Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy of Vonoprazan-Doxycycline Dual Therapy for the Treatment of *Helicobacter pylori* Infection: A Retrospective Cohort Study

Xue Zhang[1,2,*], Qingrui Li[1,2,*], Yanhong Deng[2,*], Xilong Zhang[3,*], Ruijuan Xin[2], Tingting Yang[1,2], Xiaole Guo[2], Xiaoqin Ma[2], Xue Li[2], Yuanyuan Tang[2], Ruifang Guo[2], Linke Ma[2], Zhanbin Hou[4], Jinjuan Wang[4], Na Hou[4], Shengjuan Hu[2]

[1]Department of Gastroenterology, The Third Clinical College, Ningxia Medical University, Yinchuan, Ningxia, People's Republic of China; [2]Department of Gastroenterology, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, Ningxia, People's Republic of China; [3]Department of Gastroenterology, The Third People's Hospital of Shizuishan City, Shizuishan, Ningxia, People's Republic of China; [4]Department of Gastroenterology, Yanchi County People's Hospital, Wuzhong, Ningxia, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shengjuan Hu, Department of Gastroenterology, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, Ningxia, People's Republic of China, Email hsj.judy@163.com

Objective: To compare the efficacy and safety of vonoprazan-doxycycline dual therapy versus vonoprazan-amoxicillin high-dose dual therapy as first-line eradication treatment for *Helicobacter pylori (H. pylori)* infection.

Methods: This retrospective study collected clinical data from 357 patients with confirmed *H. pylori* infection who received first-line eradication therapy at the People's Hospital of Ningxia Hui Autonomous Region, The Third People's Hospital of Shizuishan City, and Yanchi County People's Hospital between December 2024 and December 2025. Patients aged 18–80 years with active *H. pylori* infection confirmed by $^{13}C/^{14}C$ urea breath test or histopathology were included. Key exclusion criteria included allergy to study medications, severe organ dysfunction, pregnancy, and incomplete medical records. Based on the treatment regimen, patients were divided into a vonoprazan-doxycycline dual-therapy group (doxycycline group, n = 180) and a vonoprazan-amoxicillin high-dose dual-therapy group (amoxicillin group, n = 177). Eradication outcomes were assessed by $^{13}C/^{14}C$ urea breath test four weeks after treatment completion. Adverse events were recorded during follow-up.

Results: ITT eradication rates were 76.1% (137/180) in the doxycycline group and 78.0% (138/177) in the amoxicillin group, with both falling below the commonly accepted 80% threshold for first-line therapy; PP eradication rates were 87.3% (137/157) and 89.0% (138/155), respectively. No statistically significant differences were observed in either analysis (both $P > 0.05$). At least one adverse event occurred in 31 patients (19.7%) in the doxycycline group versus 17 patients (11.0%) in the amoxicillin group, with a statistically significant difference in overall adverse event rates ($P \leq 0.05$). The incidence of nausea/vomiting and decreased appetite was significantly higher in the doxycycline group (both $P \leq 0.05$), whereas no significant differences were observed for other adverse events (all $P > 0.05$). All adverse events were mild to moderate; no patient discontinued treatment, and all symptoms resolved or improved after therapy completion.

Conclusion: Vonoprazan-doxycycline dual therapy may achieve comparable eradication efficacy to vonoprazan-amoxicillin dual therapy for *H. pylori*. Although the overall incidence of adverse events was higher in the doxycycline group, all were mild to moderate and well tolerated. This regimen may serve as a potential treatment alternative for patients with penicillin allergy or those requiring simplified treatment regimens, pending confirmation by prospective multicenter randomized trials.

Keywords: *Helicobacter pylori*, vonoprazan, doxycycline, amoxicillin, eradication rate, adverse events, retrospective study

Introduction

Helicobacter pylori (*H. pylori*) is a microaerophilic, Gram-negative bacterium that colonizes the gastric mucosa and serves as a major pathogenic factor in a wide spectrum of gastrointestinal disorders, including chronic gastritis, peptic

https://doi.org/10.2147/IDR.S618691
Received: 21 April 2026
Accepted: 15 June 2026
Published: 19 June 2026

ulcer disease, and gastric cancer.[1,2] The global prevalence of *H. pylori* infection exceeds 50%; in China, the average infection rate is 42.8%, with the highest prevalence reported in the northwestern region at approximately 51.3%.[3] The International Agency for Research on Cancer (IARC) has classified *H. pylori* as a Group 1 carcinogen, and eradication of *H. pylori* has been established as a critical strategy for gastric cancer prevention.[4] Current guidelines recommend bismuth-containing quadruple therapy as the first-line eradication regimen, comprising two antibiotics, a proton pump inhibitor (PPI), and a bismuth agent.[5] However, this regimen is associated with considerable gastrointestinal adverse effects, suboptimal patient adherence due to the complexity of the dosing schedule, and increased treatment costs.[6,7] In recent years, rising resistance rates to commonly used antibiotics—including clarithromycin, metronidazole, and levofloxacin—have led to a progressive decline in the eradication efficacy of bismuth quadruple therapy, from an initial rate of 80–95% to approximately 60–85%.[8,9] Therefore, the exploration of more simplified and effective treatment regimens is of considerable clinical importance.

High-dose dual therapy, combining an acid suppressant with amoxicillin, has been recommended by multiple international guidelines for *H. pylori* eradication[4,10] and has attracted growing attention in recent years owing to its simplified dosing, favorable tolerability, and high patient adherence.[11,12] A multicenter study reported that the full analysis set (FAS) eradication rate of high-dose dual therapy was 88.6%, and the per-protocol (PP) eradication rate was 89.5%. After inverse probability of treatment weighting (IPTW) adjustment, the vonoprazan-amoxicillin 14-day regimen achieved an FAS eradication rate of 95.1%, with an adverse event rate of 8.1%.[13] Nevertheless, approximately 5–10% of patients with *H. pylori* infection have documented penicillin allergy, precluding the use of amoxicillin-based regimens in this population.[14]

Tetracycline-class antibiotics exhibit notably lower and more stable resistance rates against *H. pylori* compared with other antibiotic classes.[15] Evidence suggests that tetracycline-based dual therapy achieves eradication efficacy comparable to classic quadruple regimens while offering superior safety and adherence, making it an important alternative for penicillin-allergic patients.[16] However, the clinical application of tetracycline remains limited by inadequate drug availability in primary healthcare settings. Doxycycline, a second-generation semi-synthetic tetracycline, possesses enhanced antibacterial activity and favorable pharmacokinetic properties, offering the potential to overcome the limitations of conventional treatment regimens.[17] It is important to note that prior studies on tetracycline-class antibiotics in *H. pylori* eradication have largely evaluated their use within bismuth-containing quadruple or as components of three-drug regimens.[18,19] To our knowledge, no study has yet examined doxycycline-containing vonoprazan-based dual therapy for *H. pylori* eradication. Although vonoprazan-based dual therapy with tetracycline or minocycline has been reported, existing studies have compared vonoprazan-tetracycline dual therapy with bismuth-containing quadruple regimens,[16] or vonoprazan-minocycline with vonoprazan-amoxicillin dual therapy.[20] However, doxycycline differs from tetracycline and minocycline in its pharmacokinetic profile and antibacterial potency, and clinical evidence directly comparing vonoprazan-doxycycline dual therapy with vonoprazan-amoxicillin dual therapy for first-line *H. pylori* eradication remains lacking. The present study aimed to evaluate the efficacy and safety of vonoprazan-doxycycline dual therapy as a first-line eradication regimen for *H. pylori* infection, with the goal of providing a treatment alternative for patients with penicillin allergy or those for whom treatment simplification is desirable.

Materials and Methods

Subjects

This was a retrospective cohort study. Clinical data were collected from patients with confirmed *H. pylori* infection who underwent first-line eradication therapy at the People's Hospital of Ningxia Hui Autonomous Region, The Third People's Hospital of Shizuishan City, and Yanchi County People's Hospital between December 2024 and December 2025. The study was approved by the Ethics Committee of the People's Hospital of Ningxia Hui Autonomous Region (Ethics Approval No. 2026-LL-142). Given the retrospective nature of this study, which involved only the review of existing medical records and posed no additional risk to patients, the Ethics Committee granted a waiver of informed consent. All patient data were anonymized prior to analysis, and strict confidentiality measures were implemented throughout the study to protect patient privacy. The study was conducted in accordance with the Declaration of Helsinki. (1) Inclusion

criteria: (i) age between 18 and 80 years; (ii) active *H. pylori* infection confirmed by $^{13}C/^{14}C$ urea breath test or histopathological examination; (iii) no use of potassium-competitive acid blockers, proton pump inhibitors, H_2 receptor antagonists, or bismuth-containing agents within the preceding 2 weeks; (iv) no use of antibiotics or traditional Chinese medicines with antibacterial activity within the preceding 4 weeks. (2) Exclusion criteria: (i) known allergy or intolerance to any study medication; (ii) history of gastrointestinal bleeding, obstruction, perforation, malignancy, or other serious organic disease; (iii) severe cardiac, hepatic, or renal insufficiency, or immunocompromised status; (iv) pregnancy, lactation, or planned pregnancy; (v) comorbid psychiatric disorders or inability to cooperate with the study; (vi) incomplete clinical records. (3) Grouping: Patients were divided into two groups according to the prescribed eradication regimen: the doxycycline dual-therapy group (vonoprazan combined with doxycycline) and the amoxicillin dual-therapy group (vonoprazan combined with amoxicillin).

Medications

The medications used in this study included vonoprazan (Tianjin Takeda Pharmaceutical Co., Ltd), doxycycline (Kaifeng Pharmaceutical (Group) Co., Ltd), and amoxicillin (Shandong Lukang Pharmaceutical Co., Ltd).

Treatment Regimens

Both regimens were administered for 14 days. In the vonoprazan-doxycycline group: vonoprazan 20 mg twice daily (30 min before meals) plus doxycycline 100 mg twice daily (30 min after meals). In the vonoprazan-amoxicillin group: vonoprazan 20 mg twice daily (30 min before meals) plus amoxicillin 1000 mg three times daily (30 min after meals). All medications were taken orally.

Follow-Up

All patients were followed up at the gastroenterology outpatient clinic after completing the urea breath test. Patients who failed to attend scheduled clinic visits were contacted by telephone for follow-up. Adverse events occurring during the treatment period were systematically recorded, including abdominal pain, abdominal bloating, nausea/vomiting, dry or bitter mouth, headache/dizziness, and decreased appetite. When present, adverse events were graded by severity according to their impact on daily activities: mild (no interference with daily activities), moderate (limited interference with daily activities), or severe (significant interference with daily activities).

Outcome Measures

The primary outcome measure was the *H. pylori* eradication rate, defined as the proportion of patients achieving successful *H. pylori* eradication as confirmed by a negative $^{13}C/^{14}C$ urea breath test performed 4 weeks after the cessation of therapy. The primary outcome was assessed using both intention-to-treat (ITT) and per-protocol (PP) analyses to provide a comprehensive assessment of treatment effectiveness. The secondary outcome measure was the incidence of adverse events during the treatment period in both groups.

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.3). Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test. Non-normally distributed continuous variables are presented as median (interquartile range) [M (Q1, Q3)] and compared using the Wilcoxon rank-sum test. Categorical variables are presented as frequencies (n) and percentages (%) and compared using the chi-square test or Fisher's exact test, as appropriate. All tests were two-sided, with a significance level set at $\alpha = 0.05$. A P value of ≤ 0.05 was considered statistically significant. No formal sample size or statistical power calculation was performed, given the retrospective nature of this study; the sample size reflects the number of eligible patients identified during the study period. Treatment outcomes were evaluated using both intention-to-treat (ITT) and per-protocol (PP) analyses. The ITT analysis included all patients with confirmed *H. pylori* infection who initiated eradication therapy, grouped according to the initially recorded treatment regimen. Given the retrospective nature of this study, patients with incomplete medical records, those who did not complete the full course of

treatment, and those for whom follow-up eradication outcomes were unavailable were all classified as treatment failures. The PP analysis was restricted to patients with complete medical records who completed the full treatment course and had evaluable follow-up eradication results. To adjust for potential confounders, multivariable logistic regression analysis was performed with eradication success as the dependent variable, incorporating treatment group, age, BMI, sex, smoking status, alcohol consumption, family history of gastric cancer, and consumption of pickled foods as covariates.

Results

Baseline Characteristics of Patients

A total of 357 patients were enrolled for ITT analysis, comprising 180 in the doxycycline dual-therapy group and 177 in the amoxicillin dual-therapy group. Of these, 157 patients in the doxycycline group and 155 in the amoxicillin group completed the full course of treatment and follow-up, and were therefore included in the PP analysis.

No statistically significant differences were observed between the two groups in baseline characteristics, including age, body mass index (BMI), sex distribution, smoking history, alcohol consumption history, family history of gastric cancer, and consumption of pickled foods (all $P > 0.05$). The standardized mean differences (SMDs) for these variables were all <0.2, with most being <0.1 (age: 0.042; sex: 0.053; smoking history: 0.074; alcohol consumption: 0.089; family history of gastric cancer: 0.067), indicating good balance between groups. Although the SMDs for BMI (0.138) and consumption of pickled foods (0.174) slightly exceeded 0.1, they remained well below 0.2, further supporting the comparability of the two groups at baseline. See Table 1.

Table 1 Comparison of Baseline Characteristics Between the Doxycycline-Based Dual Therapy Group and the Amoxicillin-Based Dual Therapy Group

Characteristic	Doxycycline-Based Dual Therapy Group (n = 180)	Amoxicillin-Based Dual Therapy Group (n = 177)	Statistic	P value	SMD
Age (years), M (Q1, Q3)	49.00 [42.75, 57.00]	46.00 [39.00, 60.00]	W = 14,950.5	0.315	0.042
BMI (kg/m^2), M (Q1, Q3)	23.47 [21.32, 25.00]	23.15 [20.83, 25.15]	W = 15,016.5	0.349	0.138
Sex, n (%)					0.053
Male	81 (45.0)	75 (42.4)	χ^2 = 0.16	0.694	
Female	99 (55.0)	102 (57.6)			
Smoking history, n (%)					0.074
Yes	40 (22.2)	34 (19.2)	χ^2 = 0.33	0.568	
No	140 (77.8)	143 (80.8)			
Alcohol consumption history, n (%)					0.089
Yes	40 (22.2)	33 (18.6)	χ^2 = 0.50	0.480	
No	140 (77.8)	144 (81.4)			
Family history of gastric cancer, n (%)					0.067
Yes	12 (6.7)	9 (5.1)	χ^2 = 0.17	0.682	
No	168 (93.3)	168 (94.9)			
Consumption of pickled foods, n (%)					0.174
Yes	73 (40.6)	57 (32.2)	χ^2 = 2.34	0.126	
No	107 (59.4)	120 (67.8)			

Notes: An SMD < 0.1 indicates good balance between groups. The doxycycline-based dual therapy group received vonoprazan plus doxycycline; the amoxicillin-based dual therapy group received vonoprazan plus high-dose amoxicillin.
Abbreviations: BMI, body mass index; SMD, standardized mean difference.

H. pylori Eradication Rates

In the ITT analysis, *H. pylori* eradication rates were 76.1% (137/180) in the doxycycline dual-therapy group and 78.0% (138/177) in the amoxicillin dual-therapy group, with a risk difference of −1.9% (95% CI: −10.6% to 6.9%); no statistically significant difference was observed between the two groups (χ^2 = 0.17, P = 0.677). In the PP analysis, eradication rates were 87.3% (137/157) and 89.0% (138/155) in the doxycycline and amoxicillin groups, respectively, with a risk difference of −1.8% (95% CI: −8.9% to 5.4%); again, no statistically significant difference was detected (χ^2 = 0.23, P = 0.629). See Table 2.

Multivariable Logistic Regression Analysis

To adjust for potential confounders, we performed multivariable logistic regression with eradication success as the dependent variable, treatment group as the independent variable, and adjusted for age, BMI, sex, smoking, alcohol consumption, family history of gastric cancer, and consumption of pickled foods. After adjustment, the doxycycline group showed no statistically significant difference in eradication success compared with the amoxicillin group in the ITT analysis (adjusted OR = 0.88, 95% CI 0.53–1.46, P = 0.626). The full regression results for the ITT analysis are shown in Table 3.

Adverse Events

PP analysis revealed that at least one adverse event occurred in 31 patients (19.7%) in the doxycycline dual-therapy group and 17 patients (11.0%) in the amoxicillin dual-therapy group, with a statistically significant difference in the overall incidence of adverse events between the two groups ($P \leq 0.05$). The incidence of nausea/vomiting and decreased appetite was significantly higher in the doxycycline group than in the amoxicillin group (both $P \leq 0.05$), whereas no statistically significant differences were observed between the two groups in the rates of abdominal bloating, abdominal pain, headache/dizziness, acid reflux, or dry/bitter mouth (all $P > 0.05$). All adverse events were mild to moderate in severity; no patient discontinued treatment as a result, and all symptoms resolved or improved spontaneously following completion of eradication therapy. See Table 4.

Table 2 Comparison of *H. pylori* Eradication Rates Between the Two Groups

Analysis Set	Doxycycline-Based Dual Therapy Group	Amoxicillin-Based Dual Therapy Group	Risk Difference (95% CI)	χ^2	P value
ITT	76.1% (137/180)	78.0% (138/177)	−1.9% (−10.6%-6.9%)	0.17	0.677
PP	87.3% (137/157)	89.0% (138/155)	−1.8% (−8.9%-5.4%)	0.23	0.629

Notes: The doxycycline-based dual therapy group received vonoprazan plus doxycycline; the amoxicillin-based dual therapy group received vonoprazan plus high-dose amoxicillin.

Table 3 Multivariable Logistic Regression Analysis of Factors Associated with *H. pylori* Eradication Success (ITT Analysis)

Variable	Adjusted OR	95% CI	*P* value
Group (doxycycline vs amoxicillin)	0.88	0.53–1.46	0.626
Age (per year)	1.00	0.98–1.02	0.935
BMI (per kg/m^2)	0.99	0.92–1.06	0.713
Sex (female vs male)	1.16	0.63–2.11	0.627
Smoking (no vs yes)	0.51	0.21–1.20	0.132
Alcohol consumption (no vs yes)	0.56	0.24–1.25	0.169
Family history of gastric cancer (no vs yes)	0.50	0.11–1.56	0.279
Pickled foods (no vs yes)	1.14	0.66–1.94	0.643

Notes: For categorical variables, the reference category is indicated in parentheses (eg, "no vs yes" means the "no" group is the reference). All variables were entered simultaneously into the model.

Table 4 Comparison of Adverse Events Between the Two Groups, n (%)

Group	Doxycycline-Based Dual Therapy Group (N = 157)	Amoxicillin-Based Dual Therapy Group (N = 155)	χ^2	*P* value
Abdominal Distension	1.3% (2/157)	3.2% (5/155)	-	0.281
Abdominal Pain	5.1% (8/157)	1.3% (2/155)	-	0.104
Nausea and Vomiting	7.0% (11/157)	1.9% (3/155)	4.68	0.031
Dizziness and Headache	2.5% (4/157)	1.3% (2/155)	-	0.684
Acid Reflux	0.6% (1/157)	2.6% (4/155)	-	0.213
Dry Mouth and Bitter Taste	0.6% (1/157)	1.3% (2/155)	-	0.621
Decreased Appetite	5.1% (8/157)	0.6% (1/155)	-	0.036
Total	19.7% (31/157)	11.0% (17/155)	4.62	0.032

Notes: The doxycycline-based dual therapy group received vonoprazan plus doxycycline; the amoxicillin-based dual therapy group received vonoprazan plus high-dose amoxicillin. "-" indicates Fisher's exact test was used; rows showing a χ^2 value were analyzed using the chi-square test.

Discussion

This retrospective cohort study compared the efficacy and safety of vonoprazan-doxycycline dual therapy versus vonoprazan-amoxicillin high-dose dual therapy as first-line eradication treatment for *H. pylori* infection. The results demonstrated that ITT eradication rates were 76.1% and 78.0%, and PP eradication rates were 87.3% and 89.0%, in the doxycycline and amoxicillin groups, respectively, with no statistically significant differences observed in either analysis (both $P > 0.05$). The results suggest that vonoprazan-doxycycline dual therapy may achieve eradication outcomes broadly comparable to vonoprazan-amoxicillin dual therapy for first-line *H. pylori* eradication. Regarding safety, the overall incidence of adverse events was significantly higher in the doxycycline group than in the amoxicillin group (19.7% vs 11.0%, $P \leq 0.05$); however, all adverse events were mild to moderate in severity, no patient discontinued treatment, and overall tolerability was satisfactory.

The continued rise in antibiotic resistance poses a serious challenge to the efficacy of conventional *H. pylori* eradication regimens. In China, the primary resistance rates of *H. pylori* to clarithromycin, metronidazole, and levofloxacin are 30.72%, 70.14%, and 32.98%, respectively,[21] contributing to a progressive decline in the eradication efficacy of bismuth quadruple therapy. Although bismuth-containing quadruple therapy remains the currently recommended first-line regimen, its complex composition, high dosing frequency, and frequent adverse events have been associated with reduced patient adherence.[22] In recent years, high-dose dual therapy has attracted considerable attention owing to its simplified regimen, favorable tolerability, and high adherence, with eradication rates comparable to those of recommended first-line regimens including bismuth and non-bismuth quadruple therapies.[23] Nevertheless, the efficacy of PPI-amoxicillin high-dose dual therapy is substantially influenced by CYP2C19 metabolizer phenotype, with lower eradication rates observed in rapid metabolizers;[24] furthermore, this regimen is contraindicated in patients with penicillin allergy. The primary resistance rate of *H. pylori* to tetracycline in China has been reported at 2.53%,[21] and the 2022 Chinese national guideline on *H. pylori* eradication explicitly recommends the inclusion of tetracycline-class antibiotics in eradication regimens. However, the limited availability of tetracycline in clinical settings, particularly at the primary care level, has constrained its widespread adoption. Therefore, treatment regimens that combine the antibacterial advantages of tetracycline-class antibiotics with greater accessibility represent an important clinical need for penicillin-allergic patients or those requiring simplified therapy.

Doxycycline, a second-generation semi-synthetic tetracycline, exhibits antibacterial activity 2–4 times greater than that of tetracycline and possesses favorable pharmacokinetic properties, including high lipophilicity, superior tissue penetration, and a prolonged half-life of 12–22 hours. Its high oral bioavailability is minimally affected by food intake, and its twice-daily dosing schedule is expected to enhance patient adherence while reducing the incidence of adverse events.[25] Vonoprazan, a novel potassium-competitive acid blocker, exerts rapid, potent, and sustained acid suppression by competitively binding to the potassium ion-binding site of the H^+/K^+-ATPase on gastric parietal cells, independently of CYP2C19 genetic polymorphisms, thereby providing an optimal intragastric pH environment for antibiotic activity.[11,26] The complementary mechanisms of vonoprazan and doxycycline offer a rational pharmacological basis for combination

therapy. It should be noted, however, that no in vitro or in vivo experiments were conducted to demonstrate true synergistic interaction between vonoprazan and doxycycline; the proposed complementarity therefore remains a hypothesis requiring confirmation in future pharmacodynamic and microbiological studies.

With respect to efficacy, a multicenter randomized controlled trial conducted in China previously reported a PP eradication rate of 92.9% for a doxycycline-containing quadruple regimen (ilaprazole plus bismuth, doxycycline, and furazolidone).[27] Although the vonoprazan-doxycycline dual regimen in the present study contained neither bismuth nor a second antibiotic, it nonetheless achieved a PP eradication rate of 87.3%, which is broadly comparable to that of the aforementioned quadruple therapy and suggests clinical feasibility of the regimen for penicillin-allergic patients or those requiring treatment simplification. Furthermore, after multivariable logistic regression adjusting for age, sex, BMI, smoking, alcohol consumption, family history of gastric cancer, and pickled-food consumption, the between-group difference in eradication remained non-significant in the ITT (adjusted OR 0.88, 95% CI 0.53–1.46), indicating that the comparability between the two regimens persisted after adjustment for the measured baseline characteristics, although residual or unmeasured confounding cannot be excluded. Nonetheless, the ITT eradication rates of 76.1% and 78.0% fell short of the 80% threshold recommended by domestic and international guidelines for first-line regimens, and two factors likely account for this shortfall. First, a conservative analytical approach was applied in the ITT analysis, whereby patients with incomplete medical records, those who did not complete the full treatment course, and those without available follow-up eradication results were all classified as treatment failures, which may have led to a systematic underestimation of the true eradication rate. Second, the retrospective study design inherently precludes the active adherence management strategies employed in prospective trials—such as scheduled follow-up visits and medication reminders—resulting in relatively limited oversight of patient compliance, which is likely a major contributor to the lower ITT eradication rates observed. Notably, the PP eradication rate of 87.3% in the doxycycline group is consistent with results from recent prospective studies of comparable regimens,[16,20] indicating that acceptable eradication can be achieved among patients who complete the full treatment course, even though the corresponding ITT rates remained below the recommended first-line threshold. These findings underscore the critical importance of strengthening patient adherence management and standardizing follow-up procedures in routine clinical practice.

The higher overall incidence of adverse events in the doxycycline group was driven predominantly by gastrointestinal symptoms, particularly nausea/vomiting and decreased appetite. Doxycycline is known to exert direct irritant effects on the gastrointestinal mucosa; in the present study, administration 30 minutes after meals was adopted to mitigate this effect, though gastrointestinal adverse events remained more prevalent in the doxycycline group, and clinicians should remain vigilant for the occurrence of such reactions. The overall adverse event rate of 19.7% in the doxycycline group was lower than the 39.8% reported by Yan et al[28] in a randomized controlled trial of vonoprazan combined with bismuth, doxycycline, and metronidazole, suggesting that the simplified dual regimen may reduce the burden of adverse events through a reduction in the total number of medications. Importantly, no serious adverse events occurred in either group, and no patient discontinued treatment because of adverse effects. In clinical practice, particular attention should be paid to gastrointestinal reactions such as nausea/vomiting and decreased appetite. Individualized management strategies—including pre-prescription counseling, adjustment of administration timing, and tailored follow-up—may further optimize adherence and treatment safety.

The present study has several limitations. First, as a non-randomized retrospective cohort study, the possibility of residual or unmeasured confounding cannot be fully excluded, despite multivariable adjustment for measured covariates. Second, antibiotic susceptibility testing for *H. pylori* strains was not performed, and the potential influence of doxycycline or amoxicillin resistance on eradication rates cannot be ruled out. Third, the study was conducted exclusively in the Ningxia region of northwestern China, and the generalizability of the findings to other populations warrants further investigation. Future prospective, multicenter, large-scale randomized controlled trials incorporating antibiotic susceptibility testing and formal non-inferiority designs are warranted to validate the efficacy and safety of vonoprazan-doxycycline dual therapy and inform clinical practice.

Conclusion

In conclusion, vonoprazan-doxycycline dual therapy may achieve comparable eradication efficacy to vonoprazan-amoxicillin dual therapy for *H. pylori*. Although the overall incidence of adverse events was higher in the doxycycline group, all were mild to moderate and well tolerated. This regimen may serve as a potential treatment alternative for patients with penicillin allergy or those requiring simplified treatment regimens, pending confirmation by prospective multicenter randomized trials.

Acknowledgments

Xue Zhang, Qingrui Li, Yanhong Deng and Xilong Zhang are co-first authors for this study. We are grateful to all the researchers and staff who participated in our research.

Funding

This research was funded by Ningxia Hui Autonomous Region Key Scientific and Technological Achievement Transformation Program, grant number: 2024CJE09045.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Huang TT, Cao YX, Cao L. Novel therapeutic regimens against *Helicobacter pylori*: an updated systematic review. *Front Microbiol*. 2024;15:1418129. doi:10.3389/fmicb.2024.1418129
2. Xue Y, Zhou LY, Lu HP, Liu JZ. Recurrence of *Helicobacter pylori* infection: incidence and influential factors. *Chin Med J*. 2019;132(7):765–771. doi:10.1097/CM9.0000000000000146
3. Xie L, Liu GW, Liu YN, et al. Prevalence of *Helicobacter pylori* infection in China from 2014-2023: a systematic review and meta-analysis. *World J Gastroenterol*. 2024;30(43):4636–4656. doi:10.3748/wjg.v30.i43.4636
4. Malfertheiner P, Megraud F, Rokkas T, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. *Gut*. 2022: gutjnl–2022–327745. doi:10.1136/gutjnl-2022-327745
5. *Helicobacter pylori* study group, Chinese society of gastroenterology, Chinese medical association. 2022 Chinese national clinical practice guideline on *Helicobacter pylori* eradication treatment. *Chin J Dig*. 2022;42(11):745–756. doi:10.3760/cma.j.cn311367-20220929-00479
6. Ford AC, Malfertheiner P, Giguere M, Santana J, Khan M, Moayyedi P. Adverse events with bismuth salts for *Helicobacter pylori* eradication: systematic review and meta-analysis. *World J Gastroenterol*. 2008;14(48):7361–7370. doi:10.3748/wjg.14.7361
7. Lan QL, Sun HY, Ye Y, Wang Y, Liu Y, Weng XJ. Factors affect the eradication rate of *Helicobacter pylori* by modified quadruple therapy: a prospective cohort study. *Infect Drug Resist*. 2022;15:2339–2345. doi:10.2147/IDR.S358464
8. Zhong Z, Zhang Z, Wang J, et al. A retrospective study of the antibiotic-resistant phenotypes and genotypes of *Helicobacter pylori* strains in China. *Am J Cancer Res*. 2021;11(10):5027–5037.
9. Gao CP, Zhang D, Zhang T, et al. PPI-amoxicillin dual therapy for *Helicobacter pylori* infection: an update based on a systematic review and meta-analysis. *Helicobacter*. 2020;25(4):e12692. doi:10.1111/hel.12692
10. Chey WD, Howden CW, Moss SF, et al. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2024;119 (9):1730–1753. doi:10.14309/ajg.0000000000002968
11. Zhang MM, Wang MD, Yang SY, et al. The efficacy and safety of vonoprazan-based high-dose dual therapy for eradication of *Helicobacter pylori*: a systematic review and meta-analysis. *J Infect Public Health*. 2025;18(7):102768. doi:10.1016/j.jiph.2025.102768
12. Du RC, Hu YX, Ouyang Y, et al. Vonoprazan and amoxicillin dual therapy as the first-line treatment of *Helicobacter pylori* infection: a systematic review and meta-analysis. *Helicobacter*. 2024;29(1):e13039. doi:10.1111/hel.13039
13. Kong Q, Wang B, Zhou B, et al. Comparative analysis of high-dose dual therapies in first-line *Helicobacter pylori* eradication: an inverse probability of treatment-weighted multicenter study. *J Infect Dis*. 2026:jiag059. doi:10.1093/infdis/jiag059
14. Castells M, Khan DA, Phillips EJ. Penicillin allergy. *N Engl J Med*. 2019;381(24):2338–2351. doi:10.1056/NEJMra1807761
15. Hong TC, El-Omar EM, Kuo YT, et al. Asian pacific alliance on helicobacter and microbiota. Primary antibiotic resistance of *Helicobacter pylori* in the Asia-Pacific region between 1990 and 2022: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2024;9(1):56–67. doi:10.1016/S2468-1253(23)00281-9
16. Gao W, Liu J, Wang X, et al. Simplified *Helicobacter pylori* therapy for patients with penicillin allergy: a randomised controlled trial of vonoprazan-tetracycline dual therapy. *Gut*. 2024;73(9):1414–1420. doi:10.1136/gutjnl-2024-332640
17. Costigan C, Comerford M, Whitmarsh R, et al. Bismuth quadruple therapy with doxycycline is an effective first-line therapy for *Helicobacter pylori* in an Irish cohort. *Antibiotics*. 2025;14(8):757. doi:10.3390/antibiotics14080757
18. Xie Y, Zhu Z, Wang J, et al. Ten-day quadruple therapy comprising low-dose rabeprazole, bismuth, amoxicillin, and tetracycline is an effective and safe first-line treatment for *Helicobacter pylori* infection in a population with high antibiotic resistance: a prospective, multicenter, randomized, parallel-controlled clinical trial in China. *Antimicrob Agents Chemother*. 2018;62(9):e00432–18. doi:10.1128/AAC.00432-18
19. Bang CS, Lim H, Jeong HM, et al. Amoxicillin or tetracycline in bismuth-containing quadruple therapy as first-line treatment for *Helicobacter pylori* infection. *Gut Microbes*. 2020;11(5):1314–1323. doi:10.1080/19490976.2020.1754118

20. Yang TT, Li X, Guo XL, et al. A non-inferiority randomized controlled study on minocycline-based dual regimens in *Helicobacter pylori* eradication. *Chin J Dig*. 2025;45(11):728–734. doi:10.3760/cma.j.cn311367-20250527-00219
21. Zeng S, Kong Q, Wu X, et al. Antibiotic resistance of *Helicobacter pylori* in Mainland China: a focus on geographic differences through systematic review and meta-analysis. *Int J Antimicrob Agents*. 2024;64(5):107325. doi:10.1016/j.ijantimicag.2024.107325
22. Yang EH, Chen WY, Chiang HC, et al. 10-Day versus 14-day bismuth quadruple therapy for first-line eradication of *Helicobacter pylori* infection: a randomised, open-label, non-inferiority trial. *EClinicalMedicine*. 2024;70:102529. doi:10.1016/j.eclinm.2024.102529
23. Huang Q, Shi Z, Cheng H, Ye H, Zhang X. Efficacy and safety of modified dual therapy as the first-line regimen for the treatment of *Helicobacter pylori* infection: a meta-analysis of randomized controlled trials. *J Clin Gastroenterol*. 2021;55(10):856–864. doi:10.1097/MCG.0000000000001448
24. Yun J, Wu Z, Qi G, et al. The high-dose amoxicillin-proton pump inhibitor dual therapy in eradication of *Helicobacter pylori* infection. *Expert Rev Gastroenterol Hepatol*. 2021;15(2):149–157. doi:10.1080/17474124.2021.1826306
25. Gu L, Li S, He Y, et al. Bismuth, rabeprazole, amoxicillin, and doxycycline as first-line *Helicobacter pylori* therapy in clinical practice: a pilot study. *Helicobacter*. 2019;24(4):e12594. doi:10.1111/hel.12594
26. St Onge E, Phillips B. Vonoprazan: a new potassium-competitive acid blocker. *J Pharm Technol*. 2023;39(3):139–146. doi:10.1177/87551225231166531
27. Chi J, Xu C, Liu X, et al. A comparison of doxycycline and amoxicillin containing quadruple eradication therapy for treating *Helicobacter pylori*-infected duodenal ulcers: a multicenter, opened, randomized controlled trial in China. *Pathogens*. 2022;11(12):1549. doi:10.3390/pathogens11121549
28. Yan T, Wang J, Zhu R, et al. Vonoprazan improves the efficacy of bismuth quadruple therapy containing doxycycline and metronidazole as first-line *Helicobacter pylori* treatment in penicillin-allergic patients: a randomized controlled trial. *J Antimicrob Chemother*. 2025;80(4):927–934. doi:10.1093/jac/dkae467