Efficacy and safety of high-dose esomeprazole–amoxicillin dual therapy for *Helicobacter pylori* rescue treatment: a multicenter, prospective, randomized, controlled trial

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Abstract

Background: High-dose dual therapy (HDDT) with proton pump inhibitors (PPIs) and amoxicillin has attracted widespread attention due to its favorable efficacy in eradicating *Helicobacter pylori* (*H. pylori*). This study aimed to compare the efficacy and safety of high-dose PPI–amoxicillin dual therapy and bismuth-containing quadruple therapy for *H. pylori* rescue treatment.

Methods: This was a prospective, randomized, multicenter, non-inferiority trial. Patients recruited from eight centers who had failed previous treatment were randomly (1:1) allocated to two eradication groups: HDDT (esomeprazole 40 mg and amoxicillin 1000 mg three times daily; the HDDT group) and bismuth-containing quadruple therapy (esomeprazole 40 mg, bismuth potassium citrate 220 mg, and furazolidone 100 mg twice daily, combined with tetracycline 500 mg three times daily; the tetracycline, furazolidone, esomeprazole, and bismuth [TFEB] group) for 14 days. The primary endpoint was the *H. pylori* eradication rate. The secondary endpoints were adverse effects, symptom improvement rates, and patient compliance.

Results: A total of 658 patients who met the criteria were enrolled in this study. The HDDT group achieved eradication rates of 75.4% (248/329), 81.0% (248/306), and 81.3% (248/305) asdetermined by the intention-to-treat (ITT), modified intention-to-treat (MITT), and per-protocol (PP) analyses, respectively. The eradication rates were similar to those in the TFEB group: 78.1% (257/329), 84.2% (257/305), and 85.1% (257/302). The lower 95% confidence interval boundary (−9.19% in the ITT analysis, − 9.21% in the MITT analysis, and −9.73% in the PP analysis) was greater than the predefined non-inferiority margin of −10%, establishing a non-inferiority of the HDDT group *vs.* the TFEB group. The incidence of adverse events in the HDDT group was significantly lower than that in the TFEB group (11.1% *vs.* 26.8%, $P < 0.001$). Symptom improvement rates and patients' compliance were similar between the two groups.

Conclusions: Fourteen-day HDDT is non-inferior to bismuth-containing quadruple therapy, with fewer adverse effects and good treatment compliance, suggesting HDDT as an alternative for *H. pylori* rescue treatment in the local region.

Trial registration: Clinicaltrials.gov, NCT04678492.

Keywords: Bismuth-containing quadruple therapy; *Helicobacter pylori*; High-dose dual therapy; Rescue treatment

Introduction

Helicobacter pylori (*H. pylori*) infection is a global public health issue. Nearly 4.4 billion people worldwide are estimated to be infected with *H. pylori*.[1] China has a high occurrence rate of *H. pylori*. Approximately 50% of the Chinese population is infected.[2] Extensive clinical data

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have demonstrated that *H. pylori* infection is associated with various gastrointestinal diseases. Eradication with *H. pylori* facilitates peptic ulcer healing, eliminates chronic active gastritis,[3-5] and prevents gastric cancer.[6] Thus, domestic and foreign guidelines for *H. pylori* suggest that those who test positive should receive treatment designed to eradicate the infection.[3,4]

Currently, the eradication rate with standard triple therapy has fallen to <80%.[3] The causes for this decline could involve bacterial factors, genetic polymorphisms in CYP2C19 and patient compliance, and the antibiotic resistance of *H. pylori* among these causes has been identified as the most important factor.[7] The latest data show that primary or secondary antibiotic resistance in *H. pylori* has reached an amazingly high level, with the prevalence of drug-resistant strains to clarithromycin, metronidazole, and levofloxacin exceeding 15% within the vast majority of the regions according to the World Health Organization.[8] In particular, the resistance rate to clarithromycin has increased greatly in recent decades.[9] To address this issue, the Maastricht V Consensus recommended that bismuth or non-bismuth quadruple therapies should be used for 14 days as a first-line eradication regimen in areas of high clarithromycin resistance (>15%).[4] Moreover, bismuth quadruple therapy was proposed as the only empirical treatment for *H. pylori* by the fifth edition of the Chinese consensus report for the management of *H. pylori* infection.[3] While these quadruple therapies can be used to overcome drug resistance and improve eradication efficacy,[10-12] some deficiencies still exist. On the one hand, patient compliance has decreased due to complicated medication regimens, high costs, and adverse reactions.[13,14] On the other hand, the use of multiple antibiotics can result in increased antibiotic-resistant bacteria; thus, the risk of a future episode and decreasing eradication rates persist. Hence, it is essential to explore alternative options for *H. pylori* treatment.

High-dose dual therapy (HDDT), consisting of a proton pump inhibitor (PPI) and amoxicillin, has received a great deal of attention from researchers because of its reliable acid-suppressive efficacy and low antibiotic resistance. Studies have revealed that the eradication rate of HDDT in the first-line treatment of *H. pylori* is comparable to or better than that of the traditional triple or quadruple therapy guidelines recommended and with fewer adverse reactions.[15,16] However, the existing studies of HDDT for *H. pylori* rescue treatment have been limited due to small sample sizes and single-center settings. There is a lack of robust scientific evidence on the efficacy of HDDT in *H. pylori* rescue treatment. Therefore, we conducted this multicenter, prospective, randomized, controlled trial to identify the eradication efficacy and safety of HDDT in *H. pylori* rescue treatment for patients who had failed previous treatment at least once.

Methods

Study design

This study was a prospective, multicenter, open-label, non-inferiority, randomized, controlled study with the primary objective of confirming that HDDT is non-inferior to bismuth-containing quadruple therapy as an *H. pylori* salvage regimen.

The studies were conducted at Xijing Hospital (Xi'an, Shaanxi, China), Xianyang Central Hospital (Xianyang, Shaanxi), the Affiliated Hospital of Shaanxi University of Chinese Medicine (Xianyang), Shaanxi Nuclear Industry 215 Hospital (Xianyang), Yan'an University Affiliated Hospital (Yan'an, Shaanxi), Yan'an People's Hospital (Yan'an), Xi'an Red Cross Hospital (Xi'an), and Xi'an Daxing Hospital (Xi'an) between December 2020 and August 2021. The patients who met the inclusion criteria were consecutively included in this study. At the time of enrollment, the demographic and clinical data of all patients were recorded. The experiment adhered to a randomized block design. Patients were randomly assigned to receive a 14-day HDDT (the HDDT group) or bismuth-containing quadruple therapy (the tetracycline, furazolidone, esomeprazole, and bismuth [TFEB] group) in a 1:1 ratio after being numbered sequentially at each center (independent clinical research assistants were available at each participating hospital, and each center's randomization was performed by a third party). During follow-up visits, adverse reactions and medication status were recorded by researchers, and the symptoms of patients were assessed at baseline, at the end of the treatment period, and 4 weeks after the end of treatment. All of the participants were asked to return to the hospital for a urea breath test 4 to 8 weeks after eradication to evaluate the therapeutic effectiveness.

This study protocol was approved by the Ethics Committees of the First Affiliated Hospital of Air Force Military Medical University and all of the other participating centers (No. KY20202114-F-1), and all of the patients provided written informed consent. In parallel, it followed the principles of the CONSORT statement for randomized, controlled trials and was registered with ClinicalTrials.gov (No. NCT04678492).

Participants

Consecutive outpatients infected with *H. pylori* in whom eradication treatment had failed at least once, such as with standard triple, bismuth-containing quadruple therapy, or non-bismuth quadruple therapy, were enrolled in this study.

The inclusion criteria were as follows: the patients were 18 to 70 years old and of either sex; the patients had failed previous eradication therapy in the previous 2 years and had discontinued treatment for at least 2 months; and female patients of childbearing age were required to use contraception methods during the trial and 30 days thereafter.

The exclusion criteria were: (1) patients who had received tetracycline- and furazolidone-based antibiotics for *H. pylori* eradication therapy previously; (2) known contraindications to the study drugs; (3) severe or unstable cardiopulmonary or endocrine diseases or severe substantial organ impairments and complications; (4) constant

use of PPIs or H2-receptor antagonist within 2 weeks before the *H. pylori* assessment, antibiotics or bismuth complexes within 1 month (>3 times/week) before screening; (5) use of systemic glucocorticoid, anti-coagulants, or platelet aggregation inhibitors (except for using aspirin at <100 mg/day); (6) pregnancy and lactation; (7) having undergone upper gastrointestinal tract surgery previously; (8) gastric severe dysplasia, high-grade intra-epithelial neoplasia, or with obvious dysphagia; (9) a history of drug or alcohol abuse within 1 year; (10) a history of malignancy; (11) active bleeding or iron deficiency anemia; (12) diagnosis with mucosa associated lymphoid tissue lymphoma; (13) known psychiatric disorders; (14) participation in other clinical trials during the previous 3 months; and (15) refusal to sign an informed consent form.

Grouping and medication

Eligible patients at each center were randomly assigned to two groups for 14-day treatment: (1) HDDT: esomeprazole 40 mg thrice daily (before breakfast/lunch/dinner) and amoxicillin 1000 mg thrice daily (after breakfast/lunch/dinner); or (2) TFEB: esomeprazole 40 mg twice daily (before breakfast/dinner), bismuth potassium citrate 220 mg twice daily (before breakfast/dinner), tetracycline 500 mg thrice daily (after breakfast/lunch/dinner), and furazolidone 100 mg twice daily (after breakfast/dinner).

The drug information is as follows: esomeprazole (AstraZeneca Pharmaceutical, Södertälje, Sweden), bismuth potassium citrate capsules (Sinopharm Shantou Jinshi Pharmaceutical, Shantou, Guangdong Province, China), amoxicillin (Zhuhai United Laboratories, Zhuhai, Guangdong Province, China), tetracycline (Guangdong Huanan Pharmaceutical, Dongguan, Guangdong Province, China), and furazolidone (Yunpeng Pharmaceutical, Linfen, Shanxi Province, China).

Diagnosis of H. pylori infection

Detection of *H. pylori* infection was completed by $^{13}C/^{14}C$ urea breath test (13C/14C-UBT), rapid urease test (RUT), *H. pylori* stool antigen test (HpSAT), or histological examination. At least one positive result for the above tests was confirmed as a present *H. pylori* infection (a borderline result for $^{13}C/^{14}C$ was also regarded as an *H. pylori* infection).

Successful eradication was confirmed by negative $^{13}C/^{14}C$-UBT or HpSAT (for participants with a positive RUT result or a histological confirmation of *H. pylori* but negative $^{13}C/^{14}C$-UBT results before treatment) results at 4–8 weeks following eradication treatment.

Safety, symptom improvement, and compliance

Subjects were informed about possible adverse drug reactions before taking medication and were required to record these events on a predesigned case report form. Adverse events, graded using a four-point scale designed to evaluate the severity, were classified as none, 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). The trial investigator was available to be contacted at all times during treatment in cases of adverse events.

Additionally, clinical symptoms among the patients, including vomiting, nausea, headache, dizziness, abdominal pain, early satiety, flatulence, diarrhea, constipation, belching, hiccups, dysgeusia, fever, acid reflux, and heartburn, were evaluated at baseline, at the end of treatment and 4 weeks after the end of treatment. Both the severity and frequency of symptoms were calculated in a score of 0 to 3 (0, 1, 2, and 3 representing none, mild, moderate, and severe, respectively). The symptom score was calculated as follows: each symptom score = severity score × frequency score. The total symptom score was calculated as the sum of the scores for all symptoms. Symptom improvement was defined as a 50% reduction in the total score after treatment.

Compliance was monitored by pill count. Taking ≥80% of the study medication was defined as having good compliance. Patients with poor compliance were excluded from PP analysis.

Outcomes

The primary outcome of the study was the successful eradication of *H. pylori* 4 weeks after termination of therapy. The secondary outcomes included adverse events, the improvement rate of clinical symptoms (at the end of treatment and 4 weeks after the end of treatment), and patient compliance.

Calculation of sample size and statistical analysis

The sample size was calculated before the study. The remedial eradication rate of tetracycline- and furazolidone-based quadruple regimens was previously reported to be between 72% and 93%.[17-20] We presumed the eradication rate of the two groups to be 80%, set the non-inferiority margin at 10% with one-sided $\alpha = 0.05$ and $\beta = 0.1$, and considered a drop-out rate of 20%; thus, at least 329 subjects in each group were required (658 participants in total). HDDT was considered to be non-inferior to bismuth-containing quadruple therapy if the lower bound of the 95% confidence interval (CI) of the difference was greater than −10%; otherwise, a non-inferiority conclusion could not be drawn.

All statistical analyses were performed with IBM SPSS Statistics software, version 25.0 (IBM Inc, New York, USA). Continuous variables are presented as the mean ± standard deviations and were analyzed by Student's *t* test. Categorical variables are presented as percentages and were compared with the chi-squared test or Fisher's exact tests. The *H. pylori* eradication rate and the hypothesis of non-inferiority were assessed based on intention-to-treat (ITT; including the participants who were enrolled in the study), modified intention-to-treat (MITT; including the participants who took at least one dose of medicine and underwent the endpoint measure),

and per-protocol (PP; including the participants who were fully adherent with the protocol and excluding those with poor compliance) analysis. A P value <0.05 was considered statistically significant.

Results

Baseline characteristics of the participants

The trial profile is shown in Figure 1. A total of 701 patients were screened for eligibility from December 2020 to August 2021, and 658 were included and randomized to receive the 14-day HDDT or TFEB regimen for *H. pylori* rescue treatment. All 658 participants were included in the ITT analysis. After excluding participants who were lost to follow-up, intolerant to adverse events, or violated the protocol, the remaining participants were included in the MITT analysis. Furthermore, participants with poor compliance were excluded from the PP analysis.

As shown in Table 1, there were no significant differences in the baseline characteristics, including demographics, medical history, and history of antibiotic therapy, between the two groups (all $P > 0.05$).

Efficacy of H. pylori eradication therapy

In the ITT analysis, the eradication rates were 75.4% (248/329) for the HDDT group and 78.1% (257/329) for the TFEB group. In the MITT analysis, the eradication rates were 81.0% (248/306) for the HDDT group and 84.2% (257/305) for the TFEB group. The eradication rates in the PP analyses for the HDDT and TFEB groups were 81.3% (248/305) and 85.1% (257/302), respectively. No statistically significant differences among the groups were found ($P = 0.406$, $P = 0.294$, and $P = 0.212$ for the ITT, MITT, and PP analyses, respectively). In addition, the lower boundary of the 95% CI for the eradication rate difference was greater than the protocol-specified non-inferiority margin of −10% (−9.19% for the ITT analysis, −9.21% for the MITT analysis, and

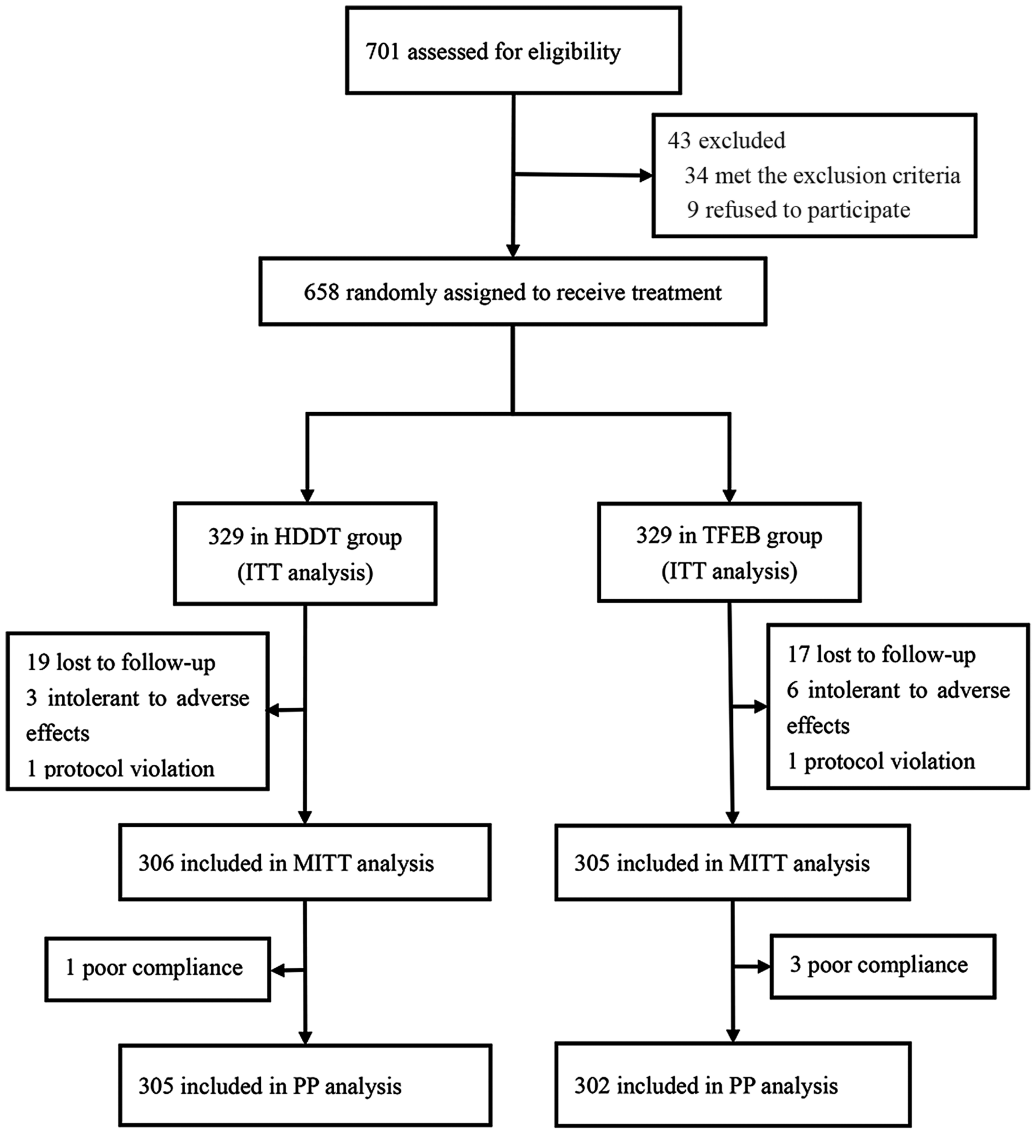

Figure 1: Flow diagram of the study. HDDT: High-dose dual therapy; ITT: Intention-to-treat; MITT: Modified intention-to-treat; PP: Per-protocol; TFEB: Tetracycline, furazolidone, esomeprazole, and bismuth.

Table 1: Baseline characteristics of the participants infected with *Helicobacter pylori* in whom eradication treatment had failed at least once.

Characteristics	HDDT group ($N = 329$)	TFEB group ($N = 329$)	Statistics	*P* value
Age (years), mean ± SD	47.6 ± 11.8	47.0 ± 12.0	0.577*	0.564
Sex, male:female	153:176	173:156	2.432†	0.119
BMI (kg/m^2), mean ± SD	22.46 ± 2.87	22.90 ± 2.98	−1.925*	0.055
Ethnicity, *n* (%)			0.406†	0.524
Han	325 (98.8)	323 (98.2)		
Others	4 (1.2)	6 (1.8)		
Smoking, *n* (%)	64 (19.5)	79 (24.0)	2.010†	0.156
Alcohol intake, *n* (%)	55 (16.7)	69 (21.0)	1.948†	0.163
Symptom, *n* (%)			0.681†	0.409
Dyspepsia	312 (94.8)	307 (93.3)		
Others	17 (5.2)	22 (6.7)		
Family history of gastric cancer, *n* (%)	18 (5.5)	12 (3.6)	1.257†	0.262
Number of previous eradication attempts, *n* (%)			1.071†	0.585
1	277 (84.2)	267 (81.2)		
2	39 (11.9)	46 (14.0)		
≥3	13 (4.0)	16 (4.4)		
Previous antibiotic therapies (person-time)			4.873†	0.582
Amoxicillin + clarithromycin	292	287		
Clarithromycin + tinidazole	32	47		
Amoxicillin + metronidazole	35	30		
Amoxicillin + levofloxacin	14	18		
Clarithromycin + metronidazole	11	13		
Amoxicillin + berberine	12	11		
Others	1	3		

Data are presented as mean ± standard deviation. * *t* test. † χ^2 values. BMI: Body mass index; SD: Standard deviation; HDDT: High-dose dual therapy; TFEB: Tetracycline, furazolidone, esomeprazole, and bismuth.

Table 2: *Helicobacter pylori* eradication rates in the HDDT and TFEB groups.

Items	HDDT group, % (*n*/*M*)	TFEB group, % (*n*/*M*)	*P* value	Rate difference 95% CI
ITT analysis	75.4 (248/329)	78.1 (257/329)	0.406	−2.74
95% CI	70.7–80.0	73.7–82.6		−9.19 to 3.71
MITT analysis	81.0 (248/306)	84.2 (257/305)	0.294	−3.22
95% CI	76.7–85.4	80.2–88.4		−9.21 to 2.79
PP analysis	81.3 (248/305)	85.1 (257/302)	0.212	−3.79
95% CI	76.9–85.7	81.1–89.1		−9.73 to 2.15

HDDT: High-dose dual therapy; TFEB: Tetracycline, furazolidone, esomeprazole, and bismuth. CI: Confidence interval; ITT: Intention-to-treat; MITT: Modified intention-to-treat; PP: Per-protocol.

−9.73% for the PP analysis), thus meeting the non-inferiority criterion [Table 2].

In addition, we performed a subgroup analysis of eradication efficacy in patients with previous eradication times in the PP population [Figure 2]. No statistically significant difference between the two groups was demonstrated in the eradication efficacy for participants who received 1 (odds ratio [OR]: 0.75; 95% CI: 0.46–1.21; $P = 0.239$) or ≥2 (OR: 0.79; 95% CI: 0.30–2.05; $P = 0.625$) prior eradication attempts.

Rates of adverse events, symptom improvement, and compliance

Adverse events were observed in 34 (11.1%) and 81 (26.8%) participants in the HDDT and TFEB groups, respectively (except melena, which was associated with bismuth usage), while on therapy [Table 3]. The total incidence rate of adverse events of participants in the HDDT group was significantly lower than that in the TFEB group ($P < 0.001$). Reported common adverse events were nausea, dysgeusia, abdominal pain, flatulence, diarrhea, headache, dizziness, decreased appetite, constipation, fatigue, and skin rash. The incidence of dysgeusia was significantly higher in the TFEB group than in the HDDT group (7.3% *vs.* 1.0%, $P < 0.001$).

All of the patients recovered from the adverse events after treatment. Three participants in the HDDT group and six in the TFEB group discontinued treatment due to severe adverse events, but there was no significant difference between the two groups ($P = 0.338$).

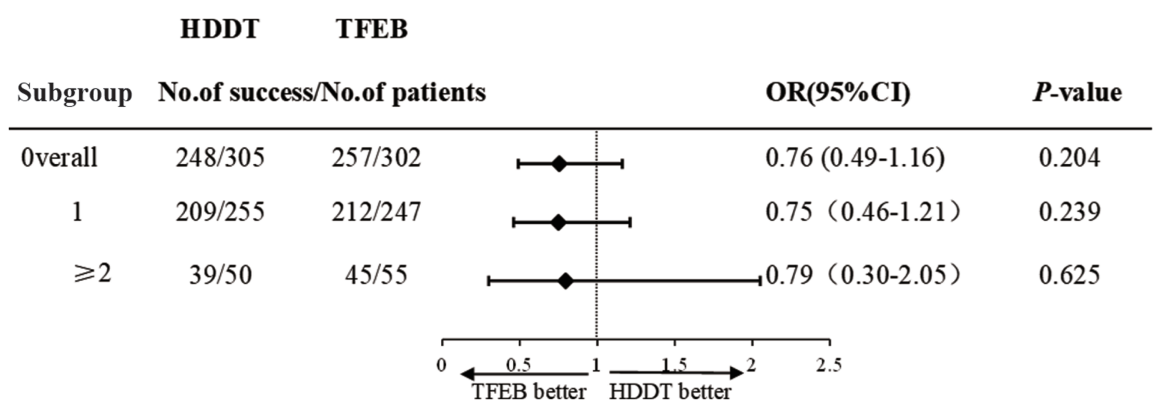

Figure 2: Subgroup analysis of eradication efficacy in patients with previous eradication times. CI: Confidence interval; HDDT: High-dose dual therapy; TFEB: Tetracycline, furazolidone, esomeprazole, and bismuth.

Table 3: Rates of adverse events in the HDDT and TFEB groups.

Items	HDDT group, *n*/*N* (%)	TFEB group, *n*/*N* (%)	Statistics	*P* value
Overall adverse events	34/305 (11.1)	81/302 (26.8)	24.276*	<0.001
Severe adverse events	3/305 (1.0)	6/302 (2.0)	Fisher†	0.338
Nausea	13/305 (4.3)	23/302 (7.6)	3.059*	0.080
Dysgeusia	3/305 (1.0)	22/302 (7.3)	15.257*	<0.001
Abdominal pain	6/305 (2.0)	11/302 (3.7)	1.564*	0.211
Bloating	5/305 (1.6)	11/302 (3.7)	2.372*	0.124
Diarrhea	12/305 (3.9)	6/302 (2.0)	2.001*	0.157
Headache	5/305 (1.6)	10/302 (3.3)	1.760*	0.185
Dizziness	6/305 (2.0)	7/302 (2.3)	0.089*	0.765
Decreased appetite	5/305 (1.6)	7/302 (2.3)	0.361*	0.548
Constipation	3/305 (1.0)	9/302 (3.0)	3.121*	0.077
Fatigue	3/305 (1.0)	4/302 (1.3)	Fisher†	0.724
Skin rash	1/305 (0.3)	3/302 (1.0)	Fisher†	0.371

* χ^2 values. † Fisher exact test. HDDT: High-dose dual therapy; TFEB: Tetracycline, furazolidone, esomeprazole, and bismuth.

Table 4: Symptom improvement and compliance in the HDDT and TFEB groups.

Items	HDDT group, *n*/*N* (%)	TFEB group, *n*/*N* (%)	χ^2-value	*P* value
2-week symptom improvement	199/289 (68.9)	186/294 (63.3)	2.033	0.154
6-week symptom improvement	244/289 (84.4)	239/294 (81.3)	1.009	0.315
Compliance rate	305/329 (92.7)	302/329 (91.8)	0.191	0.662

HDDT: High-dose dual therapy; TFEB: Tetracycline, furazolidone, esomeprazole, and bismuth.

As shown in Table 4, no statistically significant difference between the two groups was demonstrated in symptom improvement at the 2nd and 6th weeks ($P > 0.05$), and there were no significant differences in medicine compliance ($P > 0.05$).

Discussion

Currently, bismuth-containing quadruple therapy, which can achieve satisfactory clinical efficacy (>90%), has been recommended as a primary eradication strategy by the relevant consensus at home and abroad.[3] The Fifth Chinese National Consensus on the management of *H. pylori* infection has presented seven eradication regimens, including six different antibiotics, for choosing empirical therapy. However, the latest research data from China showed the high prevalence of resistance of *H. pylori* strains against clarithromycin (20%–50%), metronidazole (40%–70%), and levofloxacin (20%–50%). The rates of resistance to amoxicillin, tetracycline, and furazolidone are relatively low, at 0 to 5%, 0 to 5%, and 0 to 1%, respectively, and appear to be stabilized with time.[3] Notably, a quadruple regimen containing tetracycline and/or furazolidone has obtained a satisfactory eradication rate in China.[21,22] According to a previous study by our group, tetracycline- and furazolidone-based quadruple therapy, which has an 85% eradication rate by

PP analysis, is an ideal rescue strategy in patients with a previous eradication treatment failure.[23] Owing to adverse drug reactions[24,25] and difficulty with accessibility, the clinical use of tetracycline and furazolidone in the treatment of *H. pylori* has been severely limited. Our results demonstrated that HDDT consisting of esomeprazole plus amoxicillin achieved an eradication rate similar to that of bismuth quadruple therapy containing tetracycline and furazolidone and is an effective alternative for *H. pylori* rescue treatment.

Dual therapy for *H. pylori* eradication was first reported >30 years ago by Unge *et al*[26], but there has been no consistent evidence to indicate its efficacy, although many researchers have tried different doses, frequencies, and medication methods.[27-29] In recent years, with a deeper understanding of the growth characteristics of *H. pylori* strains and the mechanisms of PPIs and amoxicillin, the bactericidal mechanism of dual therapy has been gradually elucidated. Studies have reported that PPIs and amoxicillin three or four times daily can achieve good eradication efficacy with good safety.[30,31] First, simultaneous mutations at multiple sites within penicillin-binding protein-related genes are required to produce amoxicillin resistance,[32] which can lead to very low primary and secondary resistance rates to amoxicillin. Second, pharmacokinetic studies have shown that amoxicillin is a time-dependent antibiotic, and its bactericidal activity can be maximized by prolonging the time for which its concentration is greater than the minimum inhibitory concentration in the blood.[33] Thus, increasing the drug dosage and dosing frequency significantly enhanced the antibacterial effects of amoxicillin theoretically.[34] Third, amoxicillin was found to be pH-dependent, with excellent bioavailability in a high pH environment.[35] At the same time, *H. pylori* strains are in a state of active breeding and become more sensitive to amoxicillin while the intragastric pH remains high.[36] Strong inhibition of gastric acid secretion is, therefore, another key to improving the efficacy of *H. pylori* eradication. PPIs, which are predominantly metabolized by CYP2C19, have been established, and significant differences in the effects of gastric acid suppression are closely related to *CYP2C19* gene polymorphisms caused by corresponding gene point mutations.[37] The current study indicated that the acid suppression was sufficient and stable if esomeprazole was taken three (40 mg/time)[38] or four (20 mg/time) times[31] daily, and *H. pylori* eradication rates appeared not to be influenced by the *CYP2C19* genotype.

In our study, HDDT with esomeprazole 40 mg and amoxicillin 1000 mg thrice daily for *H. pylori* rescue treatment resulted in eradication rates of 81.3% (PP analysis). Similar results were reported in two previous studies with small sample sizes. A study from Germany reported that the application of dual therapy with omeprazole (40 mg qid) and amoxicillin (750 mg qid) for patients who had failed previous treatment achieved eradication rates of 75.6% in ITT and 83.8% in PP analysis.[39] Furthermore, a study performed in Taiwan (China) reported that the eradication rate of dual therapy (rabeprazole 40 mg qid and amoxicillin 750 mg qid) was 89.3% in both ITT and PP.[40]

In particular, subgroup analysis found no statistically significant difference between the two groups in the eradication efficacy for participants who received 1 or ≥2 prior eradication attempts. This finding suggests that the efficacy of the two regimens was not affected by the number of previous eradication treatments. Further studies are required to confirm this result.

Adverse events and participant compliance affect the efficacy of *H. pylori* eradication therapy. Our results revealed that the rate of overall adverse events in HDDT group patients was considerably less than that in the TFEB group ($P < 0.001$), and fewer subjects in the HDDT group stopped eradication therapy because of serious adverse events (three patients in the HDDT group and six patients in the TFEB group). Among all of the adverse events, the incidence of dysgeusia was significantly higher in the TFEB group than in the HDDT group ($P < 0.001$). We speculate that this outcome might be related to the use of bismuth. In parallel, the treatment compliance in both groups was comparable and satisfactory (both ≥90%), which might be attributed to our strict follow-up. Regarding symptom improvement, >60% and 80% of participants had significant symptom improvement at 2 and 6 weeks, respectively, from the start of treatment. Although there was no significant difference between the two groups, the symptom improvement rate was higher in the HDDT group than in the TFEB group.

Moreover, we analyzed the factors influencing eradication rates in the PP population for both groups. We regret that we did not find meaningful factors. These data are shown in [Supplementary Table 1, http://links.lww.com/CM9/B143].

High-dose PPI–amoxicillin dual therapy, which has simplified the dosing regimens by increasing the doses and frequencies of effective drugs and reducing unnecessary drug use, is an efficient attempt with many strengths in *H. pylori* rescue therapy. On the one hand, this regimen can reduce the irrational use of antibiotics, which can in turn decrease not only the global *H. pylori* resistance rates but also adverse effects during treatment, such as alterations in the intestinal flora.[41] On the other hand, since it is simple, safe, and inexpensive, this regimen could potentially enhance patients' acceptance and treatment compliance. Moreover, vonoprazan, a new type of potassium-competitive acid blocker, is regarded as a faster, more potent, and longer-acting agent than conventional PPIs.[42,43] Recently, the results of a clinical study in Japan showed that 7-day vonoprazan 20 mg bid and amoxicillin 750 mg bid dual therapy achieved an eradication rate of 87.1% in PP analysis.[43] Hence, whether replacing conventional PPIs with vonoprazan improves the eradication efficacy of *H. pylori* merits exploration.

Certainly, the present study has some limitations. First, all of the centers for this trial were located in northwest China, and most of the participants were from Shaanxi and its surrounding regions. Further studies are needed to confirm that HDDT is generalizable to other regions of China or to other countries. Second, the protocol choice of

this trial was empirical, and based on previous studies and considerations of compliance, the medication method with amoxicillin plus PPIs also requires further optimization. Finally, this study did not detect *CYP2C19* polymorphisms, the antimicrobial resistance of *H. pylori* strains, or intragastric pH during eradication therapy. Future evaluation of factors affecting eradication efficacy is also needed.

In conclusion, based on our results, 14-day HDDT is non-inferior to bismuth-containing quadruple therapy, with fewer adverse effects and good treatment compliance. The study suggests that HDDT can be an alternative for H. pylori rescue treatment in local regions.

Data availability statement

The datasets generated and analyzed during the current study are available from the corresponding authors on reasonable request.

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Conflicts of interest

None.

References

1. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, *et al*. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. Gastroenterology 2017;153:420–429. doi: 10.1053/j.gastro.2017.04.022.
2. Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, *et al*. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. Aliment Pharmacol Ther 2018;47:868–876. doi: 10.1111/apt.14561.
3. Liu WZ, Xie Y, Lu H, Cheng H, Zeng ZR, Zhou YL, *et al*. Fifth Chinese National Consensus Report on the management of Helicobacter pylori infection. Helicobacter 2018;23:e12475. doi: 10.1111/hel.12475.
4. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, *et al*. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut 2017;66:6–30. doi: 10.1136/gutjnl-2016-312288.
5. Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, *et al*. The Toronto consensus for the treatment of Helicobacter pylori infection in adults. Gastroenterology 2016;151:51–69e14. doi: 10.1053/j.gastro.2016.04.006.
6. Malfertheiner P. Helicobacter pylori treatment for gastric cancer prevention. N Engl J Med 2018;378:1154–1156. doi: 10.1056/NEJMe1800147.
7. Zou Y, Qian X, Liu X, Song Y, Song C, Wu S, *et al*. The effect of antibiotic resistance on Helicobacter pylori eradication efficacy: a systematic review and meta-analysis. Helicobacter 2020;25:e12714. doi: 10.1111/hel.12714.
8. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in Helicobacter pylori: a systematic review and meta-analysis in World Health Organization Regions. Gastroenterology 2018;155:1372–1382e17. doi: 10.1053/j.gastro.2018.07.007.
9. Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, *et al*. Review article: the global emergence of Helicobacter pylori antibiotic resistance. Aliment Pharmacol Ther 2016;43:514–533. doi: 10.1111/apt.13497.
10. Ge R, Chen Z, Zhou Q. The actions of bismuth in the treatment of Helicobacter pylori infections: an update. Metallomics 2012;4:239–243. doi: 10.1039/c2mt00180b.
11. Dore MP, Lu H, Graham DY. Role of bismuth in improving Helicobacter pylori eradication with triple therapy. Gut 2016;65:870–878. doi: 10.1136/gutjnl-2015-311019.
12. Nyssen OP, Bordin D, Tepes B, Perez-Aisa A, Vaira D, Caldas M, *et al*. European registry on Helicobacter pylori management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21 533 patients. Gut 2021;70:40–54. doi: 10.1136/gutjnl-2020-321372.
13. Bradley B, Singleton M, Lin Wan Po A. Bismuth toxicity – a reassessment. J Clin Pharm Ther 1989;14:423–441. doi: 10.1111/j.1365-2710.1989.tb00268.x.
14. Graham DY, Lee SY. How to effectively use bismuth quadruple therapy: the good, the bad, and the ugly. Gastroenterol Clin North Am 2015;44:537–563. doi: 10.1016/j.gtc.2015.05.003.
15. Yun J, Wu Z, Qi G, Han T, Zhang D. The high-dose amoxicillin-proton pump inhibitor dual therapy in eradication of Helicobacter pylori infection. Expert Rev Gastroenterol Hepatol 2021;15:149–157. doi: 10.1080/17474124.2021.1826306.
16. Zhu YJ, Zhang Y, Wang TY, Zhao JT, Zhao Z, Zhu JR, *et al*. High dose PPI-amoxicillin dual therapy for the treatment of Helicobacter pylori infection: a systematic review with meta-analysis. Therap Adv Gastroenterol 2020;13:1–12. doi: 10.1177/1756284820937115.
17. Liu ZX, Li H, Wang HQ. Comparison of the efficacy of quadruple therapy for eradication of Helicobacter pylori with different antibiotic combinations (in Chinese). J Mod Med Health 2016;32:3851–3852. doi: 10.3969/j.issn.1009-5519.2016.24.042.
18. Yang X, Gao CP, Qiu CH. Efficacy comparison between different quadruple rescue therapies in eradication of Helicobacter pylori (in Chinese). Chin J Pract Int Med 2015;35:424–426. doi: 10.7504/nk2015040303.
19. Wang JX. Clinical efficacy of two different rescue therapy for the Helicobacter pylori after the first failure of eradication (in Chinese). Anhui Med Pharm J 2016;20:1744–1747. doi: 10.3969/j.issn.1009-6469.2016.09.036.
20. Zhang Y, Gao W, Cheng H, Zhang X, Hu F. Tetracycline- and furazolidone-containing quadruple regimen as rescue treatment for Helicobacter pylori infection: a single center retrospective study. Helicobacter 2014;19:382–386. doi: 10.1111/hel.12143.
21. Cheng H, Hu FL. Furazolidone, amoxicillin, bismuth and rabeprazole quadruple rescue therapy for the eradication of Helicobacter pylori. World J Gastroenterol 2009;15:860–864. doi: 10.3748/wjg.15.860.
22. Delchier JC, Malfertheiner P, Thieroff-Ekerdt R. Use of a combination formulation of bismuth, metronidazole and tetracycline with omeprazole as a rescue therapy for eradication of Helicobacter pylori. Aliment Pharmacol Ther 2014;40:171–177. doi: 10.1111/apt.12808.
23. Zhang J, Han C, Lu WQ, Wang N, Wu SR, Wang YX, *et al*. A randomized, multicenter and noninferiority study of amoxicillin plus berberine vs tetracycline plus furazolidone in quadruple therapy for Helicobacter pylori rescue treatment. J Dig Dis 2020;21:256–263. doi: 10.1111/1751-298012870.
24. Zheng Q, Chen WJ, Lu H, Sun QJ, Xiao SD. Comparison of the efficacy of triple versus quadruple therapy on the eradication of Helicobacter pylori and antibiotic resistance. J Dig Dis 2010;11:313–318. doi: 10.1111/j.1751-29802010.00457x.
25. Fakheri H, Malekzadeh R, Merat S, Khatibian M, Fazel A, Alizadeh BZ, *et al*. Clarithromycin vs. furazolidone in quadruple therapy regimens for the treatment of Helicobacter pylori in a population with a high metronidazole resistance rate. Aliment Pharmacol Ther 2001;15:411–416. doi: 10.1046/j.13652001.00931x.-2036.
26. Unge P, Gad A, Gnarpe H, Olsson J. Does omeprazole improve antimicrobial therapy directed towards gastric Campylobacter pylori in patients with antral gastritis? A pilot study. Scand J Gastroenterol Suppl 1989;167:49–54. doi: 10.3109/00365528909091311.

27. Pieramico O, Zanetti MV, Innerhofer M, Malfertheiner P. Omeprazole-based dual and triple therapy for the treatment of Helicobacter pylori infection in peptic ulcer disease: a randomized trial. Helicobacter 1997;2:92–97. doi: 10.1111/j.1523-5378.1997.tb00065.x.
28. Laine L, Stein C, Neil G. Limited efficacy of omeprazole-based dual and triple therapy for Helicobacter pylori: a randomized trial employing "optimal" dosing. Am J Gastroenterol 1995;90:1407–1410. doi: 10.1016/0016-5085(95)23232-X.
29. Miehlke S, Mannes GA, Lehn N, Hele C, Stolte M, Bayerdorffer E. An increasing dose of omeprazole combined with amoxycillin cures Helicobacter pylori infection more effectively. Aliment Pharmacol Ther 1997;11:323–329. doi: 10.1046/j.13651997.140316000-2036x.
30. Yu L, Luo L, Long X, Liang X, Ji Y, Graham DY, *et al*. High-dose PPI-amoxicillin dual therapy with or without bismuth for first-line Helicobacter pylori therapy: a randomized trial. Helicobacter 2019;24:e12596. doi: 10.1111/hel.12596.
31. Song Z, Zhou L, Xue Y, Suo B, Tian X, Niu Z. A comparative study of 14-day dual therapy (esomeprazole and amoxicillin four times daily) and triple plus bismuth therapy for first-line Helicobacter pylori infection eradication: a randomized trial. Helicobacter 2020;25:e12762. doi: 10.1111/hel.12762.
32. Rimbara E, Noguchi N, Kawai T, Sasatsu M. Mutations in penicillin-binding proteins 1, 2 and 3 are responsible for amoxicillin resistance in Helicobacter pylori. J Antimicrob Chemother 2008;61:995–998. doi: 10.1093/jac/dkn051.
33. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am 2003;17:479–501. doi: 10.1016/s0891-5520(03)00065-5.
34. Furuta T, Sugimoto M, Yamade M, Uotani T, Sahara S, Ichikawa H, *et al*. Effect of dosing schemes of amoxicillin on eradication rates of Helicobacter pylori with amoxicillin-based triple therapy. J Clin Pharmacol 2014;54:258–266. doi: 10.1002/jcph.195.
35. Erah PO, Goddard AF, Barrett DA, Shaw PN, Spiller RC. The stability of amoxycillin, clarithromycin and metronidazole in gastric juice: relevance to the treatment of Helicobacter pylori infection. J Antimicrob Chemother 1997;39:5–12. doi: 10.1093/jac/39.1.5.
36. Scott D, Weeks D, Melchers K, Sachs G. The life and death of Helicobacter pylori. Gut 1998;43 (Suppl 1):S56–S60. doi: 10.1136/gut.43.2008.s56.
37. Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. Drug Metab Pharmacokinet 2005;20:153–167. doi: 10.2133/dmpk.20.153.
38. Miehlke S, Hansky K, Schneider-Brachert W, Kirsch C, Morgner A, Madisch A, *et al*. Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. Aliment Pharmacol Ther 2006;24:395–403. doi: 10.1111/j.1365 2006.02993-2036x.
39. Miehlke S, Kirsch C, Schneider-Brachert W, Haferland C, Neumeyer M, Bastlein E, *et al*. A prospective, randomized study of quadruple therapy and high-dose dual therapy for treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. Helicobacter 2003;8:310–319. doi: 10.1046/j.1523-5378.2003.00158.x.
40. Yang JC, Lin CJ, Wang HL, Chen JD, Kao JY, Shun CT, *et al*. High-dose dual therapy is superior to standard first-line or rescue therapy for Helicobacter pylori infection. Clin Gastroenterol Hepatol 2015;13:895–905e5. doi: 10.1016/j.cgh.2014.10.036.
41. Horii T, Suzuki S, Takano C, Shibuya H, Ichijima R, Kusano C, *et al*. Lower impact of vonoprazan-amoxicillin dual therapy on gut microbiota for Helicobacter pylori eradication. J Gastroenterol Hepatol 2021;36:3314–3321. doi: 10.1111/jgh.15572.
42. Kagami T, Sahara S, Ichikawa H, Uotani T, Yamade M, Sugimoto M, *et al*. Potent acid inhibition by vonoprazan in comparison with esomeprazole, with reference to CYP2C19 genotype. Aliment Pharmacol Ther 2016;43:1048–1059. doi: 10.1111/apt.13588.
43. Suzuki S, Gotoda T, Kusano C, Ikehara H, Ichijima R, Ohyauchi M, *et al*. Seven-day vonoprazan and low-dose amoxicillin dual therapy as first-line *Helicobacter pylori* treatment: a multicentre randomised trial in Japan. Gut 2020;69:1019–1026. doi: 10.1136/gutjnl-2019-319954.

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