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) as determined 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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Chinese Medical Journal 2022;135(14)

Received: 31-03-2022; Online: 04-08-2022 Edited by: Yuanyuan Ji
have demonstrated that H. pylori infection is associated with various gastrointestinal diseases. Eradication with H. pylori facilitates peptic ulcer healing, eliminates chronic active gastritis, and prevents gastric cancer. Thus, domestic and foreign guidelines for H. pylori suggest that those who test positive should receive treatment designed to eradicate the infection.

Currently, the eradication rate with standard triple therapy has fallen to <80%. 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. 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. In particular, the resistance rate to clarithromycin has increased greatly in recent decades. 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%). 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. While these quadruple therapies can be used to overcome drug resistance and improve eradication efficacy, some deficiencies still exist. On the one hand, patient compliance has decreased due to complicated medication regimens, high costs, and adverse reactions. 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. 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 (Xi’an), Xi’an University Affiliated Hospital 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, omeprazole, 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 antagonists 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...
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 \( \geq 2 \) (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 (\( P = 0.338 \)).
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. 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. Notably, a quadruple regimen containing tetracycline and/or furazolidone has obtained a satisfactory eradication rate in China.

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).

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### 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   |

*χ² 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 (%) | χ²-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)       | 1.097    | 0.315   |
| Compliance rate         | 303/329 (92.7)     | 302/329 (91.8)       | 0.191    | 0.662   |

HDDT: High-dose dual therapy; TFEB: Tetracycline, furazolidone, esomeprazole, and bismuth.
PP analysis, is an ideal rescue strategy in patients with a previous eradication treatment failure.\cite{23} Owing to adverse drug reactions\cite{22,23,25} and difficulty with accessibility, the clinical use of tetracycline and furazolidone in the treatment of \textit{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 \textit{H. pylori} rescue treatment.

Dual therapy for \textit{H. pylori} eradication was first reported >30 years ago by Unge et al\cite{26}, but there has been no consistent evidence to indicate its efficacy, although many researchers have tried different doses, frequencies, and medication methods.\cite{27,28,29} In recent years, with a deeper understanding of the growth characteristics of \textit{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.\cite{30,31} First, simultaneous mutations at multiple sites within penicillin-binding protein-related genes are required to produce amoxicillin resistance,\cite{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 or equal to the minimum inhibitory concentration in the blood.\cite{33} Thus, increasing the drug dosage and dosing frequency significantly enhanced the antibacterial effects of amoxicillin theoretically.\cite{34} Third, amoxicillin was found to be pH-dependent, with excellent bioavailability in a high pH environment.\cite{35} At the same time, \textit{H. pylori} strains are in a state of active breeding and become more sensitive to amoxicillin while the intragastric pH remains high.\cite{36} Strong inhibition of gastric acid secretion is, therefore, another key to improving the efficacy of \textit{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.\cite{37} The current study indicated that the acid suppression was sufficient and stable if esomeprazole was taken three (40 mg/time)\cite{38} or four (20 mg/time)\cite{39} daily, and \textit{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 \textit{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.\cite{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.\cite{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 \textit{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 \textit{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 \textit{H. pylori} resistance rates but also adverse effects during treatment, such as alterations in the intestinal flora.\cite{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.\cite{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.\cite{43} Hence, whether replacing conventional PPIs with vonoprazan improves the eradication efficacy of \textit{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.

**Acknowledgements**

We thank the study participants and the clinical teams. We also would like to thank Professor Lei Shang from the Statistics Teaching and Research Office of Air Force Medical University for assisting in the statistical analysis.

**Funding**

This work was partially supported by the grant of the Project from the State Key Laboratory of Cancer Biology (No. CBSKL.2019ZZ07).

**Conflicts of interest**

None.

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