

Research Article

The Efficacy, Safety, and Tolerability of Levofloxacin Quadruple Therapy for *Helicobacter pylori* Eradication: A Randomized, Double-Blind Clinical Trial

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The incidence of microbial resistance is growing, and new rescue regimens are needed to treat *Helicobacter pylori* (*H. pylori*) infection. This study aimed to evaluate levofloxacin-based quadruple therapies' efficacy, safety, and tolerability in eradicating *H. pylori*. In a randomized, double-blind clinical trial, 220 patients with dyspepsia and *H. pylori* infection were randomly assigned to receive either bismuth subcitrate 240 mg, pantoprazole 20 mg, amoxicillin 1000 mg twice a day, and levofloxacin 500 mg daily for seven days (BPAL-7) or ten days (BPAL-10). The eradication of *H. pylori* was evaluated two months after the end of treatment, and adverse drug reactions (ADRs) were assessed during the intervention. According to intention-to-treat and per-protocol, the eradication rate was significantly lower in the BPAL-7 regimen at 49.1% (95% CI: 39.3–57.8) and 47.6% (95% CI: 39.7–58.4), respectively, compared to the BPAL-10 regimen at 62.7% (95% CI: 53.6–72.8) and 62.4% (95% CI: 55.1–72.8), respectively. The ADR incidence was not statistically significant between the groups of BPAL-7 (33.6%) and BPAL-10 (36.7%). Although the ADRs were negligible in both groups, these regimens could not be an ideal alternative therapy for *H. pylori* because of their low eradication rates compared to standard regimens. *Trial Registration*. The study was reviewed and approved by the Iranian Registry of Clinical Trials (IRCT201406141155N19).

1. Introduction

Helicobacter pylori (*H. pylori*) affects about 80% of the total population in developing countries and 20–50% in developed countries [1]. This infection, as a worldwide health problem, is associated with acute and chronic gastritis, peptic ulcer disease, and gastric cancer [2–4]. The eradication of *H. pylori* has a main role in the prevention and treatment of these complications [5, 6]. However, the major concerns with *H. pylori* treatment are low compliance of

patients, adverse drug reactions (ADRs), and microbial resistance to medicines [7, 8].

The efficacy of present pharmacological treatments for *H. pylori* infection has been evaluated in different studies [9–15]. The co-administration of a proton-pump inhibitor (PPI) and two antibiotics (triple therapy) or the addition of bismuth salts to the triple therapy (bismuth-based quadruple therapy) for a period of 14 days is the most common regimens [16]. Among antibacterial agents, amoxicillin or metronidazole, along with clarithromycin, is the first-line

treatment for the eradication of *H. pylori* [10, 17]. Nevertheless, microbial resistance is one of the challenging factors of treatment, which causes the low efficacy of these regimens. Hence, effective antibiotics should be selected according to the regional pattern of *H. pylori* resistance [18, 19].

The prevalence of *H. pylori* infection is relatively high among the Iranian population [20, 21]. Moreover, novel strains that resist clarithromycin and metronidazole are prevalent in some geographical parts of Iran [22, 23]. Therefore, evidence suggested new antibiotic regimens with higher efficacy (eradication rates of >80%), lower ADRs and cost, and acceptable patient compliance. The efficacy of levofloxacin as a new-generation quinolone in the treatment of *H. pylori* infection has been assessed in several studies, and levofloxacin-containing regimens have shown various eradication rates [24–30].

The current study aimed to evaluate the efficacy, safety, and tolerability of a seven- and ten-day period of bismuth subcitrate, pantoprazole, amoxicillin, and levofloxacin regimens in the eradication of *H. pylori* among patients referred to the Gastrointestinal Outpatient Clinic of Razi Hospital, Rasht, Iran.

2. Methods

2.1. Trial Design. This study was a phase III open-label, randomized, double-blind, controlled trial carried out between July 2015 and November 2015 at the Gastrointestinal and Liver Diseases Research Center (GLDRC), Rasht, Iran. All included participants were randomly divided into one of the therapeutic regimens and signed informed consent. The eradication rate of *H. pylori* was assessed two months after the end of the intervention, and the incidence of ADRs and patient compliance were assessed at the end of treatment.

2.2. Ethical Consideration. The protocol of the study was approved by the local ethical committee of Guilan University of Medical Sciences (Ethics Committee Code: 1930175713) and also performed according to the Declaration of Helsinki for human subjects. The study was reviewed and approved by the Iranian Registry of Clinical Trials (IRCT201406141155N19).

2.3. Patients. Patients complaining of dyspeptic symptoms referred to the Gastrointestinal Outpatient Clinic of Razi Hospital, Rasht, Iran, were enrolled. The main inclusion criteria were a positive rapid urease test and being 15 to 65 years old. Patients with coexisting serious illnesses, including liver cirrhosis, renal failure, heart failure, gastrointestinal malignancies, a history of seizure or hematologic diseases, an allergy to medications, and an previous incomplete treatment course, as well as pregnant or nursing mothers, were excluded.

2.4. Randomization and Intervention. A block randomization method was used in order to assign patients randomly into permuted treatment blocks and ensure equal numbers

in each group of treatments. One of these groups received a seven-day period of bismuth subcitrate 240 mg, pantoprazole 20 mg, amoxicillin 1000 mg twice a day, and levofloxacin 500 mg daily (BPAL-7), and the other received a ten-day period of the same regimen (BPAL-10).

Patients were recommended to take bismuth subcitrate, pantoprazole, levofloxacin before meals and amoxicillin after meals at the scheduled times. It was also advised to avoid smoking, drinking alcoholic or caffeinated beverages, eating spicy foods, and taking nonsteroidal anti-inflammatory drugs or medications containing a monoamine oxidase inhibitor.

Demographic criteria, including age, gender, cigarette smoking, and alcohol drinking, were recorded.

2.5. Evaluation of *H. pylori* Eradication. Two months after the end of the intervention, a Heliprobe 14C-Urea Breath Test (14C-UBT, Kibion AB, Uppsala, Sweden) with a 95% sensitivity and 100% specificity was performed to evaluate the *H. pylori* eradication. Treatment success was defined as the result of <50 disintegrations per minute (DPM). Taking the medicines was stopped during these two months to avoid interaction with the results of 14C-UBT.

2.6. Assessment of ADRs and Patient Compliance. All patients were informed about potential ADRs, including pyrosis, anorexia, nausea, vomiting, bitter taste, abdominal colic, epigastric pain, headache, and back pain. The ADRs were evaluated during the intervention using a 0–10 scoring system (mild: 0–3, the ADRs exist but are intolerable; moderate: 4–6, ADRs sometimes interfere with daily life activity; severe: 7–10, ADRs interfere continuously with daily life activities). Acceptable patient compliance was defined as the consumption of >80% of the prescribed medicines [31].

2.7. Statistical Analyses. The eradication rates of the two regimens were determined using intention-to-treat (ITT) and per-protocol (PP) analysis. Patients who declined to proceed with the treatment or those with poor compliance were excluded from PP analysis; however, all patients, including patients who used the treatments out of the protocols or dropouts, were included in ITT analysis. The eradication rate of *H. pylori*, odd ratios, and 95% confidence interval were evaluated for each regimen. Chi-square and *t*-tests were employed to compare qualitative and quantitative variables between the two treatment groups, respectively. All statistical analyses were performed using SPSS, version 18.0 software (SPSS Inc., Chicago, IL, United States). A $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the Patients. A total of 220 patients with *H. pylori* infection were randomly assigned to either the BPAL-7 ($n = 110$) or BPAL-10 ($n = 110$) groups. Three patients in the BPAL-7 group (one female with severe

epigastric pain and diarrhoea and two males with severe anorexia and back pain) and one patient in the BPAL-10 group (one female with severe epigastric pain and nausea) were excluded from the trial because of drug intolerance and low compliance. A flow diagram describing patient selection and study outcomes is shown in Figure 1.

No significant differences were observed between the two groups regarding age, gender, cigarette smoking, and alcohol drinking ($P > 0.05$). The basic demographic characteristics of the patients are demonstrated in Table 1.

3.2. Eradication Rates. The eradication rate of the BPAL-7 regimen (49.1%, 95% CI: 39.3–57.8) was lower than that of the BPAL-10 regimen (62.7%, 95% CI: 53.6–72.8) on ITT analysis (OR = 1.75, $P < 0.05$). In addition, PP analysis also demonstrated a lower eradication rate in the BPAL-7 regimen (47.6%, 95% CI: 39.7–58.4) than that of the BPAL-10 regimen (62.4%, 95% CI: 55.1–72.8) (OR = 0.54, $P < 0.05$). The eradication rates of the two regimens are represented in Table 2. Univariate analyses showed no association between age, gender, cigarette smoking, and alcohol drinking with an eradication rate of *H. pylori* in both groups ($P > 0.05$).

3.3. ADRs and Patient Compliances. Both BPAL-7 and BPAL-10 regimens were well tolerated by a majority of patients. The number of patients with ADRs was not statistically significant between the BPAL-7 group (36 patients, 33.6%) and the BPAL-10 group (40 patients, 36.7%). ADRs were rated as mild (55 patients, 25%), moderate (17 patients, 7.7%), and severe (4 patients, 1.8%). Both regimens' most-reported ADRs were epigastric pain, nausea, vomiting, and bitter taste (Table 3).

The compliance rates were 97.3% and 99.1% for the BPAL-7 and BPAL-10 regimens, respectively. Three patients in the BPAL-7 regimen and one in the BPAL-10 regimen were excluded from the PP analysis because they failed to ingest >80% of the medications.

4. Discussion

The present study's findings showed a lower rate of *H. pylori* eradication in the BPAL-7 regimen than in the BPAL-10 regimen among patients with dyspepsia and *H. pylori* infection. Both BPAL-7 and BPAL-10 regimens were well tolerated and had acceptable patient compliance.

Recent guidelines suggest the eradication rate of triple therapy with a PPI, amoxicillin, or metronidazole and clarithromycin as first-line regimens has decreased, particularly due to increased microbial resistance to clarithromycin [2]. Moreover, some recommended bismuth-based quadruple therapy regimens also have an eradication rate of less than 80% [32]. Therefore, more effective regimens are needed to eradicate the *H. pylori* infection.

Evidence suggests using levofloxacin, a new-generation fluoroquinolone with in vitro anti-*H. pylori* activity, as an alternative agent in clarithromycin-resistant cases. Levofloxacin-containing triple, quadruple, and sequential

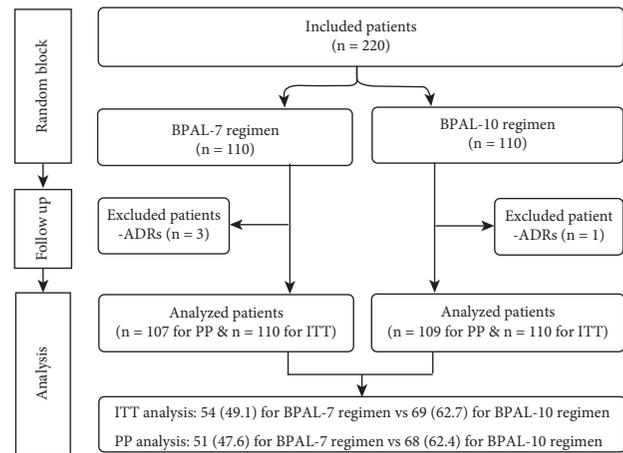


FIGURE 1: Flow chart for the process of patient randomization. ITT: intention-to-treat, PP: per-protocol, ADRs: adverse drug reactions, and BPAL-7 and BPAL-10: bismuth-based quadruple therapy containing pantoprazole, amoxicillin, and levofloxacin for seven and ten days, respectively.

regimens have demonstrated various eradication rates [33–35].

A study compared a triple therapy consisting of esomeprazole, levofloxacin (500 mg daily), and amoxicillin with a standard regimen consisting of esomeprazole, metronidazole, bismuth, and tetracycline for 14 days. The eradication rate of the levofloxacin-containing regimen (96.3%) was higher than of the standard regimen (86.0%) in ITT analysis [25].

Gisbert et al. from Spain demonstrated the eradication rate of ranitidine bismuth citrate, levofloxacin, and amoxicillin as first-line triple therapy for *H. pylori* was 84.4, and ADRs, mainly including diarrhea, were reported in 9.5% of the patients [36]. This group performed a trial with 1000 patients on the efficacy of omeprazole, levofloxacin, and amoxicillin for ten days. They reported an eradication rate of 73.8% and ADRs of 20%, which most commonly included nausea, a metallic taste, and abdominal pain [26]. The levofloxacin dosage was higher in these studies (500 mg twice daily). In a recent multicenter study conducted by Gisbert et al., 14 days of treatment with esomeprazole, amoxicillin, levofloxacin (500 mg daily), and bismuth as a rescue therapy achieved more than 90% of the eradication rate [27]. In another Spanish study, the eradication rate of omeprazole, levofloxacin (500 mg twice a day), and amoxicillin for ten days also had about a 20% failure rate [37].

A study from Kosovo randomized 105 patients to undergo either seven or ten days of levofloxacin-based regimens, including omeprazole, levofloxacin (500 mg daily), and amoxicillin. The eradication rates were 86.2% and 93.6%, respectively. About 5% of patients experienced ADRs, mainly nausea and diarrhea [28].

Several Taiwanese studies evaluated the efficacy of levofloxacin-containing regimens as rescue therapy for eradicating *H. pylori*. Kuo et al. reported the eradication rate of esomeprazole, amoxicillin, and levofloxacin (500 mg daily) regimen for seven days is similar to a second-

TABLE 1: Demographic characteristics of the study patients.

Characteristics	BPAL-7 regimen (<i>n</i> = 107)	BPAL-10 regimen (<i>n</i> = 109)	<i>P</i> value
Gender, male	39 (36.5)	40 (36.7)	0.888
Age	41.46 ± 13.25	44.16 ± 12.70	0.649
Cigarette smoking			
Yes	4 (3.7)	7 (6.4)	0.353
No	103 (96.3)	102 (93.6)	
Alcohol drinking			
Yes	1 (0.9)	3 (2.7)	0.313
No	106 (99.1)	106 (97.3)	

Values were demonstrated as numbers (percentages) and mean ± SD for categorical and continuous variables, respectively. Chi-square and *t*-tests were performed to compare categorical and continuous variables between groups, respectively. BPAL-7 and BPAL-10: bismuth-based quadruple therapies containing pantoprazole, amoxicillin, and levofloxacin for seven and ten days, respectively.

TABLE 2: The eradication rates of the BPAL-7 and BPAL-10 regimens.

Analyses	BPAL-7 regimen (<i>n</i> = 107)	BPAL-10 regimen (<i>n</i> = 109)	<i>P</i> value
Intention-to-treat	54 (49.1)	69 (62.7)	0.037
Per-protocol	51 (47.6)	68 (62.4)	0.024

Values were demonstrated as numbers (percentages). ¹⁴C-urea breath test was conducted to confirm the eradication of *H. pylori* two months after the end of treatment. A Chi-square test was performed to compare variables between groups. BPAL-7 and BPAL-10: bismuth-based quadruple therapies containing pantoprazole, amoxicillin, and levofloxacin for seven and ten days, respectively.

TABLE 3: The adverse drug reactions associated with the BPAL-7 and BPAL-10 regimens.

ADRs	BPAL-7 (<i>n</i> = 107)			BPAL-10 (<i>n</i> = 109)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Pyrosis	31 (29.0)	4 (3.7)	1 (0.9)	23 (21.1)	10 (9.2)	1 (0.9)
Anorexia	25 (23.4)	4 (3.7)	2 (1.9)	21 (19.3)	4 (3.7)	1 (0.9)
Nausea	19 (17.8)	2 (1.8)	1 (0.9)	25 (22.9)	0 (0.0)	0 (0.0)
Vomiting	2 (1.9)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Bitter taste	19 (17.8)	0 (0.0)	1 (0.9)	10 (9.2)	2 (1.8)	1 (0.9)
Abdominal colic	12 (11.2)	0 (0.0)	0 (0.0)	9 (8.2)	3 (2.7)	0 (0.0)
Epigastric pain	17 (15.9)	7 (6.5)	1 (0.9)	22 (20.2)	3 (2.7)	1 (0.9)
Headache	15 (14.0)	2 (1.9)	1 (0.9)	16 (14.7)	7 (6.4)	1 (0.9)
Back pain	6 (5.6)	1 (0.9)	2 (1.9)	9 (8.3)	6 (5.5)	1 (0.9)

Values were demonstrated as numbers (percentages). Adverse drug reactions were evaluated during the study. Chi-square test was performed to compare variables between groups. None of variables were shown statistically significant differences between two regimens in each category. ADRs: adverse drug reactions; BPAL-7 and BPAL-10: bismuth-based quadruple therapies containing pantoprazole, amoxicillin, and levofloxacin for seven and ten days, respectively.

linequadruple standard regimen (about 60–70%) [38]. Four years later, the same group published a study comparing levofloxacin-containing quadruple therapy (esomeprazole, bismuth, tetracycline, and 500 mg of levofloxacin once daily) for ten days with a high-dose metronidazole-containing standard quadruple regimen. Based on their findings, eradication rates of about 80% were reached for both regimens [39]. On the other hand, Hsu et al. showed a ten-day quadruple therapy consisting of esomeprazole, bismuth, tetracycline, and levofloxacin (500 mg daily) achieved a very high eradication rate (95.8%) in this geographical area. ADRs were detected in 25.0% of patients [40]. In another study, the efficacy of adding bismuth to a levofloxacin-based triple regimen (rabeprazole, bismuth, amoxicillin, and 500 mg of levofloxacin daily) was assessed. The results revealed no further significant eradication rate (67.6%), but no more ADRs were noted [41].

According to the results of the present study, the BPAL-7 and BPAL-10 regimens were not clinically successful in the treatment of *H. pylori*, with an eradication rate of 62.7% and

49.1% by ITT analyses, respectively. Both regimens achieved neither the cut point of an ideal regimen (eradication rates of >90%) nor the acceptable eradication rates of Maastricht and other guidelines (>80%) [42]. The low efficacy of these regimens is likely related to the regional pattern of bacterial resistance. The results of these regimens are consistent with a previous Iranian study evaluating the effectiveness of a 14-day triple therapy comprising omeprazole, levofloxacin (500 mg daily), and amoxicillin with a success rate of 75% [43]. However, studies conducted in other parts of Iran revealed fluoroquinolone-containing regimens, including a 14-day of omeprazole, levofloxacin (250 mg twice a day), and amoxicillin, as well as a 14-day of omeprazole, levofloxacin (500 mg twice a day), and amoxicillin as rescue therapies for *H. pylori*, had eradication rates of 90% and 86.7%, respectively [44, 45]. Moreover, some other Iranian investigations evaluated the efficacy of levofloxacin-based, sequential therapy in treating *H. pylori*, and the eradication rate ranged from 70.8% to 85.1% [46–48].

No relationship was observed between patient demographic characteristics, including age, gender, cigarette smoking, and alcohol drinking, and the success rate of both the BPAL-7 and BPAL-10 regimens. Previous studies have also demonstrated the eradication rate of levofloxacin-containing regimens was not associated with age [45, 46, 48], gender [45–47], smoking status [25, 46], and education level [46].

Although high efficacy and compatibility with the pattern of regional bacterial resistance are the main properties of an ideal pharmacological regimen for eradicating *H. pylori*, tolerability, patient compliance, simplicity, and cost efficacy should not be neglected [31]. The compliance rates for the BPAL-7 and BPAL-10 regimens were 97.3% and 99.1%, respectively. Despite high compliance rates, ADRs were reported in one-third of patients. The most-reported ADRs were epigastric pain, nausea, vomiting, and bitter taste. Generally, BPAL-7 and BPAL-10 regimens were patient-compatible and well-tolerated.

4.1. Limitations. The main limitations of the present study are the lack of a regional pattern of antibiotic resistance and a local estimate of the *H. pylori* eradication rate, as well as the small number of patients in the groups. The absence of pretreatment susceptibility assessment for levofloxacin is another drawback. Moreover, the finding may not apply to patients with previous treatment failure and recurrence of the disease.

5. Conclusion

The BPAL-7 and BPAL-10 regimens were patient-compatible and well-tolerated. However, both regimens showed no satisfactory eradication rate. Therefore, these regimens could not be definitive alternative therapies for *H. pylori* eradication in this region. It is better to evaluate the efficacy and tolerability of this regimen in other geographical areas through more extended studies with a larger sample size.

Abbreviations

H. pylori: *Helicobacter pylori*

ADRs: Adverse drug reactions

PPI: Proton-pump inhibitor

ITT: Intention-to-treat

PP: Per-protocol

BPAL-7: Bismuth-based quadruple therapy containing pantoprazole, amoxicillin, and levofloxacin for seven days

BPAL-10: Bismuth-based quadruple therapy containing pantoprazole, amoxicillin, and levofloxacin for ten days.

Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure

A preprint has previously been published [49]. Guilan University of Medical Sciences had no role in the execution of the study, patient recruitment, or data collection.

Conflicts of Interest

The authors declare that they have no conflicts of interest in this work.

Authors' Contributions

FJ and FMG designed and supervised the procedure of the research. FMG, HS, and BM enrolled participants, and collected data. FJ, SH, and HS analyzed data, and MF, FJ, MA, AMG, and HS drafted the manuscript. MF, SH, and AMG edited and revised the manuscript. All authors have read and approved the final draft of the paper.

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References

- [1] B. A. Salih, "Helicobacter pylori infection in developing countries: the burden for how long?" *Saudi Journal of Gastroenterology*, vol. 15, no. 3, pp. 201–207, 2009.
- [2] W. D. Chey and B. C. Wong, "American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection," *American Journal of Gastroenterology*, vol. 102, no. 8, pp. 1808–1825, 2007.
- [3] K. M. Fock, P. Katelaris, K. Sugano et al., "Second Asia–Pacific consensus guidelines for *Helicobacter pylori* infection," *Journal of Gastroenterology and Hepatology*, vol. 24, no. 10, pp. 1587–1600, 2009.
- [4] S. Shafaie, H. Kaboosi, and F. Peyravii Ghadikolaii, "Prevalence of non *Helicobacter pylori* gastric Helicobacters in Iranian dyspeptic patients," *BMC Gastroenterology*, vol. 20, no. 1, 190 pages, 2020.
- [5] M. Khatibian, Y. Ajvadi, S. Nasser-Moghaddam et al., "Furazolidone-based, metronidazole-based, or a combination regimen for eradication of *Helicobacter pylori* in peptic ulcer disease," *Archives of Iranian Medicine*, vol. 10, no. 2, pp. 161–167, 2007.
- [6] P. Malfertheiner, F. Megraud, C. A. O'morain et al., "Management of *Helicobacter pylori* infection—the Maastricht IV/Florence consensus report," *Gut*, vol. 61, no. 5, pp. 646–664, 2012.
- [7] S. Karatapanis, L. Skorda, S. Georgopoulos et al., "Levofloxacin-based triple therapy versus bismuth-based quadruple therapy as a second line treatment for the eradication of *H. pylori* infection," *Annals of Gastroenterology*, vol. 22, no. 4, pp. 263–267, 2009.

- [8] W. Wu, Y. Yang, and G. Sun, "Recent insights into antibiotic resistance in *Helicobacter pylori* eradication," *Gastroenterology Research and Practice*, vol. 2012, no. 1, Article ID 723183, pp. 1–8, 2012.
- [9] L. A. Fischbach, S. V. van Zanten, and J. Dickason, "Meta-analysis: the efficacy, adverse events, and adherence related to first-line anti-*Helicobacter pylori* quadruple therapies," *Alimentary Pharmacology & Therapeutics*, vol. 20, no. 10, pp. 1071–1082, 2004.
- [10] J. P. Gisbert, L. Gonzalez, X. Calvet et al., "Proton pump inhibitor, clarithromycin and either amoxicillin or nitroimidazole: a meta-analysis of eradication of *Helicobacter pylori*," *Alimentary Pharmacology & Therapeutics*, vol. 14, no. 10, pp. 1319–1328, 2000.
- [11] H. J. Ahn, D. P. Kim, M. S. Chu et al., "Efficacy and safety of the triple therapy containing ilaprazole, levofloxacin, and amoxicillin as first-line treatment in *Helicobacter pylori* infections," *Gastroenterology Research and Practice*, vol. 2017, Article ID 1654907, 6 pages, 2017.
- [12] W. C. Tai, C. H. Chiu, C. M. Liang et al., "Ten-day versus 14-day levofloxacin-containing triple therapy for second-line anti-*Helicobacter pylori* eradication in taiwan," *Gastroenterology Research and Practice*, vol. 2013, pp. 1–6, 2013.
- [13] A. Ohno, J. Miyoshi, A. Kato et al., "Endoscopic severe mucosal atrophy indicates the presence of gastric cancer after *Helicobacter pylori* eradication -analysis based on the Kyoto classification," *BMC Gastroenterology*, vol. 20, no. 1, p. 232, 2020.
- [14] Z. Song, W. Fu, and L. Zhou, "Cefuroxime, levofloxacin, esomeprazole, and bismuth as first-line therapy for eradicating *Helicobacter pylori* in patients allergic to penicillin," *BMC Gastroenterology*, vol. 19, no. 1, p. 132, 2019.
- [15] J. D. Kabakambira, C. Hategeka, C. Page et al., "Efficacy of *Helicobacter pylori* eradication regimens in Rwanda: a randomized controlled trial," *BMC Gastroenterology*, vol. 18, no. 1, p. 134, 2018.
- [16] D. Y. Graham and S.-Y. Lee, "How to effectively use bismuth quadruple therapy: the good, the bad, and the ugly," *Gastroenterology Clinics of North America*, vol. 44, no. 3, pp. 537–563, 2015.
- [17] F. Mansour-Ghanaei, A. Samadi, F. Joukar et al., "Efficacy and tolerability of fourteen-day sequential quadruple regimen: pantoprazole, bismuth, amoxicillin, metronidazole and or furazolidone as first-line therapy for eradication of *Helicobacter pylori*: a randomized, double-blind clinical trial," *EXCLI J*, vol. 18, no. 1, pp. 644–652, 2019.
- [18] F. Megraud, "H pylori antibiotic resistance: prevalence, importance, and advances in testing," *Gut*, vol. 53, no. 9, pp. 1374–1384, 2004.
- [19] W. Qureshi and D. Graham, "Antibiotic-resistant *H. pylori* infection and its treatment," *Current Pharmaceutical Design*, vol. 6, no. 15, pp. 1537–1544, 2000.
- [20] S. Jafar, A. Jalil, N. Soheila, and S. Sirous, "Prevalence of helicobacter pylori infection in children, a population-based cross-sectional study in west Iran," *Iranian Journal of Pediatrics (Persian edition)*, vol. 23, no. 1, pp. 13–18, 2013.
- [21] M. Nouraie, S. Latifi-Navid, H. Rezvan et al., "Childhood hygienic practice and family education status determine the prevalence of *Helicobacter pylori* infection in Iran," *Helicobacter*, vol. 14, no. 1, pp. 40–46, 2009.
- [22] H. Salmanroghani, M. Mirvakili, M. Baghbanian, R. Salmanroghani, G. Sanati, and P. Yazdian, "Efficacy and tolerability of two quadruple regimens: bismuth, omeprazole, metronidazole with amoxicillin or tetracycline as first-line treatment for eradication of *Helicobacter pylori* in patients with duodenal ulcer: a randomized clinical trial," *PLoS One*, vol. 13, no. 6, Article ID e0197096, 2018.
- [23] N. Ebrahimi-Darjani, S. Mirmomen, F. Mansour-Ghanaei et al., "The efficacy of furazolidone-based quadruple therapy for eradication of *Helicobacter pylori* infection in Iranian patients resistant to metronidazole-based quadruple therapy," *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, vol. 9, no. 8, pp. 105–108, 2003.
- [24] B. An, B. S. Moon, H. Kim et al., "Antibiotic resistance in *Helicobacter pylori* strains and its effect on *H. pylori* eradication rates in a single center in Korea," *Ann Lab Med*, vol. 33, no. 6, pp. 415–419, 2013.
- [25] S. K. Chuah, W. C. Tai, P. I. Hsu 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*, vol. 17, no. 5, pp. 374–381, 2012.
- [26] J. P. Gisbert, A. Perez-Aisa, F. Bermejo et al., "Second-line therapy with levofloxacin after failure of treatment to eradicate helicobacter pylori infection: time trends in a Spanish Multicenter Study of 1000 patients," *Journal of Clinical Gastroenterology*, vol. 47, no. 2, pp. 130–135, 2013.
- [27] J. P. Gisbert, M. Romano, A. G. Gravina et al., "*Helicobacter pylori* second line rescue therapy with levofloxacin and bismuth containing quadruple therapy, after failure of standard triple or non bismuth quadruple treatments," *Alimentary Pharmacology & Therapeutics*, vol. 41, no. 8, pp. 768–775, 2015.
- [28] S. Telaku, S. Manxhuka-Kerliu, B. Kraja, G. Qirjako, S. Prifti, and H. Fejza, "The efficacy of levofloxacin -based triple therapy for first -line *Helicobacter pylori* eradication," *Medical Archives*, vol. 67, no. 5, pp. 348–350, 2013.
- [29] S. P. Chang, H. Z. Lee, C. C. Lai, and H. J. Tang, "The efficacy and safety of nemonoxacin compared with levofloxacin in the treatment of community-acquired pneumonia: a systemic review and meta-analysis of randomized controlled trials," *Infection and Drug Resistance*, vol. 12, pp. 433–438, 2019.
- [30] C. W. Chen, Y. H. Chen, I. L. Cheng, and C. C. Lai, "Comparison of high-dose, short-course levofloxacin treatment vs. conventional regimen against acute bacterial infection: meta-analysis of randomized controlled trials," *Infection and Drug Resistance*, vol. 12, pp. 1353–1361, 2019.
- [31] P. Malfertheiner, F. Megraud, C. O'Morain et al., "Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III consensus report," *Gut*, vol. 56, no. 6, pp. 772–781, 2007.
- [32] M. Venerito, T. Krieger, T. Ecker, G. Leandro, and P. Malfertheiner, "Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of *Helicobacter pylori* infection," *Digestion*, vol. 88, no. 1, pp. 33–45, 2013.
- [33] P. Y. Chen, M. S. Wu, C. Y. Chen et al., "Systematic review with meta-analysis: the efficacy of levofloxacin triple therapy as the first- or second-line treatments of *Helicobacter pylori* infection," *Alimentary Pharmacology & Therapeutics*, vol. 44, no. 5, pp. 427–437, 2016.
- [34] S. P. Xiao, M. Gu, and G. X. Zhang, "Is levofloxacin-based triple therapy an alternative for first-line eradication of *Helicobacter pylori*? A systematic review and meta-analysis," *Scandinavian Journal of Gastroenterology*, vol. 49, no. 5, pp. 528–538, 2014.
- [35] C. L. Ye, G. P. Liao, S. He, Y. N. Pan, Y. B. Kang, and Z. Y. Zhang, "Levofloxacin and proton pump inhibitor-based

- triple therapy versus standard triple first-line therapy for *Helicobacter pylori* eradication,” *Pharmacoepidemiology and Drug Safety*, vol. 23, no. 5, pp. 443–455, 2014.
- [36] J. P. Gisbert, M. Fernandez-Bermejo, J. Molina-Infante et al., “First-line triple therapy with levofloxacin for *Helicobacter pylori* eradication,” *Alimentary Pharmacology & Therapeutics*, vol. 26, no. 3, pp. 495–500, 2007.
- [37] J. Molina-Infante, B. Perez-Gallardo, M. Fernandez-Bermejo et al., “Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential regimens for *Helicobacter pylori* eradication,” *Alimentary Pharmacology & Therapeutics*, vol. 31, no. 10, pp. 1077–1084, 2010.
- [38] C. H. Kuo, H. M. Hu, F. C. Kuo et al., “Efficacy of levofloxacin-based rescue therapy for *Helicobacter pylori* infection after standard triple therapy: a randomized controlled trial,” *Journal of Antimicrobial Chemotherapy*, vol. 63, no. 5, pp. 1017–1024, 2009.
- [39] C. H. Kuo, P. I. Hsu, F. C. Kuo et al., “Comparison of 10 day bismuth quadruple therapy with high-dose metronidazole or levofloxacin for second-line *Helicobacter pylori* therapy: a randomized controlled trial,” *Journal of Antimicrobial Chemotherapy*, vol. 68, no. 1, pp. 222–228, 2013.
- [40] P. I. Hsu, W. C. Chen, F. W. Tsay et al., “Ten-day Quadruple therapy comprising proton-pump inhibitor, bismuth, tetracycline, and levofloxacin achieves a high eradication rate for *Helicobacter pylori* infection after failure of sequential therapy,” *Helicobacter*, vol. 19, no. 1, pp. 74–79, 2014.
- [41] T. S. Wu, P. I. Hsu, C. H. Kuo et al., “Comparison of 10-day levofloxacin bismuth-based quadruple therapy and levofloxacin-based triple therapy for *Helicobacter pylori*,” *Journal of digestive diseases*, vol. 18, no. 9, pp. 537–542, 2017.
- [42] X. Z. Gao, X. L. Qiao, W. C. Song, X. F. Wang, and F. Liu, “Standard triple, bismuth pectin quadruple and sequential therapies for *Helicobacter pylori* eradication,” *World Journal of Gastroenterology*, vol. 16, no. 34, pp. 4357–4362, 2010.
- [43] A. A. Haji-Aghamohammadi, A. Bastani, A. Miroliaee, S. Oveisi, and S. Safarnejhad, “Comparison of levofloxacin versus clarithromycin efficacy in the eradication of *Helicobacter pylori* infection,” *Caspian J Intern Med*, vol. 7, no. 4, pp. 267–271, 2016.
- [44] G. Abangah, A. Raughani, P. Asadollahi, and K. Asadollahi, “Comparison between the two drug regimens of PPI+Amoxicillin+ Rifampicin and PPI+Amoxicillin+ Levofloxacin for the treatment of *H. pylori* infections resistant to the first line drug regimen among patients referred to Ilam clinics,” *Gastroenterology and hepatology from bed to bench*, vol. 12, no. 3, pp. 209–216, 2019.
- [45] M. Seyyedmajidi, L. Abbasi, S. Seyyedmajidi et al., “Levofloxacin-containing triple therapy versus bismuth-based quadruple therapy as regimens for second line anti- *Helicobacter pylori*,” *Caspian J Intern Med*, vol. 10, no. 2, pp. 211–216, 2019.
- [46] M. Moradniani, Z. Mirbeik-Sabzevari, S. Jaferian et al., “Levofloxacin based vs. clarithromycin based sequential therapy in helicobacter pylori eradication; a randomized clinical trial,” *Gastroenterology and hepatology from bed to bench*, vol. 11, no. 1, pp. 19–26, 2018.
- [47] E. Hajiani, P. Alavinejad, N. Avandi, A. R. Masjedizadeh, and A. A. Shayesteh, “Comparison of levofloxacin-based, 10-day sequential therapy with 14-day quadruple therapy for *Helicobacter pylori* eradication: a randomized clinical trial,” *Middle East J Dig Dis*, vol. 10, no. 4, pp. 242–248, 2018.
- [48] V. Sebghatollahi, M. Soheilipour, M. Khodadoostan, A. Shavakhi, and A. Shavakhi, “Levofloxacin-containing versus clarithromycin-containing therapy for *Helicobacter pylori* eradication: a prospective randomized controlled clinical trial,” *Advanced Biomedical Research*, vol. 7, no. 1, pp. 55–67, 2018.
- [49] F. Mansour-Ghanaei, B. Masihypour, M. Fathalipour et al., “The efficacy, safety, and tolerability of levofloxacin quadruple therapy for helicobacter pylori eradication: a randomized, double-blind clinical trial,” 2020.