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# Efficacy and Safety of Vonoprazan and High-Dose Amoxicillin Dual Therapy for Rescue Treatment of *Helicobacter pylori* Infection: A Multicenter Randomized Controlled Trial

Ju Zhang[1,2] | Xinzhao Wang[2] | Shujie Song[2] | Xiaoming Zhu[2] | Ting Lv[3] | Lingling Wang[3] | Lei Lei[3] | Yuhui Wang[4] | Yali Lei[4] | Yating Wang[4] | Xiaojing Zhu[1] | Lifeng Zhang[1] | Min Chen[1] | Yongquan Shi[1]

[1]State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers and National Clinical Research Center for Digestive Diseases, Department of Gastroenterology, The First Affiliated Hospital, The Fourth Military Medical University, Xi'an, China | [2]Department of Gastroenterology, Pingdingshan Medical District, 989 Hospital of PLA Joint Logistics Support Force, Pingdingshan, China | [3]Department of Gastroenterology, Shaanxi Nuclear Industry 215 Hospital, Xianyang, China | [4]Department of Gastroenterology, Weinan Central Hospital, Weinan, China

**Correspondence:** Yongquan Shi (shiyquan@fmmu.edu.cn)

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**Keywords:** adverse events | amoxicillin | compliance | dual therapy | eradication | *Helicobacter pylori* | high-dose | rescue treatment | vonoprazan

## ABSTRACT

**Background:** Vonoprazan and amoxicillin dual therapy has demonstrated favorable efficacy in the initial treatment of *Helicobacter pylori* (*H. pylori*) infection. This study aimed to evaluate the efficacy and safety of vonoprazan and high-dose amoxicillin (VHA) dual therapy for *H. pylori* rescue treatment.

**Methods:** This was an open label, multicenter, non-inferiority, and randomized controlled clinical trial conducted at four institutions in both central and northwestern China. A total of 688 *H. pylori*-infected patients who had failed previous treatments were randomly assigned (1:1) to receive either VHA dual therapy or the tetracycline- and furazolidone-based bismuth-containing quadruple therapy (TFEB) for 14 days. Eradication rates, adverse event (AE) rates, and the patient compliance were compared between the two groups.

**Results:** The eradication rates in the VHA and TFEB groups were 73.8% and 76.2% ($p = 0.481$), respectively, by intention-to-treat (ITT) analysis; 81.9% and 85.6% ($p = 0.215$), respectively, by modified ITT (MITT) analysis; and 82.1% and 85.6% ($p = 0.248$), respectively, by per-protocol (PP) analysis. VHA therapy remained non-inferior to TFEB in ITT, MITT, and PP analyses. The overall AE incidence in the VHA group was significantly lower compared with that in the TFEB group (13.4% vs.. 28.5%, $p < 0.001$). Patients' compliance was similar between the two groups. A history of multiple prior eradication failures was an independent risk factor (2 failures: OR = 0.566, $p = 0.032$; ≥ 3 failures: OR = 0.335, $p < 0.001$) reducing the efficacy of *H. pylori* rescue therapy.

**Conclusion:** The 14-day VHA dual therapy was non-inferior to bismuth-containing quadruple therapy, with a lower incidence of adverse events and good compliance, and may represent an effective alternative for *H.pylori* rescue treatment.

**Trial Registration:** This trial was registered at ClinicalTrials.gov (No. NCT06168084)

**Summary**

- Summarise the established knowledge on this subject
  - VHA dual therapy demonstrated significant efficacy in first-line *H. pylori* treatment.
  - BQT remains the recommended rescue regimen in most guidelines.
  - BQT may pose challenges such as higher adverse events and potential secondary resistance risk in *H. pylori.*
- What are the significant and/or new findings of this study?
  - VHA dual therapy was non-inferior to BQT and may represent an effective alternative for *H. pylori* rescue treatment.
  - A history of multiple prior eradication failures was an independent risk factor reducing the efficacy of *H. pylori* rescue therapy.

## 1 | Introduction

*Helicobacter pylori* (*H. pylori*) is an infectious pathogen that affects more than 40% of the global population [1, 2]. *H. pylori* infection is associated with many gastrointestinal diseases, such as chronic gastritis, peptic ulcers, gastric lymphoma, and gastric cancer [3]. In principle, eradicating treatment is required for every patient with *H. pylori* infection [4].

Since the resistance rates of metronidazole, clarithromycin, and levofloxacin significantly increased over the past 10 years [5], traditional treatment regimens that contain these antibiotics showed reduced efficacy. Consequently, an increasing number of patients require rescue therapy (treatment following failed *H. pylori* eradication). Approximately 15% of Chinese patients experience primary *H. pylori* eradication failure [6]. Bismuth supplementation has gained increasing acceptance for improving eradication rates, with bismuth-containing quadruple therapy (BQT) being a prime example. In China, BQTs containing two low-resistance antibiotics, such as amoxicillin, tetracycline, and furazolidone, are recommended for empirical rescue treatment [7]. Among those regimens, the tetracycline- and furazolidone-based BQT is a commonly used and effective option. Recently, high-dose dual therapy (HDDT), including high-dose proton pump inhibitors (PPIs) and high-dose amoxicillin, was recommended by several guidelines as a second-line regimen for its good efficiency and fewer adverse events [4, 7, 8].

Vonoprazan, the first potassium-competitive acid blocker (PCAB), demonstrates more rapid, robust, and prolonged acid suppression than standard-dose PPIs [9]. As a potential replacement for PPIs, vonoprazan may further enhance the efficacy of HDDT. Several randomized controlled trials (RCTs) have demonstrated that vonoprazan and high-dose amoxicillin (VHA) dual therapy, the vonoprazan-based HDDT, is not inferior to BQT and even superior to rabeprazole-based HDDT in the first-line treatment [10–12]. However, no high-quality studies have investigated the application of VHA dual therapy in the rescue treatment of *H. pylori.* Therefore, we conducted a multicenter randomized controlled trial to evaluate the efficacy and safety of 14-day VHA dual therapy regimen in comparison with tetracycline- and furazolidone-based BQT for the management of treatment-experienced patients with persistent *H. pylori* infection.

## 2 | Methods

### 2.1 | Study Design and Ethical Issues

This study was designed as a multicenter, open-label, non-inferiority, randomized controlled trial and registered at ClinicalTrials.gov (No. NCT06168084). The study protocol follows the Declaration of Helsinki, and was approved by the Ethics Committees of the First Affiliated Hospital of The Fourth Military Medical University (No. KF20232236-F-2). Written informed consent was obtained from all participants before enrollment. All authors had access to the study data and reviewed and approved the final manuscript.

### 2.2 | Study Population

*H. pylori*-infected patients who had failed previous treatment at least once from outpatient clinics of four medical centers in both central and northwestern China between June 2023 and June 2024 were screened for eligibility.

The inclusion criteria were: (1) participants were aged between 18 and 70 years; (2) treatment-experienced patients with persistent *H. pylori* infection; and (3) patients with childbearing potential were required to use contraception during the trial and 30 days thereafter.

The exclusion criteria were: (1) prior *H. pylori* eradication using tetracycline-/furazolidone-based regimens or vonoprazan-amoxicillin dual therapy; (2) contraindications to study drugs or use of PPIs/$H_2$RA/PCABs within 2 weeks or antibiotics/bismuth (> 3 times/week) within 4 weeks before *H. pylori* testing; (3) current use of systemic corticosteroids, NSAIDs, anticoagulants, or antiplatelet agents (excluding aspirin < 100 mg/day); (4) severe comorbidities including cardiopulmonary/endocrine diseases, organ dysfunction, active bleeding, iron deficiency anemia, malignancy (including MALT lymphoma), or psychiatric disorders; (5) gastrointestinal conditions such as prior upper GI surgery, severe gastric dysplasia, or dysphagia; (6) pregnancy/lactation; (7) drug or alcohol abuse within 1 year; (8) concurrent clinical trial participation, or declined informed consent.

### 2.3 | Randomization and Treatment

Eligible patients at each center were randomly assigned to two groups in a 1:1 ratio using a computer-generated block randomization sequence (generated by an independent third party and concealed in sequentially numbered, opaque, sealed envelopes stored by independent research assistants at each center, to be opened only after enrollment) for 14-day treatment: (i) VHA group (vonoprazan 20 mg twice daily and amoxicillin

1000 mg three times daily); or (ii) TFEB group (tetracycline 500 mg three times daily, furazolidone 100 mg twice daily, esomeprazole 40 mg twice daily, and colloidal bismuth tartrate 220 mg twice daily). Vonoprazan, esomeprazole and colloidal bismuth tartrate were administered 30 min before breakfast and supper, while furazolidone 30 min after breakfast and supper. Tetracycline and amoxicillin were administered 30 min after 3 meals.

The drug information is as follows: vonoprazan (Takeda Pharmaceutical, Tianjin, China), amoxicillin (Zhongnuo Pharmaceutical, Shijiazhuang, Hebei Province, China), esomeprazole (Jiangxi shanxiang Pharmaceutical, Ganzhou, Jiangxi Province, China), colloidal bismuth tartrate (Shanxi Shuangyan Pharmaceutical, Datong, Shanxi Province, China), tetracycline (Guangdong Huanan Pharmaceutical, Dongguan, Guangdong Province, China), and furazolidone (Yunpeng Pharmaceutical, Linfen, Shanxi Province, China).

### 2.4 | Diagnosis of *H. pylori* Infection

*H. pylori* infection was diagnosed by $^{13}C/^{14}C$ urea breath test ($^{13}C/^{14}C$-UBT), rapid urease test (RUT), *H. pylori* stool antigen test (HpSAT), or histological examination. A positive result on any of these tests confirmed current *H. pylori* infection. Successful eradication was confirmed by negative $^{13}C/^{14}C$-UBT results at least 4 weeks after treatment or, in cases where participants had a positive RUT result or histological confirmation of *H. pylori* infection but negative pre-treatment $^{13}C/^{14}C$-UBT results, by negative HpSAT results.

### 2.5 | Follow Up and Outcomes

All the participants were informed of possible adverse drug reactions and detailed medication instructions before treatment, and were asked to record all adverse events and daily medication intake. Follow-up was performed at the end of treatment and 4 weeks later through WeChat or mobile phone calls. Adverse events were categorized as minor (discomfort that did not interfere with normal activities), moderate (sufficient discomfort to cause interference with normal activities), or severe (severe discomfort that required discontinuation of therapy). Patient compliance was systematically assessed through two complementary approaches: (1) inquiring about the remaining pill count after 14 days of treatment during telephone follow-up, and (2) patient-reported medication diaries. Good compliance was defined as taking ≥ 80% of the prescribed drugs.

The primary outcome of this study was the *H. pylori* eradication rates in intention-to-treat (ITT) and per-protocol (PP) analyses. All the enrolled participants were included in the ITT analysis; only those with good compliance and underwent the endpoint measure were included in the PP analysis. In addition, patients who toke < 80% of the medication but underwent the endpoint measure were included in the modified ITT (MITT) analysis.

The secondary outcomes were the incidence of adverse events and compliance in both groups.

### 2.6 | Sample Size Calculation and Statistical Analysis

The sample size was calculated using PASS 2020. According to previous studies, we assumed that the *H. pylori* eradication rates were 80% for both VHA dual therapy and TFEB quadruple therapy in rescue treatment [13, 14]. We set the non-inferiority margin at 10% (VHA was considered non-inferior to standard TFEB if the lower bound of the 95% confidence interval for the treatment difference did not exceed a 10% reduction in efficacy) with one-sided $\alpha$ of 0.05 and a power of 90%, and considered a 20% dropout rate. This calculation yielded a required sample size of 688 participants (344 per group).

Statistical analyses were performed using SPSS 26.0. Normally distributed continuous variables were presented as mean ± standard deviation (mean ± SD) and compared using t-tests, non-normally distributed variables as median (interquartile range [IQR]) and analyzed using the Mann–Whitney *U* test. Categorical variables were presented as numbers and percentages and were compared through the chi-squared test or Fisher's exact test. Comparative non-inferiority of VHA dual therapy and TFEB quadruple therapy was assessed through hypothesis testing (1-sided test) and derivation of a 2-sided 95% confidence interval (CI). Univariate analysis was performed to explore significant variables affecting the *H. pylori* eradication rate, followed by a multivariate binary logistic regression. A $p$ value < 0.05 was considered statistically significant.

## 3 | Results

### 3.1 | Patient Enrollment and Baseline Characteristics

As shown in Figure 1, a total of 688 participants were randomly assigned to the 14-day VHA or TFEB regimen. Among the VHA and TFEB groups, 310 and 306 subjects were included in MITT analysis, respectively, after excluding those lost to follow-up, who refused endpoint assessment, violated medication protocols, or discontinued treatment due to intolerable adverse events. In addition, 2 patients in the VHA group and 1 in the TFEB group were excluded from the PP analysis for poor compliance.

No significant difference was found in baseline characteristics, including demographics, time to rescue therapy (interval between last failed treatment and rescue therapy), previous failed eradication times, and previous antibiotic therapies between the 2 groups (Table 1).

### 3.2 | *H. pylori* Eradication Rates

The *H. pylori* eradication rates and differences between groups are presented in Table 2. In the ITT analysis, the eradication rates were 73.8% (254/344) in the VHA group and 76.2% (262/344) in the TFEB group. The eradication rates in the PP analyses for the VHA and TFEB groups were 82.1% (254/310) and 85.6% (261/305), respectively. No statistically significant between-

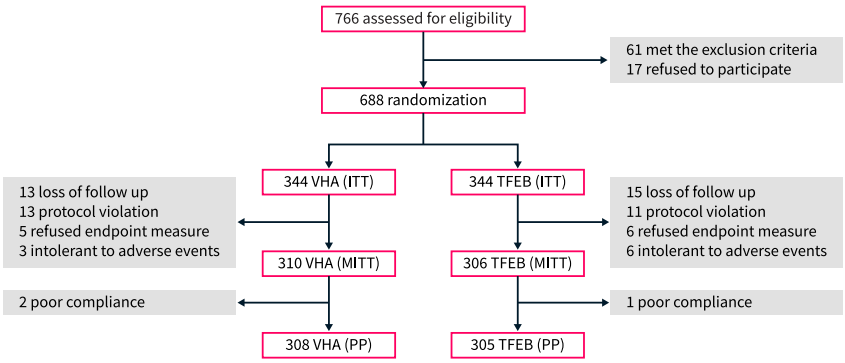


**FIGURE 1** | Flowchart of subjects enrollment.

group differences were observed ($p = 0.481$, $p = 0.248$ for the ITT and PP analysis, respectively).

In the non-inferiority analysis, the eradication rate differences and their respective 95% CIs between the VHA and TFEB groups were −2.3% (−8.8%–4.1%) in the ITT analysis and −3.4% (−9.3%–2.4%) in the PP analysis. All lower 95% CI boundaries exceeded the protocol-specified non-inferiority margin of −10%. According to the 1-sided Z test, assuming that the lower boundaries of the confidence interval for the eradication rate difference above were equal to −10%, the corresponding $p$ values were 0.010 and 0.013, respectively.

### 3.3 | Adverse Events and Compliance

As shown in Table 3, fewer adverse events were observed in the VHA group compared with the TFEB group (13.4% vs.. 28.5%, $p < 0.001$). Among all the adverse events, nausea and vomiting (4.4% vs.. 17.2%, $p < 0.001$) and dysgeusia (0.9% vs.. 4.9%, $p < 0.001$) occurred more frequently in the TFEB group than in the VHA group, while the rates of other adverse events (abdominal pain, bloating, diarrhea, constipation, headache, dizziness, tinnitus, fatigue, and skin rash) were comparable between the groups. Treatment discontinuation due to severe adverse events occurred in 0.9% (3/344) of the VHA group and 1.7% (6/344) of the TFEB group ($p = 0.505$). Notably, the 3 cases in the VHA group were discontinued due to intolerable nausea and vomiting, abdominal distension, and abdominal pain, respectively. In the TFEB group, all 6 cases reported intolerable nausea and vomiting, with two also experiencing dizziness and one each reporting diarrhea and abdominal pain.

Three hundred thirteen patients in the VHA group and 311 in the TFEB group had taken ≥ 80% of the prescribed medication. The rates of good compliance were similar in the two groups (91.0% vs. 90.4%, $p = 0.793$).

### 3.4 | Risk Factors Influencing Efficacy

As shown in Table 4, in the PP analysis population, univariate analysis results showed that the eradication rate was higher in males than in females (87.2% vs. 81.1%, $p = 0.041$), and it decreased significantly with an increasing number of prior eradication failures ($p = 0.001$). In contrast, age, body mass index (BMI), ethnicity, ethnicity, marital status, family history of gastric cancer, education level, family sizes, monthly household income, smoking, drinking, rescue treatment interval for this time, and the intake of coffee, tea, dairy products, vegetables and fruits were not significantly associated with *H. pylori* eradication rates.

Further multivariate logistic regression analysis identified a history of multiple prior eradication failures as an independent risk factor reducing the efficacy of *H. pylori* rescue therapy (Table 5). Compared to patients with only one previous failure, those with two failed attempts exhibited significantly lower success rates (OR = 0.566, 95% CI: 0.337–0.952, $p = 0.032$), whereas patients with ≥ 3 failures showed a further reduction in efficacy (OR = 0.335, 95% CI: 0.184–0.611, $p < 0.001$), indicating a dose-dependent relationship between prior failure frequency and treatment efficacy. Although female sex showed a trend toward higher eradication rates (OR = 0.65), this trend did not reach statistical significance ($p = 0.06$).

## 4 | Discussion

To the best of our knowledge, this is the first multicenter RCT evaluating the efficacy and safety of VHA dual therapy in rescue treatment of *H. pylori* infection compared with BQT. In this study, the 14-day VHA dual therapy of vonoprazan 20 mg twice daily and amoxicillin 1000 mg 3 times daily as a rescue regimen resulted in eradication rates of 73.8% (ITT analysis), 81.9% (MITT analysis), 82.1% (PP analysis), demonstrating non-inferiority to the tetracycline- and furazolidone-based BQT.

Amoxicillin has remained the most consistently effective for *H. pylori*, with pH dependence and time dependence [5, 15, 16]. First, a high gastric pH could enhance amoxicillin's optimal stability and bioavailability. Moreover, prolonged acid suppression induces *H. pylori* to enter a replicative state, enhancing its susceptibility to amoxicillin that targets cell wall synthesis. As a potent PPI alternative, vonoprazan maintains intragastric pH > 5 consistently at a daily 40 mg dose, independent of the CYP2C19 genotype [17], creating an ideal microenvironment for amoxicillin monotherapy. Second, the time above minimal inhibitory concentration (MIC) of amoxicillin could be maximized by administered three or four times daily [16]. These are the theoretical basis for the high efficiency of vonoprazan and high-dose amoxicillin dual therapy.

**TABLE 1** | Baseline characteristics of the participants.

| Variables | VHA group | TFEB group | *p* value |
|---|---|---|---|
| Age (years), median (IQR) | 50.0 (41.0–59.0) | 51.0 (40.0–59.0) | 0.265 |
| Gender (male/female) | 172/172 | 147/197 | 0.056 |
| BMI (kg/m$^2$), median (IQR) | 22.65 (20.53–24.78) | 22.98 (20.80–25.15) | 0.419 |
| Family history of gastric cancer | 20 (5.8%) | 29 (8.4%) | 0.182 |
| Cigarette smoking | 63 (18.3%) | 59 (17.2%) | 0.690 |
| Alcohol drinking | 35 (10.2%) | 36 (10.5%) | 0.900 |
| Ethnicity | | | 0.129 |
| Han | 333 (96.8%) | 339 (98.5%) | |
| Others | 11 (3.2%) | 5 (1.5%) | |
| Education level | | | 0.701 |
| High school or less | 194 (56.4%) | 189 (54.9%) | |
| College or more | 150 (43.6%) | 155 (45.1%) | |
| Family size | | | 0.427 |
| < 4 people | 215 (62.5%) | 225 (65.4%) | |
| ≥ 4 people | 129 (37.5%) | 119 (34.6%) | |
| Monthly household income | | | 0.265 |
| < 4000 Chinese yuan | 24 (7.0%) | 32 (9.3%) | |
| ≥ 4000 Chinese yuan | 320 (93.0%) | 312 (90.7%) | |
| Time to rescue therapy | | | 0.100 |
| < 6 months | 123 (35.8%) | 144 (41.9%) | |
| ≥ 6 months | 221 (64.2%) | 200 (58.1%) | |
| Previous failed eradication times | | | 0.526 |
| 1 | 244 (70.9%) | 232 (67.4%) | |
| 2 | 67 (19.5%) | 71 (20.6%) | |
| ≥ 3 | 33 (9.6%) | 41 (11.9%) | |
| Previous antibiotic therapies (person-time) | | | 0.554 |
| Amoxicillin + clarithromycin | 304 (60.8%) | 324 (61.7%) | |
| Amoxicillin + metronidazole | 42 (8.4%) | 41 (7.8%) | |
| Clarithromycin + tinidazole | 34 (6.8%) | 28 (5.3%) | |
| Amoxicillin + levofloxacin | 9 (1.8%) | 9 (1.7%) | |
| Amoxicillin + tetracycline | 17 (3.4%) | 10 (1.9%) | |
| Amoxicillin + furazolidone | 17 (3.4%) | 24 (4.6%) | |
| Clarithromycin + metronidazole | 4 (0.8%) | 9 (1.7%) | |
| Others[a] | 73 (14.6%) | 80 (15.2%) | |

Abbreviation: BMI, body mass index.
[a]Others refer to antibiotic therapies with fewer than 5 person-times in both groups as well as unspecified antibiotic therapies.

A previous study of our team showed that the eradication rate of 14-day HDDT (esomeprazole 40 mg and amoxicillin 1000 mg thrice daily) for *H. pylori* rescue treatment was 81.3% in PP analysis [14]. Compared with our previous HDDT regimen using ultra-high dose esomeprazole, the VHA dual therapy with a double standard dose of vonoprazan achieved similar efficiency. Substitution of PPIs with vonoprazan in HDDT can reduce the use of gastric acid suppressants and improve cost-effectiveness. A recent study in Southwest China reported an eradication rate of 87.5% (105/120) with the same 14-day VHA dual therapy (vonoprazan 20 mg twice daily plus amoxicillin 1000 mg three times daily) as rescue regimen [18], which is higher than our PP analysis result of 82.1% (254/310). This discrepancy might be attributed to regional variations in *H. pylori* resistance to amoxicillin or variations in patient demographics. A single arm study with a small sample from China showed that the 14-day VAS rescue regimen (vonoprazan 20 mg twice daily, amoxicillin 750 mg thrice daily, and *Saccharomyces boulardii* [*S. boulardii*] 250 mg twice daily) achieved an excellent eradication rate of 92.3% (60/65) in PP analysis [19]. Whether

**TABLE 2** | *Helicobacter pylori* eradication rates of each group and difference.

| Items | VHA group (*n*/*N*) | TFEB group (*n*/*N*) | *p* value for difference[a] | Difference from TFEB | *p* value for noninferiority[b] |
|---|---|---|---|---|---|
| ITT analysis | 73.8% (254/344) | 76.2% (262/344) | 0.481 | −2.3% | 0.010[c] |
| 95% CI | 69.2%–78.5% | 71.7%–80.7% | | −8.8%–4.1% | |
| PP analysis | 82.1% (254/310) | 85.6% (261/305) | 0.248 | −3.4% | 0.013[a,c] |
| 95% CI | 77.9%–86.4% | 81.6%–89.5% | | −9.3%–2.4% | |

*Note:* MITT analysis results are shown in Table S1.
[a]*p* values were obtained from two-sided comparisons of the difference between the VHA group and the TFEB RA group.
[b]*p* values were obtained from one-sided test comparisons of non-inferiority between the VHA group and the TFEB group.
[c]*p* value is statistically significant.

**TABLE 3** | Adverse events in each group.

| Items | VHA group $N = 344$ | TFEB group $N = 344$ | *p* value |
|---|---|---|---|
| Overall AEs | 46 (13.4%) | 98 (28.5%) | < 0.001[a] |
| Severe AEs | 3 (0.9%) | 6 (1.7%) | 0.505 |
| Nausea | 15 (4.4%) | 59 (17.2%) | < 0.001[a] |
| Dysgeusia | 3 (0.9%) | 17 (4.9%) | < 0.001[a] |
| Abdominal pain | 7 (2.0%) | 9 (2.6%) | 0.613 |
| Bloating | 9 (2.6%) | 21 (6.1%) | 0.025 |
| Diarrhea | 7 (2.0%) | 3 (0.9%) | 0.203 |
| Constipation | 1 (0.3%) | 3 (0.9%) | 0.624 |
| Headache | 1 (0.3%) | 2 (0.6%) | 1.0 |
| Dizziness | 4 (1.2%) | 8 (2.3%) | 0.244 |
| Tinnitus | 0 (0%) | 1 (0.3%) | 1.0 |
| Fatigue | 2 (0.6%) | 5 (1.5%) | 0.451 |
| Skin rash | 2 (0.6%) | 7 (2.0%) | 0.177 |

[a]*p* value is statistically significant.

supplementation with *S. boulardii* can significantly enhance the efficacy of VHA dual therapy still needs to be confirmed with carefully designed randomized controlled trials.

Adverse events and patient compliance are also important aspects in evaluating *H. pylori* eradication regimens. In our study, the good compliance rates of both groups were above 90%, partly due to the fact that almost all follow-up visits were conducted through WeChat, the most convenient and prevalent social application in China. The overall incidence of adverse events in the VHA group was significantly lower than that in the TFEB group ($p < 0.001$) as were the adverse events of nausea, vomiting, and dysgeusia. These symptoms may be attributed to the use of bismuth agents and relatively more antibiotics in the TFEB regimen. In addition, the number of serious adverse events in the TFEB group was twice that in the VHA group, although there was no statistically significant difference in incidence. Probiotic supplementation may reduce the incidence of adverse events associated with microbial dysbiosis in the TFEB group. These findings further underscore the need to investigate novel dual-therapy regimens.

We further explored factors that may affect the results of rescue eradication by univariate analysis and multivariate binary logistic regression analysis. In this study, a history of multiple previous eradication failures was the risk factor affecting rescue treatment of *H. pylori*. Perhaps multiple treatment failures have increased the antibiotic resistance of *H. pylori*. Moreover, a study investigating iatrogenic factors contributing to *H. pylori* treatment failure suggested that the optimal interval for rescue therapy should exceed 6 months [20]. However, our study showed no significant difference in eradication rates between patients receiving rescue therapy within 6 months versus after 6 months of last failed eradication (83.4% vs. 84.1%, $p = 0.809$).

To be sure, there are some limitations to this study. First, all the centers for this trial were located in central or northwestern China, and most of the participants were from Shaanxi province and its surrounding regions. Given the potential influence of regional characteristics—including dietary patterns (e.g., prevalent high-salt diets), variations in treatment protocols (e.g., drug dosage/frequency), and possible local heterogeneity in *H. pylori* strains—findings should be extrapolated cautiously to other populations. Second, the control group received empirical TFEB therapy without prior antimicrobial susceptibility testing (AST). Although this mirrors real-world Chinese practice given limited AST accessibility, our suboptimal eradication rates (< 90%) underscore two critical findings: (1) even in a

**TABLE 4** | Univariate analysis of factors affecting eradication rates in the PP populations.

| Affecting factors | Eradication rates (*n*/*N*) | *p* value | Affecting factors | Eradication rates (*n*/*N*) | *p* value |
|---|---|---|---|---|---|
| Gender | | 0.041[b] | Family size | | 0.595 |
| Male | 87.2% (239/274) | | < 4 people | 83.2% (323/388) | |
| Female | 81.1% (275/339) | | ≥ 4 people | 84.9% (191/225) | |
| Age (years) | | 0.073 | Monthly household income | | 0.528 |
| < 51[a] | 86.4% (279/323) | | < 4000 Chinese yuan | 80.8% (42/52) | |
| ≥ 51[a] | 81.0% (235/290) | | ≥ 4000 Chinese yuan | 85.8% (472/561) | |
| BMI(kg/m$^2$) | | 0.658 | Time to rescue therapy | | 0.809 |
| < 24 | 83.4% (236/403) | | < 6 months | 83.4% (201/241) | |
| ≥ 24 | 84.8% (178/210) | | ≥ 6 months | 84.1% (313/372) | |
| Ethnicity | | 1.000 | Cigarette smoking | | 0.964 |
| Han | 83.9% (505/602) | | Yes | 84.0% (84/100) | |
| Others | 81.8% (9/11) | | No | 83.8% (430/513) | |
| Marital status | | 0.189 | Alcohol drinking | | 0.158 |
| Yes | 83.4% (481/577) | | Yes | 90.2% (55/61) | |
| No | 91.7% (33/36) | | No | 83.2% (459/552) | |
| Family history of gastric cancer | | 0.100 | Coffee drinking | | 0.318 |
| Yes | 92.9% (39/42) | | Yes | 88.7% (47/53) | |
| No | 83.2% (475/571) | | No | 83.4% (467/560) | |
| Education level | | 0.253 | Tea drinking | | 0.479 |
| High school or less | 82.4% (290/352) | | Yes | 82.3% (158/192) | |
| College or more | 85.8% (224/261) | | No | 84.6% (356/421) | |
| Fruit intake | | 0.300 | Intake of dairy products | | 0.712 |
| ≤ 1 unit a week | 84.1% (159/189) | | ≤ once a week | 84.0% (273/325) | |
| 2–4 units a week | 88.0% (110/125) | | 2–4 days a week | 85.6% (113/132) | |
| ≥ 5 units a week | 81.9% (245/299) | | 5–7 days a week | 82.1% (128/156) | |
| Vegetable intake | | 0.081 | Previous failed eradication times | | 0.001[b] |
| < 250 g a day | 80.4% (115/143) | | 1 | 87.2% (368/422) | |
| 2.0–500 g a day | 87.1% (276/317) | | 2 | 80.0% (100/125) | |
| > 500 g a day | 80.4% (123/153) | | ≥ 3 | 69.7% (46/66) | |

[a]51 is the median age of all PP populations.
[b]*p* value is statistically significant.

**TABLE 5** | Risk factors for *Helicobacter pylori* rescue treatment failure.

| Risk factors | *β* | SE | Wald | *p* value | OR | 95% CI of OR |
|---|---|---|---|---|---|---|
| Gender | | | | | | |
| Male | | | | Ref | | |
| Female | −0.431 | 0.229 | 3.535 | 0.06 | 0.65 | 0.415–1.018 |
| Previous failed eradication times | | | | | | |
| 1 | | | | Ref | | |
| 2 | −0.569 | 0.265 | 4.609 | 0.032[a] | 0.566 | 0.337–0.952 |
| ≥ 3 | −1.094 | 0.306 | 12.751 | < 0.001[a] | 0.335 | 0.184–0.611 |

*Note:* Ref: reference indicator.
[a]*p* value is statistically significant.

population with historically low resistance rates (national data: amoxicillin 2.41%, tetracycline 2.53%, furazolidone 1.54%) [21], empirical rescue therapy may fail to achieve ideal efficacy; and (2) significant regional disparities exist—notably in Shaanxi Province, where resistance rates for both amoxicillin (7.46%) and furazolidone (7.05%) exceed national averages [21]. These findings strongly advocate AST-guided therapy when accessible, particularly for treatment-experienced patients. Future studies incorporating AST would facilitate both comparative effectiveness research and personalized therapy. Third, the use of inconsistent *H. pylori* testing methods in therapeutic efficacy evaluation may compromise the accuracy and reliability of the research findings. Fourth, worldwide differences in BQT regimens may limit TFEB protocol applicability elsewhere. Fifth, the open-label nature of the study design may have affected the reporting of adverse events by participants in the absence of blinding. Finally, patients with amoxicillin allergies are not suitable for VHA dual therapy and have been excluded from the study.

In conclusion, the 14-day VHA dual therapy is not inferior to bismuth-containing quadruple therapy, with fewer adverse reactions and good compliance, and may represent an effective alternative for *H. pylori* rescue treatment.

### Ethics Statement

The study protocol was approved by the Ethics Committees of the First Affiliated Hospital of The Fourth Military Medical University (No. KF20232236-F-2), Xian, China.

### Consent

All patients agreed to participate in this study and gave informed consent.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**Supporting Information**

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