International Journal of Antimicrobial Agents 63 (2024) 107159

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Helicobacter pylori eradication with high-dose proton pump inhibitor-amoxicillin dual therapy: A systematic review and meta-analysis

Jia-Ai Yeh[a,b], Huei-Kai Huang[c], Ai-Li Chou[a,b], Hwai-Jeng Lin[d,e], Chun-Lung Feng[f,g,h], Chia-Jung Kuo[a,i,j,*], Chih-Ho Lai[b,h,k,l,m,**]

[a] *School of Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan*
[b] *Department of Microbiology and Immunology, Graduate Institute of Biomedical Sciences, Chang Gung University, Taoyuan, Taiwan*
[c] *Department of Family Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan*
[d] *Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[e] *Division of Gastroenterology and Hepatology, Department of Internal Medicine, Shuang-Ho Hospital, New Taipe, Taiwan*
[f] *Division of Gastroenterology and Hepatology, Department of Internal Medicine, China Medical University Hsinchu Hospital, Hsinchu, Taiwan*
[g] *Department of Internal Medicine, China Medical University and Hospital, Taichung, Taiwan*
[h] *Department of Medical Research, School of Medicine, China Medical University and Hospital, Taichung, Taiwan*
[i] *Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan*
[j] *Chang Gung Microbiota Therapy Center, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan*
[k] *Molecular Infectious Disease Research Center, Department of Pediatrics, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan*
[l] *Department of Nursing, Asia University, Taichung, Taiwan*
[m] *Research Center for Emerging Viral Infections, Chang Gung University, Taoyuan, Taiwan*

ARTICLE INFO

Article history:
Received 2 September 2023
Accepted 22 March 2024

Editor: Professor Seok Hoon Jeong

Keywords:
Helicobacter pylori
High-dose dual therapy
Antimicrobial resistance
Eradication rate

ABSTRACT

Background: Resistance of *Helicobacter pylori* to many antibiotics, which lowers the efficacy of eradication therapy, is increasingly prevalent. High-dose proton pump inhibitor (PPI)-amoxicillin dual therapy (HDDT) has been used for *H. pylori* eradication for years, and resistance to amoxicillin is relatively rare. Although many studies have compared the eradication rate of HDDT with that of guideline therapies, the reported efficacy of HDDT varies greatly and is inconsistent.

Aims: This study investigated the eradication rate and adverse effects of HDDT compared with the guidelines at the time of the study.

Methods: Several open public databases, including Cochrane, EMBASE, PubMed, and MEDLINE, were searched. The results of the current literature on the eradication and adverse event rates of HDDT compared with the latest recommended first-line therapies were analysed. Notably, 14 out of the 16 included studies were conducted in Asian regions.

Results: The eradication rate of HDDT was lower but not significantly different from those of control therapies (odds ratio [OR] = 0.92, 95% confidence interval [CI] = 0.67–1.26) in the intent-to-treat (ITT) analysis. A similar trend was observed in the per-protocol (PP) analysis (OR = 0.88, 95% CI = 0.47–1.63). Notably, the adverse effect risk in HDDT was significantly lower than in other therapies (I^2 = 67.75%, OR = 0.42, 95% CI = 0.33–0.54, P = 0.00004). When the eradication rate of the control group was lower than 81%, HDDT was significantly better than control therapies (OR = 2.44, 95% CI = 1.23–4.84).

Conclusion: HDDT used four times a day for 14 days showed better efficacy and safety than the guideline treatments for *H. pylori* infection in areas with high antimicrobial resistance.

1. Introduction

Helicobacter pylori infection had a global prevalence of >50% and is associated with many gastrointestinal diseases, including gastritis, peptic ulcers, gastric cancer, and mucosa-associated lym-

* Corresponding author. Chia-Jung Kuo, Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
** Corresponding author. Chih-Ho Lai, Department of Microbiology and Immunology, Chang Gung University, Taoyuan, Taiwan
E-mail addresses: m7011@cgmh.org.tw (C.-J. Kuo), chlai@mail.cgu.edu.tw (C.-H. Lai).

https://doi.org/10.1016/j.ijantimicag.2024.107159
0924-8579/

phoid tissue lymphoma [1]. Accordingly, eradicating *H. pylori* could reduce the risk of the aforementioned diseases. The recommended first-line eradication therapy is the standard triple therapy (TT), using a proton pump inhibitor (PPI), amoxicillin, and clarithromycin [2]. The 2022 Maastricht VI/Florence consensus guidelines recommend bismuth quadruple therapy or clarithromycin TT as the first-line therapy for *H. pylori* eradication treatment when local clarithromycin resistance is below 15% [3]. Although the standard TT regimen is the regimen of choice when local clarithromycin resistance is <5%, the eradication rate is suboptimal when resistance is >15% [4]. When local resistance to clarithromycin is >15%, bismuth or non-bismuth quadruple therapy is recommended as the first-line therapy [3]. However, these two therapies with multiple antibiotics for 14 days are prone to increase antimicrobial resistance

Eradication failure of standard TT was primarily caused by antibiotic resistance, poor adherence, and rapid PPI metabolism. A multicentre report from Taiwan in 2019 demonstrated that the rates of resistance to clarithromycin, metronidazole, levofloxacin, amoxicillin, and tetracycline were 81%, 77%, 51%, 0%, and 0%, respectively [5]. The lack of amoxicillin resistance indicates that amoxicillin and PPI dual therapy could be a promising therapy.

The concept of dual therapy's antibacterial effects was introduced during the 1980s, initially exhibiting a modest eradication rate. Numerous studies have suggested that increasing the PPI dosage and frequency can achieve a high eradication rate [6]. For example, a study using high-dose and high-frequency HDDT in 2015 achieved 95.3% *H. pylori* eradication, suggesting the potential of high-dose and high-frequency HDDT [7]. Therefore, investigations on the *H. pylori* eradication rate and adverse effects of HDDT compared with the different PPIs used in this regimen are required.

Many studies have compared the eradication rates of HDDT with those of standard TT. However, the reported efficacy of HDDT varies greatly and is inconsistent. In this study, we investigated several publicly available databases, including Cochrane, EMBASE, PubMed, and Medline. We summarized the results of the current literature on the eradication and adverse event rates of HDDT compared with the latest recommended first-line therapy. We further compared the efficacy and safety of amoxicillin-containing rescue therapy with other rescue regimens.

2. Methods

2.1. Searching strategy and selection criteria

A literature search in PubMed, EMBASE, Medline, and the Cochrane Library was conducted up to July 2023 with the following strategy ("*Helicobacter pylori*" OR "*H. pylori*) AND ("amoxicillin") AND ("dual therapy"). This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Fig. 1).

Two reviewers independently extracted data, and disagreements were resolved after discussion and consultation with a third reviewer. The inclusion criteria of HDDT were as follows: (a) studies in which amoxicillin was administered at ≥2.0 g/d and PPI was taken at least three times daily for 14 days, (b) the studies were randomized controlled trials, and (c) adverse event rates were reported.

2.2. Data extraction

The extracted information included (a) the name of the first author and year of publication; (b) the location where the study was conducted; (c) the regimens used in the study; (d) the number of patients in intent-to-treat (ITT) and per-protocol (PP) analyses of compared groups; and (e) primary outcomes, including ITT and PP analyses of eradication and adverse event rates of the compared groups.

2.3. Risk of bias

Two investigators independently rated the risk of bias using the risk of bias assessment tools, RoB2, a revised Cochrane risk-of-bias tool for randomized trials (Figs. S1 and S2).

2.4. Statistical analysis

Statistical analyses were performed using a standard software package (Stata, version 17; StataCorp, College Station, TX). We analysed the odds ratios (ORs) and 95% confidence intervals (CIs). The endpoints of interest in the pooled analysis were eradication rate and incidence of adverse effects. Heterogeneity among the pooled studies was also evaluated. A high degree of heterogeneity was suggested when the inconsistency index (I^2) was >50%. A random-effects model was used for high heterogeneity analysis, and a fixed-effects model with Mantel-Haenszel weight was used for low heterogeneity analysis. A funnel plot was used to estimate publication bias (Fig. S3).

3. Results

3.1. HDDT has the same eradication rate as guideline therapies

The experimental process and analysis protocol for the included studies are shown in Fig. 1, and the characteristics and demographic data of the included studies are shown in Tables S1 and S2, respectively. Finally, we selected 16 articles with 6255 patients for the meta-analysis. Of the 16 articles, 2 studies were performed in Europe and 14 in Asian countries. PPIs were administered 3 and 4 times daily in 4 and 12 articles, respectively. Furthermore, among the 16 articles, 13 focused on first-line therapy, 2 on rescue therapy, and 1 covered both approaches.

In the meta-analysis of *H. pylori* eradication rates, the eradication rate of HDDT was not significantly different from those of the guideline therapies. There were 6255 and 5931 patients in the ITT and PP analyses of 13 of the analysed studies. In the ITT analysis, the eradication rate of HDDT was not significantly different from that of the control group (I^2 = 60.7%, OR = 1.18, 95% CI = 0.92–1.51, P = 0.20) (Fig. 2a). Similarly, the eradication rate of HDDT was not different from that of the control group in the PP analysis (I^2 = 63.6%, OR = 1.13, 95% CI = 0.83–1.54, P = 0.44) (Fig. S4). There were no significant differences in both first-line and rescue therapies. We then assessed the 13 articles included in the first-line therapy analysis. In the ITT analysis, the eradication rate was not significantly different from that of other therapies (OR = 1.24, 95% CI = 0.92–1.66) (Fig. S5), and so it was in the PP analysis (OR = 1.20, 95% CI = 0.84–1.72, P = 0.20). There were four articles included in the rescue therapy analysis. The eradication rate of HDDT was lower but not significantly different from those of the control therapies (OR = 0.92, 95% CI = 0.67–1.26) in ITT analysis, and a similar trend was shown in PP analysis (OR = 0.88, 95% CI = 0.47–1.63).

There were no significant differences in the subgroup analysis of different PPI frequencies. In the 13 articles where PPIs were administered 4 times daily, the eradication rate was higher but not significantly different from those of other therapies both in ITT (OR = 1.30, 95% CI = 0.95–1.77) and PP (OR = 1.23, 95% CI = 0.83–1.23) analyses (Fig. S6). When using PPI three times a day, there were lower but no significant differences in ITT (OR = 0.88, 95% CI = 0.67–1.15) and PP (OR = 0.82, 95% CI = 0.60–1.13) analyses.

We further assessed the subgroup dataset using different PPIs, including esomeprazole and rabeprazole. When using

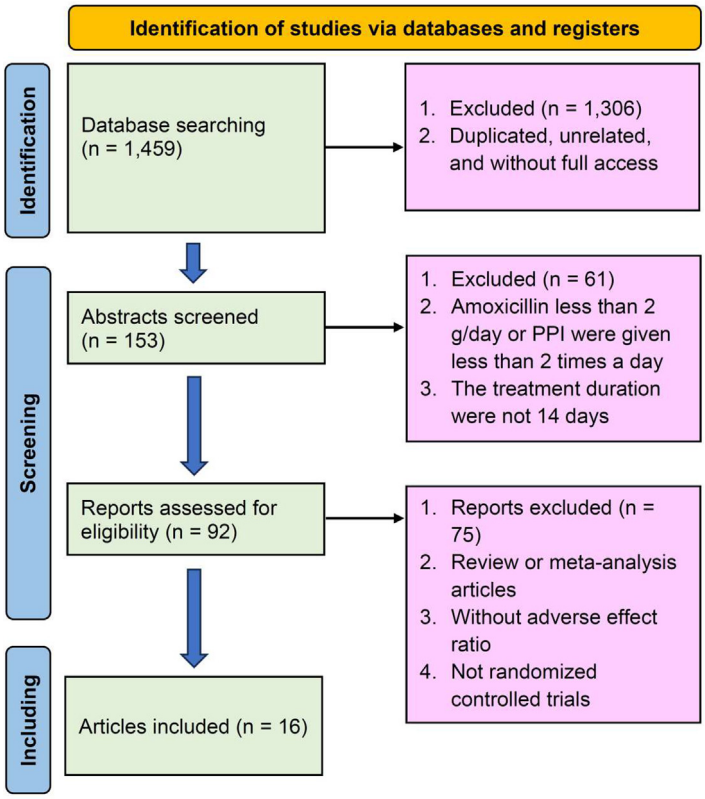

Fig. 1. Experimental protocol for the study design and data analysis.

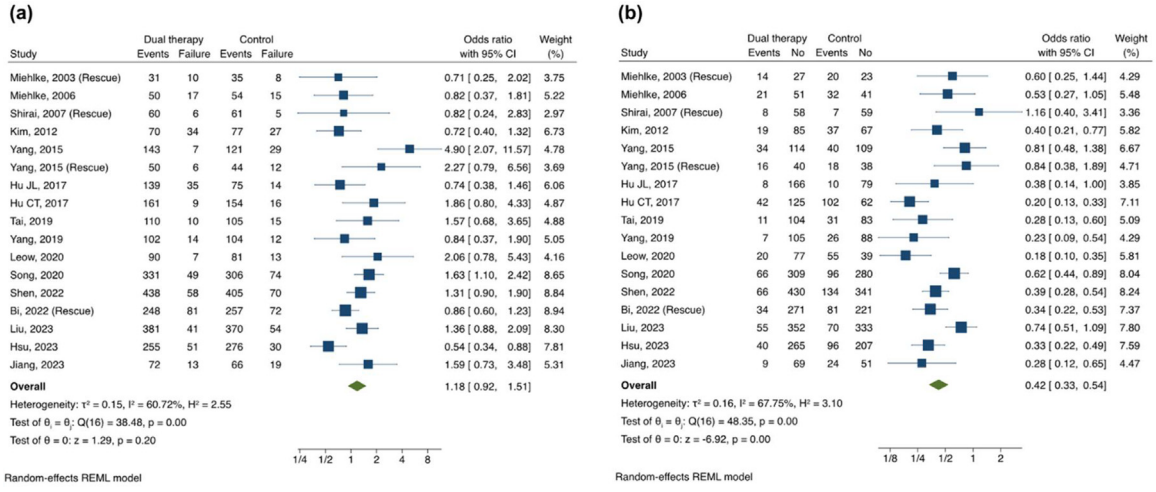

Fig. 2. Forest plots of (a) *H. pylori* eradication rate in ITT analysis and (b) adverse events rate of HDDT compared with the current mainstream guideline-recommended therapies (control).

esomeprazole-amoxicillin HDDT, the eradication rate was higher but not significantly different from the guideline therapy in ITT (OR = 1.23, 95% CI = 0.96–1.56) (Fig. S7) and PP (OR = 1.17, 95% CI = 0.87–1.56) analyses. In the rabeprazole-amoxicillin HDDT analysis, ITT (OR = 1.42, 95% CI = 0.83–2.42) and PP (OR = 1.36, 95% CI = 0.71–2.61) analyses showed no significant differences.

3.2. HDDT has a lower adverse effect risk

A total of 6118 patients were recruited in the adverse effects analysis. The results showed that the adverse effect risk in HDDT was significantly lower than in other therapies (I^2 = 67.75%, OR = 0.42, 95% CI = 0.33–0.54, P = 0.00004) (Fig. 2b). In the subgroup analysis of studies using different frequencies of PPI, the adverse effects were significantly lower when using PPI three times (OR = 0.37, 95% CI = 0.28–0.50) and four times (OR = 0.44, 95% CI = 0.32–0.60) a day. Analysis of different PPIs showed significantly lower ratios of adverse effects in the use of esomeprazole (OR = 0.43, 95% CI = 0.31–0.61) and rabeprazole (OR = 0.40, 95% CI = 0.25–0.65).

In the subgroup analysis of first-line and rescue therapies, the results showed a significantly lower ratio of adverse effects in first-line therapies (OR = 0.39, 95% CI = 0.29–0.51), while no significant difference in rescue therapy (OR = 0.59, 95% CI = 0.34–1.05) was observed.

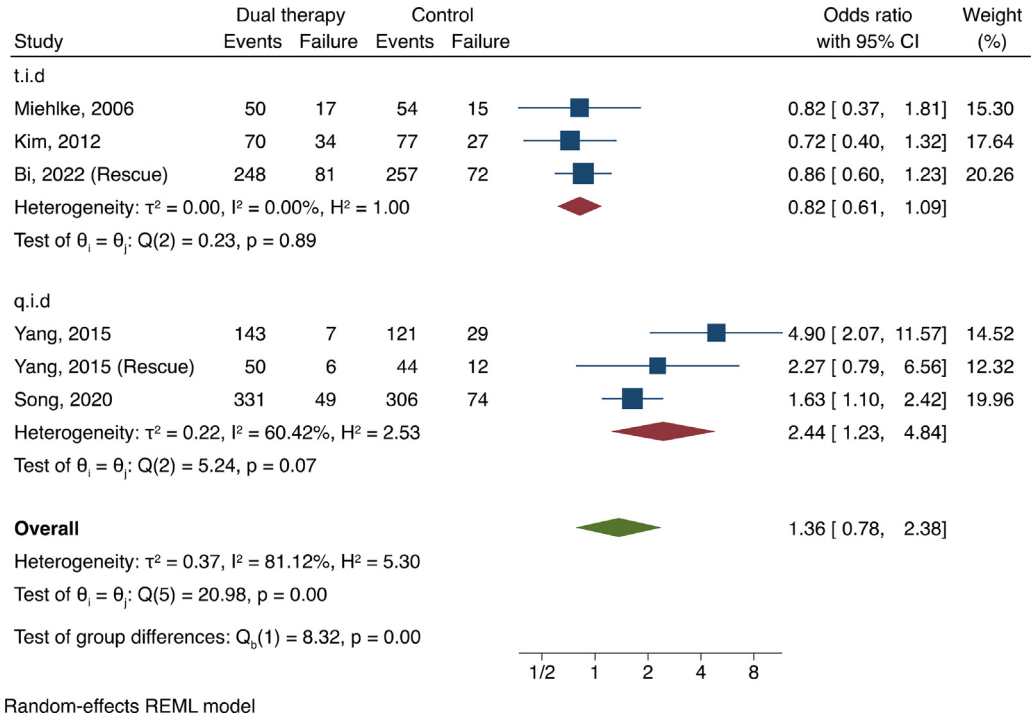

Fig. 3. *H. pylori* eradication rate of HDDT compared with the current mainstream guideline-recommended therapies (control) in low eradication rate areas in intention to treat analysis.

3.3. HDDT is more effective in high antibiotic-resistant circumstances

We further conducted an analysis when the eradication rate of the control group was <81%, which may have occurred in areas with high resistance. Since *H. pylori* infection treatment suggested that the 14 days TT eradication rate was 81.9%, and the eradication rate for quadruple therapy was higher [8,9], we considered 81% as the standard eradication rate for guideline therapies. In this analysis, the eradication rate of HDDT was higher but not significantly different from that of the control group (OR = 1.36, 95% CI = 0.78–2.38, P = 0.04). However, when in different frequencies, it was significantly higher when using PPI four times a day (OR = 2.44, 95% CI = 1.23–4.84); whereas it was not significantly different when using PPI three times a day (OR = 0.82, 95% CI = 0.61–1.09) (Fig. 3).

3.4. Sensitivity analysis

We further performed a sensitivity analysis by removing one study at a time, and the results from the statistical significance were not changed in the relative risk analysis.

4. Discussion

Our meta-analysis showed that PPI-amoxicillin containing HDDT for 14 days had no different eradication and lower adverse reaction rates as first-line therapy than the existing recommended guideline therapies. A previous study showed that HDDT for 10 days had lower efficacy; therefore, we considered 14 days as the criterion [10]. HDDT was defined as ≥2 g of amoxicillin per day and PPI administered at least 3 times a day. There was no significant difference in efficacy between HDDT and existing guidelines when used as both first-line and rescue therapies. Notably, the overall resistance of *H. pylori* to amoxicillin was low.

We conducted the analysis when the eradication rate in the control group was below the average global eradication rate of 81%, which may have occurred in areas with high antibiotic resistance. A previous study has suggested that the primary cause of unsuccessful eradication attributed to resistance against clarithromycin and metronidazole [11]. In this situation, the eradication rate of HDDT when using PPI four times a day may be significantly higher than that of the control group but not significantly different when using PPI three times a day. Therefore, the results indicated that a HDDT with PPI taken four times daily should be considered in the low eradication rate area.

A 2020 meta-analysis showed that HDDT has similar efficacy to mainstream recommended therapies [12]. TT studies with antibiotic resistance rates of >15% were excluded. A 2021 meta-analysis showed that HDDT with PPI and amoxicillin administered four times a day for 14 days was superior to guideline therapy in efficacy and safety as first-line therapy but not as salvage treatment [13]. Our results are consistent with those of previous studies. We collected data from more studies, including patients taking PPI thrice daily. The difference was not significant when PPIs were taken three times a day. In the two most recent studies using meta-analysis in 2023, one compared HDDT and bismuth-containing quadruple therapy, and the other compared PPI-amoxicillin HDDT with HDDT of vonoprazan and amoxicillin [14,15]. In the present study, we performed the amoxicillin analysis more comprehensively.

Other factors, such as intragastric pH and doses used in treatment, may influence the efficacy of HDDT. Our study included PPI at least three times daily and amoxicillin at least 2 g daily as a HDDT. PPIs play an essential role in *H. pylori* eradication. They inhibit proton pump function and block gastric acid secretion's terminal steps. Elevated intragastric pH prevents the degradation of antibiotics by acids. Larger doses of PPIs reduce periodic acid-Schiff-positive substances in the gastric mucosa, thus lowering the mucus layer viscosity and exposing organisms under the mucus layer to antibiotics [16]. Dosing PPIs more frequently is more

suitable than reducing the frequency with a higher dosage due to their short half-lives. Regardless of the genotype of CYP2C19, a CYP isoenzyme in the liver that controls the catabolism of several PPIs, a high-dose of PPI included in HDDT can maintain the intragastric pH > 6.5 and the plasma concentration of amoxicillin above the minimal inhibitory concentration for *H. pylori* [17]. Moreover, the amoxicillin concentration in the stomach is important. Amoxicillin has a half-life of 1 h, indicating that four times a day is better than three times a day [18].

Most reports of HDDT included in this study were from Asia, which may also influence resistance to amoxicillin. The reported amoxicillin resistance rates of *H. pylori* differ significantly between Eastern and Western countries. For instance, a systematic analysis reported that he prevalence of *H. pylori* resistance to amoxicillin is 18–75% in Eastern countries (China, India, and South Korea) and 0–35% in Western countries (the United States, France, and the United Kingdom) [19]. Therefore, when resistance to amoxicillin continues to increase, the effect of PPI-amoxicillin-containing HDDT should be retested [20].

The present study has some limitations. First, except for the two earliest studies (2003 and 2006) from Germany, all included studies were from Asia, and most were from China. The effects of ethnicity or the more prevalent CYP2C19 genotype in Western countries could not be estimated [13]. Therefore, the effects of HDDT in Western countries require further investigation. Second, the risk of bias was high in most studies because of inadequate blinding. Accordingly, some study estimates, such as adverse event rates, may be biased.

5. Conclusion

Our results indicated that HDDT four times a day for 14 days had better efficacy and safety than the guideline treatments in high-resistant areas. Furthermore, HDDT could offer enhanced safety without compromising its effectiveness across all regions. When the same daily dose was administered in three divided doses per day, the evidence was inconclusive and required further studies. Moreover, the safety of HDDT may be higher than that of the recommended guidelines. However, more attention should be paid to the changing rate of amoxicillin resistance during this treatment. These meta-analysis results indicate that PPI-amoxicillin-containing HDDT for *H. pylori* eradication is more efficacious and safer in high-resistant areas.

Declarations

Funding: This work was supported by the National Science and Technology Council, Taiwan (112-2320-B-182-036-MY3 and 112-2320-B-182-042-MY3), Chang Gung Memorial Hospital, Linkou, Taiwan (CMRPG3F0551-2, CMRPG3H0031-2, CMRPG3K0691, CORPG3L0191, CMRPD1M0491-2, and CORPD1M0021-3), Research Center for Emerging Viral Infections from the Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Taiwan Ministry of Education, and Tomorrow Medical Foundation, Taiwan.

Competing interests: None declared.

Ethical approval: Not required.

Sequence information: Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2024.107159.

References

[1] Crowe SE. *Helicobacter pylori* infection. N Engl J Med 2019;380:1158–65.
[2] Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212–239.
[3] Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. Gut 2022:1–39.
[4] Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, et al. Review article: the global emergence of *Helicobacter pylori* antibiotic resistance. Aliment Pharmacol Ther 2016;43:514–33.
[5] Liang CM, Tai WC, Hsu PI, Wu DC, Kuo CH, Tsay FW, et al. Trend of changes in antibiotic resistance in *Helicobacter pylori* from 2013 to 2019: a multicentre report from Taiwan. Therap Adv Gastroenterol 2020;13:1756284820976990.
[6] Graham DY, Javed SU, Keihanian S, Abudayyeh S, Opekun AR. Dual proton pump inhibitor plus amoxicillin as an empiric anti-*H. pylori* therapy: studies from the United States. J Gastroenterol 2010;45:816–20.
[7] Yang JC, Lin CJ, Wang HL, Chen JD, Kao JY, Shun CT, et al. High-dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* infection. Clin Gastroenterol Hepatol 2015;13:895–905.e5.
[8] Yuan Y, Ford AC, Khan KJ, Gisbert JP, Forman D, Leontiadis GI, et al. Optimum duration of regimens for *Helicobacter pylori* eradication. Cochrane Database Syst Rev 2013:Cd008337.
[9] Liou JM, Chen CC, Chen MJ, Chen CC, Chang CY, Fang YJ, et al. Sequential versus triple therapy for the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomised trial. Lancet 2013;381:205–13.
[10] Zhang Y, Zhu YJ, Zhao Z, Zhao JT, Wang TY, Yang J, et al. Efficacy of modified esomeprazole-amoxicillin dual therapies for *Helicobacter pylori* infection: an open-label, randomized trial. Eur J Gastroenterol Hepatol 2020;32:563–568.
[11] Branca G, Spanu T, Cammarota G, Schito AM, Gasbarrini A, Gasbarrini GB, et al. High levels of dual resistance to clarithromycin and metronidazole and in vitro activity of levofloxacin against *Helicobacter pylori* isolates from patients after failure of therapy. Int J Antimicrob Agents 2004;24:433–8.
[12] Gao CP, Zhang D, Zhang T, Wang JX, Han SX, Graham DY, et al. PPI-amoxicillin dual therapy for *Helicobacter pylori* infection: an update based on a systematic review and meta-analysis. Helicobacter 2020;25:e12692.
[13] Li C, Shi Y, Suo B, Tian X, Zhou L, Song Z. PPI-amoxicillin dual therapy four times daily is superior to guidelines recommended regimens in the *Helicobacter pylori* eradication therapy within Asia: a systematic review and meta-analysis. Helicobacter 2021;26:e12816.
[14] Zhang C, Zhang J, Cheng YJ. High-dose dual therapy versus bismuth-containing quadruple therapy for the treatment of *helicobacter pylori* infection: a meta-analysis of randomized controlled trials. Saudi J Gastroenterol 2023;29:88–94.
[15] Zhang WL, Lin BS, Li YY, Ding YM, Han ZX, Ji R. Efficacy and safety of vonoprazan and amoxicillin dual therapy for *Helicobacter pylori* eradication: a systematic review and meta-analysis. Digestion 2023;104:249–61.
[16] Perry IE, Sonu I, Scarpignato C, Akiyama J, Hongo M, Vega KJ. Potential proton pump inhibitor-related adverse effects. Ann N Y Acad Sci 2020;1481:43–58.
[17] Adachi K, Katsube T, Kawamura A, Takashima T, Yuki M, Amano K, et al. CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. Aliment Pharmacol Ther 2000;14:1259–66.
[18] Shirai N, Sugimoto M, Kodaira C, Nishino M, Ikuma M, Kajimura M, et al. Dual therapy with high doses of rabeprazole and amoxicillin versus triple therapy with rabeprazole, amoxicillin, and metronidazole as a rescue regimen for *Helicobacter pylori* infection after the standard triple therapy. Eur J Clin Pharmacol 2007;63:743–9.
[19] Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399:629–55.
[20] Kuo CJ, Ke JN, Kuo T, Lin CY, Hsieh SY, Chiu YF, et al. Multiple amino acid substitutions in penicillin-binding protein-1A confer amoxicillin resistance in refractory *Helicobacter pylori* infection. J Microbiol Immunol Infect 2023;56:40–7.