicillin depends on the time above the minimum inhibitory concentration (MIC), as amoxicillin has minimal post-antibiotic effect [42,43]. Furuta et al. compared amoxicillin 750 mg b.i.d., 500 mg t.i.d., and 500 mg q.i.d. in a PPI–metronidazole–amoxicillin regimen, and reported eradication rates of 80.5%, 90.5%, and 95.2%, respectively, indicating that four times daily amoxicillin dosing maximised the eradication rate [44]. This study indicated that the optimal amoxicillin dose was 2000 mg/day (500 mg q.i.d.). The amoxicillin dose in the vonoprazan–sitafloxacin–amoxicillin regimen needs to be further investigated in future studies.

Regarding the optimal duration for *H. pylori* eradication therapy, a meta-analysis showed that increasing the duration of PPI-based triple therapy increased the eradication rates [45]. There are many reports that the eradication rates of fluoroquinolone-based therapy were increased by extending the duration to 14 days [46–52]. Conversely, Furura et al. compared 7-day and 14-days regimens of PPI–sitafloxacin–amoxicillin in their RCT, and found no significant difference. Mori et al. also compared 7-day and 10-days regimens of PPI–sitafloxacin–amoxicillin, and found no significant difference. However, the number of patients was limited, and hence these studies might be underpowered. As for the vonoprazan–sitafloxacin–amoxicillin regimen, there is no data other than 7-days regimen. The 14-day regimen with vonoprazan–sitafloxacin–amoxicillin may achieve excellent eradication rates. The optimal duration of the vonoprazan–sitafloxacin–amoxicillin regimen needs to be further investigated in future studies.

In Japan, the primary resistance of *H. pylori* to levofloxacin is 15% [1]. In contrast, the sitafloxacin resistance rates reported in the included studies ranged between 21.7% and 60.3%; these resistance rates were relatively high. This could be attributed to the fact that patients who failed to demonstrate successful eradication twice might have a history of prior antibiotic use, including fluoroquinolones for non-eradication purposes [53,54]. Fluoroquinolone resistance is caused by gyrA mutation [55–58]. Three studies reported both sitafloxacin resistance rates and gyrA mutation rates. Accordingly, the sitafloxacin resistance rates and gyrA mutation rates were 42.5% and 55.1% in Matsuzaki et al.’s study [21], 58.7% and 60.3% in Mori et al.’s 2016 study [24], and 50.0% and 50.0% in Mori et al.’s 2020 study [25]. When the sitafloxacin resistance was defined as MIC, the sitafloxacin resistance rate was found to be similar to the gyrA mutation rate. Eradication rates for gyrA mutation-negative and mutation-positive groups were 96.7% and 74.4% in Matsuzaki et al.’s study [21], 100% and 70.3% in Mori et al.’s 2016 study [24], and 89.5% and 68.4% in Mori et al.’s 2020 study, respectively [25]. Sitafloxacin-based triple therapy showed excellent eradication rates for gyrA mutation-negative *H. pylori*. Sitafloxacin-based therapy should be used for sitafloxacin susceptible or gyrA mutation-negative *H. pylori*. Sitafloxacin resistant or gyrA mutation-positive *H. pylori* would require alternate treatments such as rifabutin-based therapy [13,59–61].

The United States Food and Drug Administration recently enhanced warnings about disabling and potentially permanent side effects involving the tendons, muscles, joints, nerves, and central nervous system [62]. Balancing risk and benefit should be considered.

Our systematic review has several limitations. The included studies were all from Japan, as sitafloxacin is only available in Japan and Thailand. The availability of vonoprazan is also limited. In Japan, the first-line regimen is PPI–clarithromycin–amoxicillin and the second-line regimen is PPI–metronidazole–amoxicillin. Therefore, the results of the current study may not directly applicable to the populations who were administered bismuth containing regimens as first-line or second-line regimens. Therefore, these results may not be generalisable to other ethnicities and countries.
In conclusion, the 7-day regimen with vonoprazan 20 mg b.i.d., sitafloxacin 100 mg b.i.d., and amoxicillin 750 mg b.i.d. or 500 mg q.i.d. is a good option as the third-line *H. pylori* eradication treatment, at least in Japan. However, the extension of treatment duration should be considered to further improve the eradication rate. Considering the safety concern of fluoroquinolones, sitafloxacin should be used after confirming drug susceptibility.

**Author Contributions:** T.N. analysed data. T.N. wrote the manuscript. T.N., M.M. and O.T. performed the systematic literature search. T.N. and H.E. performed quality assessment. H.S. supervised the study. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was supported by a Grant-in-Aid for Scientific Research B (20H036672, to H.S.), from the Japan Society for the Promotion of Science.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** No new data were created or analyzed in this study. Data sharing is not applicable to this article.

**Conflicts of Interest:** The author H.S. received scholarship funds for the research from Daiichi-Sankyo, Otsuka Pharmaceutical Co, Ltd., MSD Co., Mylan EPD, Tanabe, and Takeda Pharmaceutical Co., and received service honoraria from Astellas Pharm, AstraZeneca K.K., EA Pharma Co, Ltd., Mylan EPD, Otsuka Pham, Takeda Pharm.

**References**

1. Suzuki, H.; Mori, H. World trends for *H. pylori* eradication therapy and gastric cancer prevention strategy by *H. pylori* test-and-treat. *J. Gastroenterol.* 2018, 53, 354–361. [CrossRef]

2. Suzuki, H.; Nishizawa, T.; Tsugawa, H.; Hibi, T. Molecular approaches and modern clinical strategies for the management of *Helicobacter pylori* infection in Japan. *Keio J. Med.* 2012, 61, 109–119. [CrossRef]

3. Watanabe, T.; Nadatani, Y.; Suda, W.; Higashimori, A.; Otani, K.; Fukunaga, S.; Hosomi, S.; Tanaka, F.; Nagami, Y.; Taira, K.; et al. Long-term persistence of gastric dysbiosis after eradication of *Helicobacter pylori* in patients who underwent endoscopic submucosal dissection for early gastric cancer. *Gastric Cancer* 2021, 24, 710–720. [CrossRef] [PubMed]

4. Ford, A.C.; Yuan, Y.; Moayyedi, P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: Systematic review and meta-analysis. *Gut* 2020, 69, 2113–2121. [CrossRef]

5. Suzuki, H.; Nishizawa, T.; Hibi, T. *Helicobacter pylori* eradication therapy. *Future Microbiol.* 2010, 5, 639–648. [CrossRef]

6. Farzi, N.; Yadegar, A.; Sadeghi, A.; Asadzadeh Aghdasi, H.; Marian Smith, S.; Raymond, J.; Suzuki, H.; Zali, M.R. High prevalence of antibiotic resistance in iranian *Helicobacter pylori* isolates: Importance of functional and mutational analysis of resistance genes and virulence genotyping. *J. Clin. Med.* 2019, 8, 2004. [CrossRef]

7. Murata, M.; Sugimoto, M.; Mizuno, H.; Kanno, T.; Satoh, K. Clarithromycin versus metronidazole in first-line *Helicobacter pylori* triple eradication therapy based on resistance to antimicrobial agents: Meta-analysis. *J. Clin. Med.* 2020, 9, 543. [CrossRef] [PubMed]

8. Olmedo, L.; Azagra, R.; Aguye, A.; Pascual, M.; Calvet, X.; Gene, E. High effectiveness of a 14-day concomitant therapy for *Helicobacter pylori* treatment in primary care. An observational multicenter study. *J. Clin. Med.* 2020, 9, 2410. [CrossRef] [PubMed]

9. Suzuki, H.; Mori, H. Update on quinolone-containing rescue therapies for *Helicobacter pylori* infection. *World J. Gastroenterol.* 2020, 26, 1733–1744. [CrossRef] [PubMed]

10. Mori, H.; Suzuki, H.; Matsuoka, Y.; Nishizawa, T.; Iwasaki, E.; Masaoka, T.; Hibi, T. Clarithromycin and garenoxacin may overcome the antibiotic resistance of *Helicobacter pylori* with gyrA mutation. *Antimicrob. Agents Chemother.* 2009, 53, 1720–1721. [CrossRef]

11. Suzuki, H.; Nishizawa, T.; Matsuoka, Y.; Hibi, T. Clarithromycin and garenoxacin may overcome the antibiotic resistance of *Helicobacter pylori* with gyrA mutation.
16. Murakami, K.; Furuta, T.; Ando, T.; Nakajima, T.; Inui, Y.; Oshima, T.; Tomita, T.; Mabe, K.; Sasaki, M.; Suganuma, T.; et al. Multi-center randomized controlled study to establish the standard third-line regimen for Helicobacter pylori eradication in Japan. J. Gastroenterol. 2013, 48, 1128–1135. [CrossRef] [PubMed]

17. Kato, M.; Ota, H.; Okuda, M.; Kikuchi, S.; Sato, K.; Shimoyama, T.; Suzuki, H.; Handa, O.; Furuta, T.; Mabe, K.; et al. Guidelines for the management of Helicobacter pylori infection in Japan: 2016 revised edition. Helicobacter 2019, 24, e12597. [CrossRef]

18. Hirata, Y.; Ommae, T.; Yanai, A.; Sakitani, K.; Hayakawa, Y.; Yoshida, S.; Sugimoto, T.; Mitsuno, Y.; Akahama, M.; Yamaji, Y.; et al. Sitafoxacin resistance in Helicobacter pylori isolates and sitafoxacin-based triple therapy as a third-line regimen in Japan. Int. J. Antimicrob. Agents 2012, 39, 352–355. [CrossRef]

19. Hirata, Y.; Serizawa, T.; Shichijo, S.; Suzuki, N.; Sakitani, K.; Hayakawa, Y.; Yamada, A.; Koike, K. Efficacy of triple therapy with esomeprazole, amoxicillin, and sitafoxacin as a third-line Helicobacter pylori eradication regimen. Int. J. Infect. Dis. 2016, 51, 66–69. [CrossRef]

20. Sue, S.; Shibata, W.; Sasaki, T.; Kaneko, H.; Irie, K.; Kondo, M.; Maeda, S. Randomized trial of vonoprazan-based versus proton-pump inhibitor-based third-line triple therapy with sitafoxacin for Helicobacter pylori. J. Gastroenterol. Hepatol. 2019, 34, 686–692. [CrossRef]

21. Matsuzaki, J.; Suzuki, H.; Nishizawa, T.; Hirata, K.; Tsugawa, H.; Saito, Y.; Okada, S.; Fukuhara, S.; Hibi, T. Efficacy of Sitafloxacin-based rescue therapy for Helicobacter pylori after failures of first- and second-line therapies. Antimicrob. Agents Chemother. 2011, 56, 1643–1645. [CrossRef]

22. Saito, Y.; Konno, K.; Sato, M.; Nakano, M.; Kato, Y.; Saito, H.; Serizawa, H. Vonoprazan-based third-line therapy has a higher eradication rate against sitafoxacin-resistant Helicobacter pylori. Cancers 2019, 11, 116. [CrossRef]

23. Furuta, T.; Sugimoto, M.; Kodaira, C.; Nishino, M.; Yamade, M.; Uotani, T.; Sahara, S.; Ichikawa, H.; Yamada, T.; Osawa, S.; et al. Sitafoxacin-based third-line rescue regimens for Helicobacter pylori infection in Japan. J. Gastroenterol. Hepatol. 2014, 29, 487–493. [CrossRef] [PubMed]

24. Mori, H.; Suzuki, H.; Matsuzaki, J.; Tsugawa, H.; Fukuhara, S.; Miyoshi, S.; Hirata, K.; Seino, T.; Matsuhashi, M.; Masaoka, T.; et al. Efficacy of 10-day Sitafloxacin-containing third-line rescue therapies for Helicobacter pylori strains containing the gyrA mutation. Helicobacter 2016, 21, 286–294. [CrossRef]

25. Mori, H.; Suzuki, H.; Matsuzaki, J.; Masaoka, T.; Kanai, T. 10-Year trends in Helicobacter pylori eradication rates by Sitafloxacin-based third-line rescue therapy. J. Gastroenterol. Hepatol. 2020, 35, 641–650. [CrossRef] [PubMed]

26. Sugimoto, M.; Sahara, S.; Ichikawa, H.; Kagami, T.; Uotani, T.; Furuta, T. High Helicobacter pylori cure rate with Sitafloxacin-based triple therapy. Aliment. Pharmacol. Ther. 2015, 42, 477–483. [CrossRef] [PubMed]

27. Sugimoto, M.; Hira, D.; Murata, M.; Kawai, T.; Terada, T. Effect of antibiotic susceptibility and CYP3A4/5 and CYP2C19 genotype on the outcome of vonoprazan-containing Helicobacter pylori eradication therapy. Antibiotics 2020, 9, 645. [CrossRef] [PubMed]

28. Murakami, K.; Sakurai, Y.; Shiino, M.; Funao, N.; Nishimura, A.; Asaka, M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: A phase III, randomised, double-blind study. Gut 2016, 65, 1439–1446. [CrossRef]

29. Sugimoto, M.; Yamaoka, Y. Role of vonoprazan in Helicobacter pylori eradication therapy in Japan. Front. Pharmacol. 2019, 9, 1560. [CrossRef] [PubMed]

30. Nishizawa, T.; Nishizawa, Y.; Yahagi, N.; Kanai, T.; Takahashi, M.; Suzuki, H. Effect of supplementation with rebamipide for Helicobacter pylori eradication therapy: A systematic review and meta-analysis. J. Gastroenterol. Hepatol. 2014, 29, 20–24. [CrossRef]

31. Moher, D.; Jadad, A.R.; Nichol, G.; Penman, M.; Tugwell, P.; Walsh, S. Assessing the quality of randomized controlled trials: An annotated bibliography of scales and checklists. Control. Clin. Trials 1995, 16, 62–73. [CrossRef]

32. Nishizawa, T.; Mori, K.; Yoshida, S.; Ebinuma, H.; Toyoshima, O.; Suzuki, H. Additional mosapride to proton pump inhibitor for gastroesophageal reflux disease: A meta-analysis. J. Clin. Med. 2020, 9, 2705. [CrossRef]

33. Andreev, D.N.; Maey, I.V.; Dicheva, D.T. Efficacy of the inclusion of rebamipide in the eradication therapy for Helicobacter pylori infection: Meta-analysis of randomized controlled studies. J. Clin. Med. 2019, 8, 1498. [CrossRef] [PubMed]

34. Nishizawa, T.; Suzuki, H.; Higuchi, H.; Ebinuma, H.; Toyoshima, O. Effects of encircled abdominal compression device in colonoscopy: A meta-analysis. J. Clin. Med. 2020, 9, 11. [CrossRef] [PubMed]

35. Sue, S.; Sasaki, T.; Kaneko, H.; Irie, K.; Kondo, M.; Maeda, S. Helicobacter pylori rescue treatment with vonoprazan, metronidazole, and sitafoxacin in the presence of penicillin allergy. JGH Open 2021, 5, 307–311. [CrossRef] [PubMed]

36. Mori, H.; Suzuki, H.; Matsuzaki, J.; Masaoka, T.; Kanai, T. Antibiotic resistance and gyrA mutation affect the efficacy of 10-day sitafoxacin-metronidazole-esomeprazole therapy for Helicobacter pylori in penicillin allergic patients. United Eur. Gastroenterol. J. 2017, 5, 796–804. [CrossRef]

37. Ono, S.; Kato, M.; Nakaqawa, S.; Mabe, K.; Sakamoto, N. Vonoprazan improves the efficacy of Helicobacter pylori eradication therapy with a regimen consisting of clarithromycin and metronidazole in patients allergic to penicillin. Helicobacter 2017, 22, e12374. [CrossRef] [PubMed]

38. Furuta, T.; Sugimoto, M.; Yamade, M.; Uotani, T.; Sahara, S.; Ichikawa, H.; Kagami, T.; Yamada, T.; Osawa, S.; Sugimoto, K.; et al. Eradication of H. pylori infection in patients allergic to penicillin using triple therapy with a PPI, metronidazole and sitafoxacin. Intern. Med. 2014, 53, 571–575. [CrossRef]
40. Tokunaga, K.; Tanaka, A.; Takahashi, S. Clinical problems of *H. pylori* eradication therapy after application expansion of the health insurance. *J. Germfree Life Gnotobiol.* 2014, 44, 38–40.

41. Ikeda, F. Antibioactivity of sitafloxacin to *Helicobacter pylori*. *Jpn. J. Helicobacter Res.* 2011, 12, 58–62.

42. Athamna, A.; Athamna, M.; Meledj, B.; Bast, D.J.; Rubinstein, E. In vitro post-antibiotic effect of fluoroquinolones, macrolides, beta-lactams, tetracyclines, vancomycin, clindamycin, linezolid, chloramphenicol, quinupristin/dalfopristin and rifampicin on *Bacillus anthracis*. *J. Antimicrob. Chemother.* 2004, 53, 609–615. [CrossRef]

43. Nishizawa, T.; Suzuki, H.; Maekawa, T.; Harada, N.; Toyokawa, T.; Kuwai, T.; Ohara, M.; Suzuki, T.; Kawanishi, M.; Noguchi, K.; et al. Dual therapy for third-line *Helicobacter pylori* eradication and urea breath test prediction. *World J. Gastroenterol.* 2012, 18, 2735–2738. [CrossRef]

44. Furuta, T.; Sugimoto, M.; Yamade, M.; Uotani, T.; Sahara, S.; Ichikawa, H.; Yamada, T.; Osawa, S.; Sugimoto, K.; Watanabe, H.; et al. Effect of dosing schemes of amoxicillin on eradication rates of *Helicobacter pylori* with amoxicillin-based triple therapy. *J. Clin. Pharmacol.* 2014, 54, 258–266. [CrossRef]

45. Yuan, Y.; Ford, A.C.; Khan, K.J.; Gisbert, J.P.; Forman, D.; Leontiadis, G.I.; Tse, F.; Calvet, X.; Fallone, C.; Fischbach, L.; et al. Optimum duration of regimens for *Helicobacter pylori* eradication. *Cochrane Database Syst. Rev.* 2010, 12, 008337.

46. Noh, H.M.; Hong, S.J.; Han, J.P.; Park, K.W.; Lee, Y.N.; Lee, T.H.; Ko, B.M.; Lee, J.S.; Lee, M.S. Eradication rate by duration of third-line therapy with levofloxacin treatment after *Helicobacter pylori* treatment failure in clinical practice. *Korean J. Gastroenterol.* 2016, 68, 260–264. [CrossRef]

47. Ercin, C.N.; Uygun, A.; Toros, A.B.; Kantarcıoglu, M.; Kilciler, G.; Polat, Z.; Bagci, S. Comparison of 7- and 14-day first-line therapies including levofloxacin in patients with *Helicobacter pylori* positive non-ulcer dyspepsia. *Turk. J. Gastroenterol.* 2010, 21, 12–16. [CrossRef]

48. Miehlke, S.; Krasz, S.; Schneider-Bracht, W.; Kuhlisch, E.; Berning, M.; Madisch, A.; Laass, M.W.; Neumeyer, M.; Jębens, C.; Zekorn, C.; et al. Randomized trial on 14 versus 7 days of esomeprazole, moxifloxacin, and amoxicillin for second-line or rescue treatment of *Helicobacter pylori* infection. *Helicobacter* 2011, 16, 420–426. [CrossRef]

49. Li, B.Z.; Threapleton, D.E.; Wang, J.Y.; Xu, J.M.; Yuan, J.Q.; Zhang, C.; Li, P.; Ye, Q.L.; Guo, B.; Mao, C.; et al. Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: Systematic review and network meta-analysis. *BMJ* 2015, 351, h4052. [CrossRef]

50. Chuah, S.K.; Tai, W.C.; Hsu, P.I.; Wu, D.C.; Wu, K.L.; Kuo, C.M.; Chiu, Y.C.; Hu, M.L.; Chou, Y.P.; Kuo, Y.H.; et al. The efficacy of second-line anti-*Helicobacter pylori* therapy using an extended 14-day levofloxacin/amoxicillin/proton-pump inhibitor treatment—A pilot study. *Helicobacter* 2012, 17, 374–381. [CrossRef]

51. Liao, J.; Zheng, Q.; Liang, X.; Zhang, W.; Sun, Q.; Liu, W.; Xiao, S.; Graham, D.Y.; Lu, H. Effect of fluoroquinolone resistance on 14-day levofloxacin triple and triple plus bismuth quadruple therapy. *Helicobacter* 2013, 18, 373–377. [CrossRef]

52. Ozdil, K.; Calhan, T.; Sahin, A.; Senators, E.; Kahraman, R.; Yuzbasioğlu, B.; Demirdag, H.; Demirsoy, H.; Sokmen, M.H. Levofloxacin based sequential and triple therapy compared with standard plus probiotic combination for *Helicobacter pylori* eradication. *Hepatogastroenterology* 2011, 58, 1148–1152. [CrossRef] [PubMed]

53. Nishizawa, T.; Suzuki, H.; Kurabayashi, K.; Masaoka, T.; Muraoka, H.; Mori, M.; Iwasaki, E.; Kobayashi, I.; Hibi, T. Gatifloxacin resistance and mutations in gyrB after unsuccessful *Helicobacter pylori* eradication. *World J. Gastroenterol.* 2013, 19, 36–42. [CrossRef]

54. Oro, B.Z.; Threapleton, D.E.; Wang, J.Y.; Xu, J.M.; Yuan, J.Q.; Zhang, C.; Li, P.; Ye, Q.L.; Guo, B.; Mao, C.; et al. Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: Systematic review and network meta-analysis. *BMJ* 2015, 351, h4052. [CrossRef]

55. Rimbara, E.; Noguchi, N.; Kawai, T.; Sasatsu, M. Fluoroquinolone resistance in *Helicobacter pylori*: Role of mutations at position 87 and 91 of GyrA on the level of resistance and identification of a resistance conferring mutation in GyrB. *Helicobacter* 2012, 17, 36–42. [CrossRef] [PubMed]

56. Nishizawa, T.; Suzuki, H.; Mechanisms of *Helicobacter pylori* antibiotic resistance and molecular testing. *Front. Mol. Biosci.* 2014, 1, 19. [CrossRef]

57. Nishizawa, T.; Suzuki, H.; Umezawa, A.; Muraoka, H.; Iwasaki, E.; Masaoka, T.; Kobayashi, I.; Hibi, T. Rapid detection of point mutations conferring resistance to fluoroquinolone in gyrA of *Helicobacter pylori* by allele-specific PCR. *J. Clin. Microbiol.* 2006, 45, 303–305. [CrossRef]

58. Mori, H.; Suzuki, H.; Matsuoka, J.; Masaoka, T.; Kanai, T. Acquisition of double mutation in gyrA caused high resistance to sitafloxacin in *Helicobacter pylori* after unsuccessful eradication with sitafloxacin-containing regimens. *United Eur. Gastroenterol. J.* 2018, 6, 391–397. [CrossRef]

59. Hirata, Y.; Yamada, A.; Niikura, R.; Shichijo, S.; Hayakawa, Y.; Koike, K. Efficacy and safety of a new rifabutin-based triple therapy with vonoprazan for refractory *Helicobacter pylori* infection: A prospective single-arm study. *Helicobacter* 2020, 25, e12719. [CrossRef]

60. Gingold-Belfer, R.; Niv, Y.; Levi, Z.; Boltin, D. Rifabutin triple therapy for first-line and rescue treatment of *Helicobacter pylori* infection: A systematic review and meta-analysis. *J. Gastroenterol. Hepatol.* 2020. [CrossRef]
61. Nishizawa, T.; Suzuki, H.; Matsuzaki, J.; Muraoka, H.; Tsugawa, H.; Hirata, K.; Hibi, T. Helicobacter pylori resistance to rifabutin in the last 7 years. *Antimicrob. Agents Chemother.* **2011**, *55*, 5374–5375. [CrossRef] [PubMed]

62. Buehrle, D.J.; Wagener, M.M.; Clancy, C.J. Outpatient fluoroquinolone prescription fills in the United States, 2014–2020: Assessing the impact of food and drug administration safety warnings. *Antimicrob. Agents Chemother.* **2021**. [CrossRef] [PubMed]