JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Effectiveness of 14-day high-dose dual therapy for *Helicobacter pylori* infection in Vietnam

Nam T Phan[1], Long H Truong[1,2]

[1] Gastroenterology and Endoscopy Center, Hospital of Hue University of Medicine and Pharmacy, Hue University, Hue, Vietnam
[2] Family Hospital, Danang, Vietnam

Abstract

Introduction: The eradication rates of *Helicobacter pylori* (*H. pylori*) in Vietnam, with both triple therapy and non-bismuth quadruple therapy, have significantly declined due to increasing antibiotic resistance. This prospective study aimed to evaluate the eradication efficacy of high-dose dual therapy (HDDT) with esomeprazole and amoxicillin in a region with high resistance rates to clarithromycin, metronidazole, and levofloxacin.

Methodology: A total of 82 patients with active *H. pylori* infection, confirmed by either a rapid urease test or a ^{13}C urea breath test, were enrolled at our hospital. All participants received esomeprazole (40 mg) and amoxicillin (1,000 mg), 3 times daily for 14 days. Treatment success was assessed using a ^{13}C urea breath test 4–6 weeks post-treatment. Safety was evaluated based on reported adverse effects.

Results: Gastritis, gastric ulcer, and duodenal ulcer were present in 80.5%, 10.4%, and 9.1% of cases, respectively. The eradication rates according to intention-to-treat (ITT) and per-protocol (PP) analyses were 76.8% (63/82) and 81.8% (63/77), respectively. In the PP analysis, the eradication rate was 86.0% (49/57) in first-line treatment, and 70.0% (14/20) in patients with prior *H. pylori* treatment failure. Mild side effects, including nausea, abdominal discomfort, pruritus, diarrhea, and fatigue, were reported in 22.1% (17/77) of patients.

Conclusions: This study demonstrates that a 14-day HDDT regimen provides relatively high efficacy and a favorable safety profile for first-line *H. pylori* eradication. Given the widespread resistance to clarithromycin, levofloxacin, and metronidazole in Vietnam; HDDT may serve as an alternative first-line therapy for *H. pylori* eradication in this region.

Key words: *Helicobacter pylori*; treatment; HDDT; amoxicillin; PPIs.

J Infect Dev Ctries 2025; 19(3):404-408. doi:10.3855/jidc.20820

(Received 06 September 2024 – Accepted 25 February 2025)

Introduction

Helicobacter pylori (*H. pylori*) is one of the most common chronic bacterial infections, affecting more than 70% of the Vietnamese population [1,2]. It is a major cause of peptic ulcer, primary gastric lymphoma, and gastric cancer; therefore, eradication is recommended when the infection is detected [3–5]. *H. pylori* eradication therapy requires a combination of proton pump inhibitors (PPIs) with antibiotics [5,6].

High-dose dual therapy (HDDT), which consists of a PPI and amoxicillin, has recently gained attention and is being used for both first-line and rescue *H. pylori* eradication. This regimen offers several advantages, including simplicity, fewer side effects, better patient tolerance, and promising efficacy in recent studies [7–9]. Moreover, HDDT was recommended as a rescue therapy in the *H. pylori* treatment guidelines of the American College of Gastroenterology [6]. More recently, it has been accepted as a second-line therapy in the European *H. pylori* management guideline—Maastricht VI 2022 [5].

In Vietnam, *H. pylori* treatment faces significant challenges due to high and complex antibiotic resistance rates [10,11]. Specifically, resistance rates have been reported at 42.4% for clarithromycin, 41.3% for levofloxacin, and 76.1% for metronidazole. Additionally, multidrug resistance has emerged in 56.5% of cases, making clarithromycin- or levofloxacin-based triple therapy, as well as non-bismuth quadruple therapy, less effective [12,13].

Currently, only a 14-day bismuth-containing quadruple therapy is recommended for *H. pylori* treatment in Vietnam [2]. However, this regimen has drawbacks, including complexity and multiple side effects, which reduce patient adherence. Moreover, *H. pylori* eradication treatment based on antibiotic susceptibility testing is not feasible in real-world clinical practice. Recently, HDDT regimens have been evaluated in several studies, showing variable efficacy

but good tolerability. Furthermore, *H. pylori* resistance to amoxicillin remains relatively low in Vietnam [12–14]. Therefore, this study aimed to evaluate the eradication efficacy of a HDDT regimen (esomeprazole and amoxicillin) in patients with *H. pylori*-infected gastroduodenal diseases in the central region of Vietnam.

Methodology

Patients

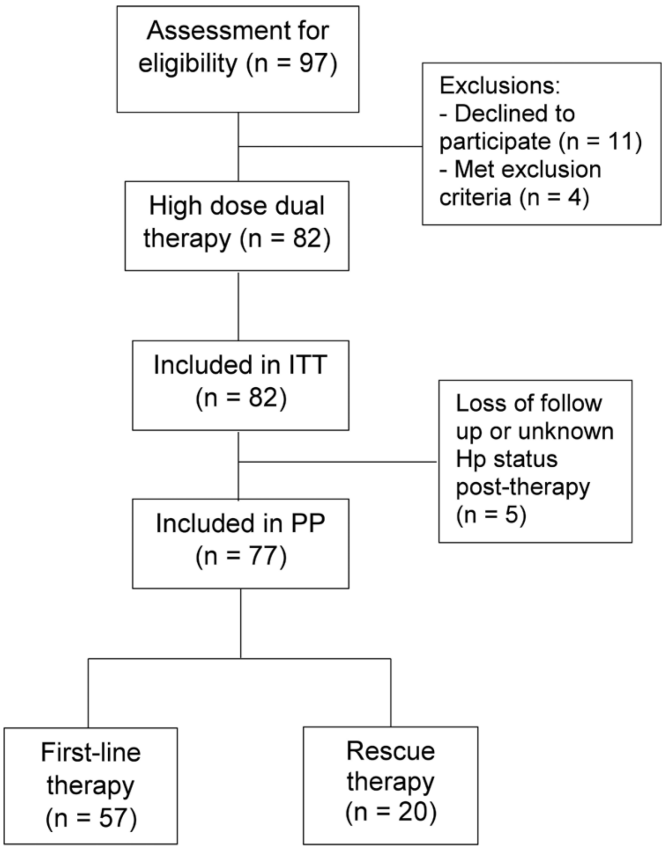
This prospective cohort study included patients aged 16 years or older with upper abdominal symptoms who were referred to the Danang Family Hospital between July 2021 and September 2022. The patients were evaluated for their history of *H. pylori* treatment; underwent clinical examinations including upper gastrointestinal endoscopy, and *H. pylori* infection test; and received eradication therapy with a HDDT regimen.

Upper endoscopic examinations were performed using forward-viewing standard electronic video gastroscopes to diagnose peptic ulcer or gastritis. Peptic ulcer is characterized by a discontinuation in the inner lining of the gastrointestinal tract due to gastric acid or pepsin secretion, extending into the muscularis propria layer of the gastric epithelium. Ulcers are differentiated from erosions and gastritis based on size: lesions smaller than 5 mm in diameter are classified as erosions, whereas those larger than 5 mm are classified as ulcers. Endoscopic gastritis was diagnosed based on the Kyoto Classification.

The inclusion criteria were patients who had not used antibiotics within the past 4 weeks, and had not taken PPIs, H_2 blockers, or bismuth within the past 2 weeks. *H. pylori* infection was diagnosed if the patient tested positive in either a rapid urease test (defined as a color change from yellow to bright pink within 4 hours) or a ^{13}C urea breath test (Otsuka Pharmaceutical Co. Ltd, Tokyo, Japan; with a cutoff value of 2.5‰).

Patients were excluded if they had contraindications to upper gastrointestinal endoscopy, a history of partial gastrectomy, gastric cancer, concurrent critical illness, pregnancy, known allergies or contraindications to the treatment drugs, or if they did not provide consent to participate in the study.

Figure 1. Recruitment and flow through the study.



Hp: Helicobacter pylori; ITT: intention to treat; PP: per-protocol.

High-dose dual therapy (HDDT) regimen

All enrolled patients received amoxicillin 1,000 mg (after meals) and esomeprazole 40 mg (before meals), 3 times daily for 14 days. The study medications were supplied in prepackaged doses, and treatment compliance was assessed by instructing the patients to return any unused medication. The patients were provided with a phone number for consultation regarding medication use and recorded their adherence in a patient diary. After completing treatment, the patients completed a questionnaire regarding medication side effects. Treatment success was evaluated 4–6 weeks post-treatment using the ^{13}C urea breath test.

Ethical considerations

The study was approved by the Institutional Review Board of Hue University of Medicine and Pharmacy and Danang Family Hospital (Approval No. H2021/372). Informed consent was obtained from all participants, and the study protocol adhered to the ethical principles outlined in the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using Microsoft® Excel and SPSS version 20 (SPSS Inc., Chicago, IL, USA). The results were expressed as absolute (n) and relative (%) frequencies. The χ^2 test was used to analyze differences in categorical data. A p

Table 1. General characteristics and distribution of gastroduodenal diseases in *Helicobacter pylori* infected patients.

Characteristics	(n = 82)
Age in years (mean ± SD)	38.3 ± 12.3
Gender ratio (male/female)	39/43
Endoscopic findings	**N (%)**
Gastritis	67 (81.7)
Gastric ulcer	8 (9.8)
Duodenal ulcer	7 (8.5)

value of < 0.05 was considered statistically significant, and all *p* values were two-sided.

Results

The steps in participant recruitment and study flow are presented in Figure 1. A total of 97 eligible patients with endoscopically confirmed peptic ulcer or gastritis were invited to participate; and finally, 82 patients were enrolled in the intention-to-treat (ITT) analysis. Ultimately, 5 patients were lost to follow-up, resulting in 77 patients being included in the per-protocol (PP) analysis.

The general characteristics of the 82 enrolled patients included a mean age of 38.3 ± 12.3 years and male-to-female ratio of 39:43. Most patients presented with upper abdominal pain or dyspepsia. Upper gastrointestinal endoscopic findings revealed gastritis in 81.7% of cases, gastric ulcer in 9.8%, and duodenal ulcer in 8.5% (Table 1).

Among the 77 patients who completed follow-up, all had treatment compliance of over 90% based on pill counts, while 5 patients were lost to follow-up. The overall eradication rates were 76.8% (63/82) in the ITT analysis and 81.8% (63/77) in the PP analysis (Table 2). Among the 77 follow-up patients, 57 received HDDT as a first-line treatment, achieving an *H. pylori* eradication rate of 86.0% (49/57). The remaining 20 patients, who had previously failed *H. pylori* treatment and were undergoing rescue therapy, had a successful eradication rate of 70.0% (14/20) (Table 3).

A total of 17 out of 77 patients (22.1%) reported mild side effects during treatment, with some experiencing more than one adverse effect. The most commonly reported side effects were nausea, abdominal discomfort, pruritus, and mild fatigue (Table 4).

Discussion

This study is one of the few evaluations of a 14-day esomeprazole- and amoxicillin-based HDDT regimen for *H. pylori* eradication in patients with gastroduodenal disease residing in the central region of Vietnam; where resistance to clarithromycin, metronidazole, and levofloxacin is highly prevalent.

Table 2. *Helicobacter pylori* eradication rate of high dose dual therapy (HDDT).

***H. pylori* eradication**	**Intention-to-treat (n = 82)**	**Per-protocol (n = 77)**
Success rate	63 (76.8%)	63 (81.8%)
Failure rate	19 (23.2%)	14 (18.2%)

The increasing rate of antibiotic resistance is the primary factor contributing to the declining success of *H. pylori* eradication therapy. Continuous surveillance of antibiotic resistance in *H. pylori* is essential to ensure that the treatment regimens are adapted to the local resistance patterns [5,6]. This is particularly relevant for clarithromycin, as resistance to this antibiotic can reduce the efficacy of the standard triple therapy by approximately 70% in patients infected with clarithromycin-resistant strains, compared to those with susceptible strains [15]. Furthermore, resistance to levofloxacin, an alternative drug used after failure of first-line triple therapy, is also remarkably high in the central region of Vietnam, with primary resistance rates ranging from 18.4% to 35.6%, and secondary resistance reaching 63.2% [12,14]. These resistances occur against a background of high metronidazole resistance (> 70%) and multidrug resistance in over 56% of cases [12]. However, the resistance rate to amoxicillin remains low in Vietnam, with reports indicating resistance in less than 2% of cases [14]. This provided the rationale for our study, which aimed to assess the efficacy of an HDDT regimen in eradicating *H. pylori*.

A total of 82 *H. pylori*-infected patients, primarily young and middle-aged individuals, with upper digestive symptoms, were diagnosed with gastritis (81.7%), gastric ulcer (9.8%), or duodenal ulcer (8.5%) based on upper endoscopy.

The *H. pylori* eradication rates with HDDT in these 82 patients were 76.8% in the ITT analysis and 81.8% in the PP analysis. Among the 57 patients receiving

Table 4. Side effects of high dose dual therapy (HDDT).

Side effects	N (%) (n = 77)
Nausea	7 (9.1)
Abdominal discomfort	6 (7.8)
Pruritus	5 (6.5)
Diarrhea	2 (2.6)
Mild fatigue	7 (9.1)

Table 3. *Helicobacter pylori* eradication rate of high dose dual therapy (HDDT) according to history of treatment.

***H. pylori* eradication**	**First-line therapy (n = 57)**	**Rescue therapy (n = 20)**	**Total therapy (n = 77)**
Successful rate	49 (86.0%)	14 (70.0%)	63 (81.8%)
Failure rate	8 (14.0%)	6 (30.0%)	14 (18.2%)

HDDT as first-line therapy, the eradication rate was 86.0%; whereas among the 20 patients who had previously failed *H. pylori* treatment (rescue therapy), the eradication rate was 70.0%. The first-line treatment results of our HDDT regimen are consistent with recent studies worldwide, particularly in Asian countries, where eradication rates following the protocol exceeded 87% [7–9]. However, the lower eradication rate of 70.0% in the rescue therapy group highlights the ongoing challenges in treating *H. pylori* infection in patients with prior treatment failure.

This failure may be attributed to the emergence of secondary resistance to amoxicillin; although simultaneous mutations at multiple sites in the *pbp1A* gene which is associated with reduced affinity between amoxicillin and penicillin-binding protein transpeptidase occur at a low frequency [16,17]. Recent surveillance of *H. pylori* antibiotic resistance in Vietnam has shown an increasing trend in amoxicillin resistance, particularly when using a resistance breakpoint of > 0.125 mg/L [13,18]. Additionally, treatment failure may be influenced by polymorphisms in *CYP2C19*, which affect the metabolism of PPIs, especially in patients with a history *of H. pylori* treatment failure. However, Vietnamese individuals generally have a lower prevalence of *CYP2C19* genotypes associated with rapid PPI metabolism, compared to Europeans [19]. Furthermore, in our study, both esomeprazole and amoxicillin were administered 3 times daily, which may be less effective than the 4-times-daily dosing used in some studies [7,9]. This is particularly relevant for antibiotics like amoxicillin, whose *H. pylori* eradication efficacy is highly dependent on sustained high gastric pH [20]. Recent studies suggest that replacing PPIs with potassium-competitive acid blockers (P-CABs) in the HDDT regimen results in higher *H. pylori* eradication rates [21,22] indicating that PPI-based acid suppression may still be suboptimal.

HDDT offers several advantages, including a favorable side effect profile, good tolerability, and improved patient compliance compared to other treatment regimens. In our study, only 17 patients (22.1%) reported mild side effects; primarily nausea, abdominal discomfort, pruritus, diarrhea, and mild fatigue. These findings are consistent with previous studies, which have reported that HDDT is generally well tolerated, with a low incidence of mild side effects [7–9].

Our study has some limitations. The single-center design and relatively small sample size may limit the generalizability of our findings, particularly due to the impact of the coronavirus disease 2019 (COVID-19) pandemic on patient recruitment. Additionally, we did not perform *H. pylori* culture to confirm amoxicillin resistance among enrolled patients, which would have provided further insight into the relationship between antibiotic resistance and treatment outcomes.

Conclusions

In this study, an HDDT regimen consisting of 1,000 mg amoxicillin and 40 mg esomeprazole, administered 3 times daily for 14 days, demonstrated considerable efficacy in eradicating *H. pylori* infection, while maintaining a low rate of side effects when used as a first-line treatment. Given the high prevalence of resistance to clarithromycin, levofloxacin, and metronidazole in Vietnam; this regimen has the potential to serve as an alternative first-line therapy for *H. pylori* eradication.

Acknowledgements

We would like to thank Prof. VH Tran, Director of Gastroenterology and Endoscopy Center, Hospital of University of Medicine and Pharmacy, Hue University; the Vice president of Vietnam Association of Gastroenterology; and our staff at the Family Hospital for their support.

Corresponding author

Trung Nam Phan, MD, PhD.
Gastroenterology and Endoscopy Center, Hospital of Hue University of Medicine and Pharmacy,
Hue University, 06 Ngo Quyen street, Hue city, Vietnam.
Tel: (+84) 0914156622
Fax: (+84) 234.3826269
Email: ptnam@huemed-univ.edu.vn

Conflict of interests

No conflict of interests is declared.

References

1. Aumpan N, Mahachai V, Vilaichone RK (2023) Management of *Helicobacter pylor*i infection. JGH Open 7: 3–15. doi: 10.1002/jgh3.12843.
2. Quach DT, Mai BH, Tran MK, Dao LV, Tran HV, Vu KT, Pham HT-T, Bui HH, Ho DD-Q, Trinh DT, Nguyen VT, Duong TH, Tran TT-K, Nguyen HT-V, Nguyen TT, Nguyen TD, Nguyen LC, Dao HV, Thai KD, Phan NT, Le LT, Vo CH-M, Ho PT, Nguyen TL, Le QD, Le NV, Phan HQ, Nguyen BC, Tran TT, Tran TV, Ta L (2023) Vietnam Association of Gastroenterology (VNAGE) consensus on the management of *Helicobacter pylori* infection. Front Med (Lausanne) 9: 1065045. doi: 10.3389/fmed.2022.1065045.
3. McColl KE (2010) *Helicobacter pylori* infection. N Engl J Med 362: 1597-1604. doi: 10.1056/NEJMcp1001110.
4. Katelaris P, Hunt R, Bazzoli F, Cohen H, Fock KM, Gemilyan M, Malfertheiner P, Mégraud F, Piscoya A, Quach D, Vakil N, Vaz Coelho LG, LeMair A, Melberg J (2023) *Helicobacter*

pylori World Gastroenterology Organization global guideline. J Clin Gastroenterol 57: 111–126. doi: 10.1097/MCG.0000000000001719.
5. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou J-M, Schulz C, Gasbarrini A, Hunt RH, Leja M, O'Morain C, Rugge M, Suerbaum S, Tilg H, Sugano K, El-Omar EM (2022) Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. Gut 71: 1724–1762. doi: 10.1136/gutjnl-2022-327745.
6. Chey WD, Leontiadis GI, Howden CW, Moss SF (2017) ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 112: 212–239. doi: 10.1038/ajg.2016.563.
7. Yang J-C, Lin C-J, Wang H-L, Chen J-D, Kao JY, Shun C-T, Lu C-W, Lin B-R, Shieh M-J, Chang M-C, Chang Y-T, Wei S-C, Lin L-C, Yeh W-C, Kuo J-S, Tung C-C, Leong Y-L, Wang T-H, Wong J-M (2015) High-dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* infection. Clin Gastroenterol Hepatol 13: 895–905.e5. doi: 10.1016/j.cgh.2014.10.036.
8. Gao CP, Zhang D, Zhang T, Wang JX, Han SX, Graham DY, Lu H (2020) PPI-amoxicillin dual therapy for *Helicobacter pylori* infection: an update based on a systematic review and meta-analysis. Helicobacter 25: e12692. doi: 10.1111/hel.12692.
9. Zhu Y-J, Zhang Y, Wang T-Y, Zhao J-T, Zhao Z, Zhu J-R, Lan C-H (2020) High dose PPI-amoxicillin dual therapy for the treatment of *Helicobacter pylori* infection: a systematic review with meta-analysis. Therap Adv Gastroenterol 13: 1756284820937115. doi: 10.1177/1756284820937115.
10. Dang NQH, Ha TMT, Nguyen S-T, Le NDK, Nguyen TMT, Nguyen TH, Pham TTH, Tran VH (2020) High rates of clarithromycin and levofloxacin resistance of *Helicobacter pylori* in patients with chronic gastritis in the south east area of Vietnam. J Glob Antimicrob Resist 22: 620–624. doi: 10.1016/j.jgar.2020.06.007.
11. Tran VH, Nguyen TMN, Le PTQ, Nguyen THT, Nguyen TCL, Ha TMT (2024) Current status of *Helicobacter pylori* resistance to clarithromycin and levofloxacin in Vietnam: results from molecular analysis of gastric biopsy specimens. J Glob Antimicrob Resist 36: 76–82. doi: 10.1016/j.jgar.2023.12.026.
12. Phan TN, Santona A, Tran TNH, Cappuccinelli P, Rubino S, Paglietti B (2015) High rate of levofloxacin resistance in a background of clarithromycin- and metronidazole-resistant *Helicobacter pylori* in Vietnam. Int J Antimicrob Agents 45: 244–248. doi: 10.1016/j.ijantimicag.2014.10.019.
13. Van-Khien V, Thang DM, Hai TM, Duat NQ, Khanh PH, Ha DT, Binh TT, Dung HDQ6, Trang TTH, Yamaoka Y (2019) Management of antibiotic-resistant *Helicobacter pylori* infection: perspectives from Vietnam. Gut Liver 13: 483. doi: 10.5009/gnl18137.
14. Phan TN, Tran TNH, Santona A, Rubino S, Paglietti B (2015) Antimicrobial resistance in *Helicobacter pylori*: current situation and management strategy in Vietnam. J Infect Dev Ctries 9: 609–613. doi: 10.3855/jidc.6942.
15. Graham DY, Moss SF (2022) Antimicrobial susceptibility testing for *Helicobacter pylori* is now widely available: when, how, why. Am J Gastroenterol 117: 524–528. doi: 10.14309/ajg.0000000000001659.
16. Rimbara E, Noguchi N, Kawai T, Sasatsu M (2008) Mutations in penicillin-binding proteins 1, 2 and 3 are responsible for amoxicillin resistance in *Helicobacter pylori*. J Antimicrob Chemother 61: 995–998. doi: 10.1093/jac/dkn051.
17. Kuo C-J, Ke J-N, Kuo T, Lin C-Y, Hsieh S-Y, Chiu Y-F, Wu H-Y, Huang M-Z, Bui N-N, Chiu C-H, Chiu C-T, Lai C-H (2023) Multiple amino acid substitutions in penicillin-binding protein-1A confer amoxicillin resistance in refractory *Helicobacter pylori* infection. J Microbiol Immunol Infect 56: 40–47. doi: 10.1016/j.jmii.2022.07.006.
18. Tran TT, Nguyen AT, Quach DT, Pham DT-H, Cao NM, Nguyen UT-H, Dang AN-T, Tran MA, Quach LH, Tran KT, Le NQ, Ung VV, Vo MN-Q, Nguyen DT, Ngo KD, Tran TL, Nguyen VT (2022) Emergence of amoxicillin resistance and identification of novel mutations of the *pbp1A* gene in *Helicobacter pylori* in Vietnam. BMC Microbiol 22: 41. doi: 10.1186/s12866-022-02463-8.
19. Vu NP, Nguyen HTT, Tran NTB, Nguyen TD, Huynh HTT, Nguyen XT, Nguyen DT, Nong HV, Nguyen HH (2019) *CYP2C19* genetic polymorphism in the Vietnamese population. Ann Hum Biol 46: 491–497. doi: 10.1080/03014460.2019.1687750.
20. Berry V, Jennings K, Woodnutt G (1995) Bactericidal and morphological effects of amoxicillin on *Helicobacter pylori*. Antimicrob Agents Chemother 39: 1859–1861. doi: 10.1128/AAC.39.8.1859.
21. Chey WD, Mégraud F, Laine L, López LJ, Hunt BJ, Howden CW (2022) Vonoprazan triple and dual therapy for *Helicobacter pylori* infection in the United States and Europe: randomized clinical trial. Gastroenterology 163: 608–619. doi: 10.1053/j.gastro.2022.05.055.
22. Peng X, Yao J-Y, Ma Y-q, Li G-h, Chen H-w, Wan Y, Liang D-s, Zhang M, Zhi M (2024) Efficacy and safety of vonoprazan-amoxicillin dual regimen with varying dose and duration for *Helicobacter pylori* eradication: a multicenter, prospective, randomized study. Clin Gastroenterol Hepatol 22: 1210–1216. doi: 10.1016/j.cgh.2024.01.022.