ORIGINAL ARTICLE

Helicobacter **WILEY**

Optimized dual therapy for treatment-naive patients of *Helicobacter pylori* infection: A large-scale prospective, multicenter, open-label, randomized controlled study

Ying-Ying Han[1] | Hui Long[2] | Ya Lin[3] | Qiong He[4] | Wei-Gang Chen[5] |
Xiang-Wu Ding[6] | Lin Zhou[7] | Ping An[8] | Fen Wang[9] | Zhen-Yu Zhang[10] |
Yun-Lian Hu[11] | Pei-Yuan Li[1,3]

[1]Division of Gastroenterology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[2]Department of Gastroenterology, Tianyou Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, China

[3]Department of Gastroenterology, Wenchang People's Hospital, Wenchang, China

[4]Department of Gastroenterology, Wuhan Red Cross Hospital, Wuhan, China

[5]Department of Gastroenterology, The First Affiliated Hospital of Shihezi University Medical College, Shihezi, China

[6]Department of Gastroenterology, Wuhan Fourth Hospital, Wuhan, China

[7]Department of Gastroenterology, Suizhou Central Hospital, Suizhou, China

[8]Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, China

[9]Department of Gastroenterology, The Third Xiangya Hospital, Central South University, Changsha, China

[10]Department of Gastroenterology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China

[11]Department of Gastroenterology, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, China

Correspondence
Pei-Yuan Li, Division of Gastroenterology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and

Abstract

Background: The efficacy and safety of high-dose amoxicillin (AMX) and proton pump inhibitors (PPI) dual therapy raises much more attention in recent years. Comparative studies among the dual therapies are required to explore more suitable regimens. This study compared the efficacy, adverse events, and patient compliance of three different high-dose dual regimens in treatment-naive patients of *Helicobacter pylori* (*H. pylori*) infection.

Materials and Methods: The study was a prospective, multicenter, open-label, randomized controlled trial, including *H. pylori*-infected treatment-naive patients at 12 tertiary hospitals in China. The eligible subjects received high-dose AMX and esomeprazole (ESO) dual therapy of different regimens. They were randomly assigned to group A (ESO 20 mg plus AMX 750 mg, Qid for 14 days), group B (ESO 40 mg Bid plus AMX 1 g Tid for 14 days), or group C (ESO 20 mg plus AMX 1 g, Tid for 14 days). The eradication rates, adverse events, and patient compliance of the three groups were compared.

Results: Between April 2021 and January 2022, a total of 1080 subjects were screened and 945 were randomized. The eradication rates in groups A, B, and C were 88.6% (95% CI 84.5%–91.9%), 84.4% (95% CI 80.0%–88.3%), and 86.7% (95% CI 82.4%–90.2%; $p = .315$), respectively, based on intention-to-treat analysis; 90.3% (95% CI 86.4%–93.3%), 85.5% (95% CI 81.1%–89.2%), and 87.8% (95% CI 83.6%–91.2%; $p = .197$), respectively, according to modified intention-to-treat analysis; and 90.4% (95% CI 86.5%–93.5%), 85.8% (95% CI 81.4%–89.5%), and 88.3% (95% CI 84.1%–91.7%; $p = .202$) in per-protocol analysis. History of antibiotics use in 2 years reduced eradication effect in group B (ESO 40 mg Bid, AMX 1 g Tid). The modified intention-to-treat eradication rates were 81.4% vs 90.0% among those with or without a history of antibiotics use in group B ($p = .031$). The adverse event rates were 13.7%, 12.7%,

Technology, Wuhan, China.
Email: pyli@tjh.tjmu.edu.cn

Yun-Lian Hu, Department of
Gastroenterology, Hubei Provincial
Hospital of Traditional Chinese Medicine,
Wuhan, China.
Email: 843214365@qq.com

and 12.1% in groups A, B, and C, respectively ($p = .834$). Patient compliance of the three groups was similar.

Conclusions: Two optimized AMX and PPI dual regimens (ESO 40 mg Bid or 20 mg Tid plus AMX 1 g Tid for 14 days) had similar efficacy, safety and compliance as compared with classical dual regimen (ESO 20 mg plus AMX 750 mg Qid for 14 days) in *H. pylori*-infected treatment-naive patients.

KEYWORDS
eradication rate, *Helicobacter pylori*, high-dose dual therapy, optimized

1 | INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral, microaerobic, highly infectious gram-negative bacteria parasitizing in the human stomach. It is reported that this bacterium infects more than 50% of the world's population, with rates as high as 79% in Africa, 69.4% in South America, 54.7% in Asia, and 47% in Europe.[1] *H. pylori* infection is closely correlated to chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer. It has even been reported to link to non-digestive diseases, such as unexplained iron-deficiency anemia (IDA), idiopathic thrombocytopenic purpura (ITP), and vitamin B12 deficiency.[2,3] Eradication of *H. pylori* infection prevents or delays mucosal atrophy and intestinal metaplasia and reduces the incidence of gastric cancer in some cases.[4] *H. pylori* infection can also be transmitted from person to person. Therefore, it is an infectious disease regardless of symptoms and complications, and eradication treatment can be extended to asymptomatic patients.[2,5]

Various *H. pylori* eradication treatment regimens have been recommended worldwide, including clarithromycin-containing triple therapy, quadruple therapy, sequential therapy, concomitant quadruple therapy, and so on.[2,6] Until now, the eradication rate of traditional clarithromycin-containing triple therapy has decreased to an unacceptable level (lower than 80%). The primary factor of treatment failure is presumed to be bacterial resistance to clarithromycin. According to the Maastricht V/Florence Consensus Report,[2] Toronto Consensus,[6] American College of Gastroenterology Clinical Guideline,[7] and the Fifth Chinese National Consensus Report,[8] bismuth quadruple or non-bismuth concomitant therapy for 10–14 days are recommended as the first-line treatment for patients in areas with high *H. pylori* clarithromycin resistance. Bismuth quadruple therapy consists of a PPI, bismuth, and a combination of two antibiotics, among furazolidone, tetracycline, metronidazole, or amoxicillin (AMX). Zhang et al[9] reported a 14-day bismuth quadruple therapy, composed of lansoprazole, bismuth, AMX and metronidazole, achieved the eradication rate of more than 90% in areas with a high prevalence of metronidazole and clarithromycin resistance. Concomitant quadruple therapy includes a PPI and 3 types of antibiotics, typically including AMX, clarithromycin, and metronidazole. This regimen has been proved to be successful in high clarithromycin resistance (15%–40%) but low to intermediate metronidazole resistance (<40%) regions.[2] Although these new quadruple programmes seem to have achieved a high rate of eradication, a large number of tablets, higher side effect rates, and secondary antibiotic resistance are their main disadvantages.[10] Increasing the type and dosage of antibiotics may lead to the emergence of potentially antibiotic-resistant strains and reduce the options for rescue treatment after failure of first-line therapies. Antibiotic-susceptibility-guided therapy has been recommended in areas of high antibiotic resistance.[11] However, *H. pylori* culture and antibiotic sensitivity tests are not routinely carried out clinically in many countries including China, because of invasive examination (endoscopy), expensive costs, and tedious procedures.[12] Thus, treatment protocols with a high eradication rate, simple and well-tolerated medication, and cost-effective drug combinations are needed.

Unlike clarithromycin and metronidazole, the prevalence of *H. pylori* primary resistance to AMX remains below 5% in most areas.[13] In recent years, high-dose AMX and proton pump inhibitors (PPI), named "high-dose dual therapy or dual therapy", have been proposed and studied. Several clinical studies showed that high-dose dual therapy was as effective as the present first-line treatment (triple or bismuth quadruple therapy), but had fewer adverse events.[14,15] In 2020, our research also found that high-dose dual therapy (ESO 20 mg Qid plus AMX 1 g Tid) had similar efficacy as the bismuth-containing quadruple therapy, but the former had fewer adverse events (12.9% vs. 28.1%, $p < .001$), and lower costs (¥590.2 vs. ¥723.22).[16] There were several regimens of high-dose dual therapy with different doses, frequencies, and durations of AMX and PPI, lacking mutual comparative studies among the dual therapies. In addition, AMX and PPI in dual therapy are typically administered four times daily, which may decrease treatment adherence or even potentially increase the frequency of side effects. Further investigations are required to develop a more optimized dual therapy.

Therefore, the present prospective study was designed to evaluate the efficacy, adverse events, and patient adherence of three high-dose dual regimens with different doses and frequencies of AMX and PPI in treatment-naive patients with *H. pylori* infection.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This study was a prospective, multicenter, open-label, randomized controlled trial, which was approved by the Institutional Ethics Board of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (2021S052). Informed consent was obtained from all participants. The study was also registered in the Chinese Clinical Trials Registration Center (chictr.org.cn: ChiCTR2100045059). The recommendations of the CONSORT statement for the quality of reporting randomized control trials were followed. Between April 2021 and January 2022, consecutive treatment-naive patients infected with H pylori, who were diagnosed at 12 tertiary hospitals in China, were considered for recruitment.

Inclusion criteria were as follows: (i) age 18 to 65 years, male or female; (ii) diagnosis of H. pylori infection by carbon-13/14 urea breath test (13C/14C-UBT) or immunohistochemical staining of biopsy samples; (iii) treatment-naive; (iv) did not take antibiotics, bismuth, or Chinese traditional medicines with antibacterial effects in the previous month, and did not take PPI, H_2 receptor antagonists, or other drugs that affect H. pylori activity within the previous 2 weeks; and (v) provided informed consent to participate in this study.

Exclusion criteria were as follows: (i) presence of severe diseases or clinical conditions, such as liver disease, lung disease, and cardiovascular disease; (ii) allergy to penicillin or other medications used in this clinical trial; (iii) pregnancy or lactation; (iv) presence of severe gastrointestinal diseases, such as malignant tumor, gastrointestinal bleeding, or Zollinger-Ellison syndrome; and (v) considered inappropriate due to non-compliance or safety reasons after assessment by researchers.

2.2 | Randomization and interventions

The eligible subjects were instructed to fill-in an electronic questionnaire in Questionnaire Star (Changsha Ranxing Information Technology Co., Ltd.), a professional online questionnaire platform. Demographic and clinical data were collected. After signing informed consent, the recruited patients were randomly assigned into one of three treatment groups (Group A, B or C) according to the ratio of 1:1:1 by a computer-generated randomized digital table. The detailed process was as follows: A list of random numbers was generated by the computer in advance. Then, we divided each random number by 3 to get a remainder of 0, 1, or 2. Those with a remainder of 0 were included into group A, a remainder of 1 into group B, and a remainder of 2 into group C. The patients from different centers were assigned to the random number list in the order of inclusion after completing the online questionnaire. Each patient corresponded to only one group according to the remainder of the random number divided by 3.

Group A received 20 mg esomeprazole (ESO) and 750 mg AMX four times daily (ESO 20 mg plus AMX 750 mg Qid) for 14 days. ESO was given 30 min before meals and 1 h before sleep, and AMX was given 30 min after meals and 1 h before sleep. Group B received 40 mg ESO twice daily and 1 g AMX three times daily (ESO 40 mg Bid plus AMX 1 g Tid) for 14 days. ESO was given 30 min before breakfast and dinner, and AMX was given 30 min after meals. Group C received 20 mg ESO and 1 g AMX three times daily (ESO 20 mg plus AMX 1 g Tid) for 14 days. ESO was given 30 min before meals, and AMX was given 30 min after meals. Patients were asked to refrain from consuming alcohol during the study. They were instructed on the details of the regimen and the importance of regular medication. During treatment, all subjects need to be followed up at least 3 times through Wechat, text message, telephone, etc., to record the adverse reactions and compliance. For mild to moderate adverse events, patients would be advised to continue medication with/without symptomatic treatment. Patients with severe adverse events would be recommended to stop the medication and come to the outpatient clinic. At least 4 weeks after the end of the treatment, a 13C/14C-UBT was proceeded again to evaluate the status of the H. pylori infection.

2.3 | Outcomes

The primary outcome of this study was the eradication rate of H. pylori infection, which was defined when H. pylori infection was negative at least 4 weeks after completion of the treatment. The eradication rates with 95% confidence interval (CI) were calculated and compared by intention-to-treat (ITT), modified intention-to-treat (mITT), and per-protocol (PP) analysis. All registered patients were included in the ITT analysis, and those who lost to follow-up or lacked 13C/14C-UBT results were scored as treatment failure. Patients who received at least one dose of medication and follow-up of UBT were included in the mITT analysis. The PP analysis excluded patients who violated the protocol, such as those who took <80% of treatment drugs, or did not return for UBT.

The secondary outcomes were the incidence of adverse events and compliance. Adverse events were reported by participants as instructed according to the influence of adverse reactions on their daily life and graded as "mild" (transient, tolerable, and does not affect daily life), "moderate" (psychological or physical discomfort, partly affect daily life), and "severe" (severe interruption of their daily life). The frequency of adverse events was assessed by counting the number of patients with each event. Multiple adverse reactions may occur in one patient and should be counted separately. Compliance was defined as good when participants took at least 80% of the total medication.

2.4 | Sample size estimation and statistical analysis

PASS ver.15.0.5 (NCSS LLC.) was used for sample size estimation. Based on previous studies,[16,17] we assumed that the eradication rates would be 90.4% and 83.2% in the classical dual therapy group (ESO 20 mg plus AMX 750 mg Qid) and optimized dual therapy group (ESO 40 mg Bid or 20 mg Tid plus AMX 1 g Tid), respectively. Thus,
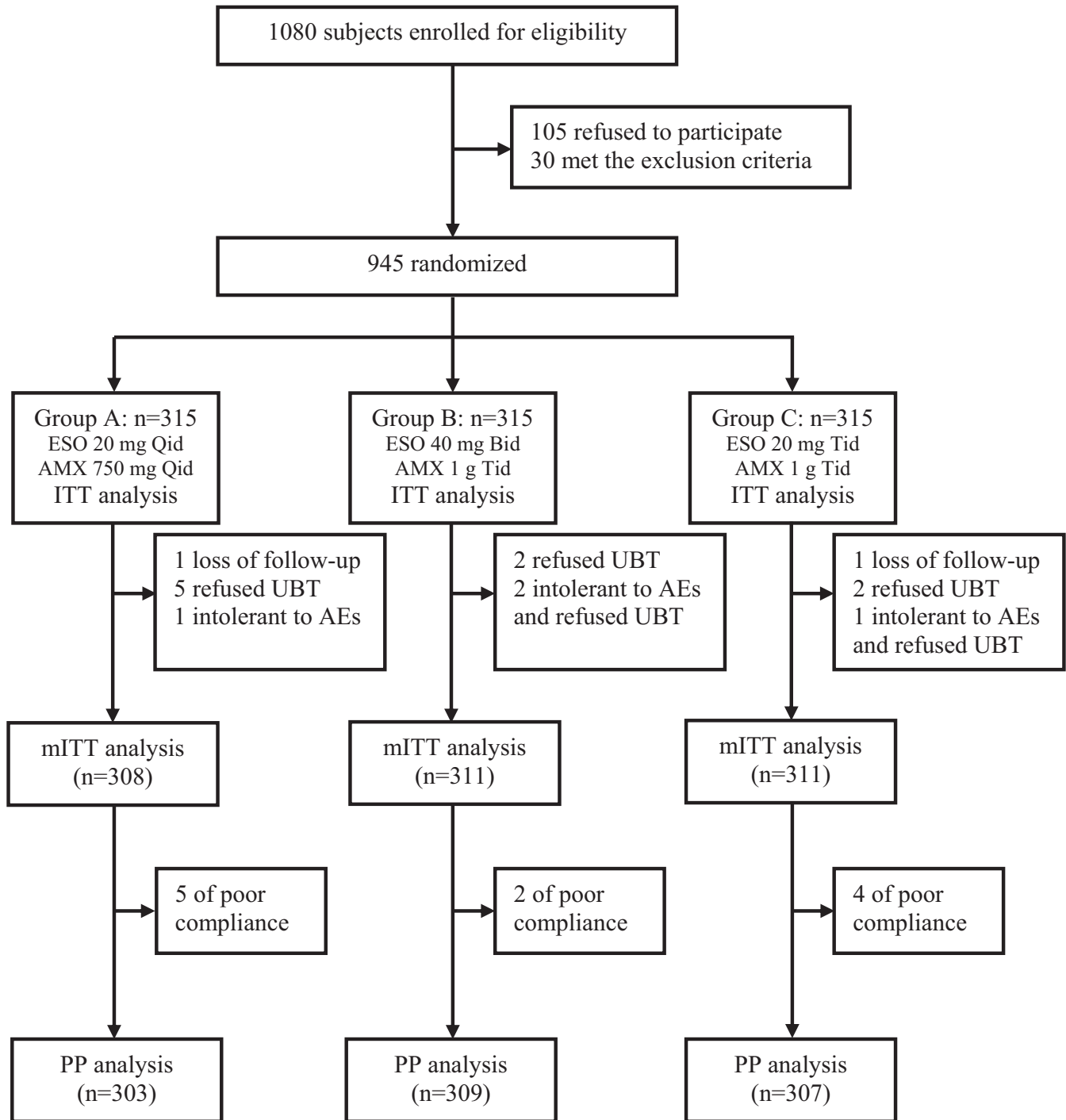
FIGURE 1 Flow diagram of this study. ESO, esomeprazole; AMX, amoxicillin; Qid, four times a day; Bid, twice a day; Tid, three times a day; ITT analysis, intention-to-treat analysis; mITT analysis, modified intention-to-treat analysis; PP analysis, per-protocol analysis; UBT, urea breath test; AEs, adverse events.

we estimated that at least 301 subjects in each group were required, with a power of 80% at a 5% statistically significant level, and assuming a 10% drop-off rate.

IBM SPSS statistics ver. 26.0 (IBM Corp.) was used for data analysis. Counting variables were described by mean ± SD, and categorical data were described by absolute numbers and percentage frequencies. Differences in baseline information, eradication rates, adverse events, and compliance among multiple groups were evaluated by one-way ANOVA, Pearson chi-square test or Fisher's exact test where appropriate, followed by both multiple comparisons with Bonferroni correction and the Tukey's method for all-pairwise comparisons. Univariate analysis was performed to explore significant predictive variables, followed by a multiple logistic regression analysis. A backward/forward strategy and the Wald statistic were used for model comparisons. A two-tailed p-value of <.05 was considered statistically significant.

TABLE 1 Baseline demographics and clinical data of patients

Baseline factors	Group A (n = 315) ESO 20 mg Qid AMX 750 mg Qid	Group B (n = 315) ESO 40 mg Bid AMX 1 g Tid	Group C (n = 315) ESO 20 mg Tid AMX 1 g Tid	p-value
Sex (female:male)	169:146	168:147	169:146	.996
Age (years)	41.8 ± 12.2	42.2 ± 11.7	43.7 ± 12.1	.109
Body mass index (kg/m^2)	22.8 ± 3.4	22.8 ± 3.2	22.9 ± 3.4	.936
Family population (<3:≥3)	58:257	64:251	70:245	.494
Place of residence (suburban area:urban area)	41:274	41:274	45:270	.865
Smoking	56 (17.8%)	69 (21.9%)	67 (21.3%)	.383
Drinking	61 (19.4%)	75 (23.8%)	69 (21.9%)	.398
Digestive symptoms	224 (71.1%)	219 (69.5%)	219 (69.5%)	.882
Stomach ache	77 (24.4%)	74 (23.5%)	72 (22.9%)	.894
Abdominal distension	112 (35.6%)	119 (37.8%)	100 (31.7%)	.276
Belching	94 (29.8%)	90 (28.6%)	80 (25.4%)	.440
Acid reflux	65 (20.6%)	70 (22.2%)	74 (23.5%)	.687
Heartburn	45 (14.3%)	41 (13.0%)	45 (14.3%)	.868
Abdominal discomfort	77 (24.4%)	83 (26.3%)	74 (23.5%)	.699
Other	22 (7.0%)	13 (4.1%)	25 (7.9%)	.125
Endoscopy diagnosis	167 (53.0%)	156 (49.5%)	181 (57.5%)	.135
Reflux esophagitis	20 (6.3%)	8 (2.5%)	18 (5.7%)	.059
Superficial gastritis	50 (15.9%)	58 (18.4%)	61 (19.4%)	.497
Erosive gastritis	56 (17.8%)	57 (18.1%)	74 (23.5%)	.129
Hemorrhagic gastritis	7 (2.2%)	3 (1.0%)	6 (1.9%)	.438
Peptic ulcer	33 (10.5%)	29 (9.2%)	34 (10.8%)	.784
Atrophic gastritis	31 (9.8%)	26 (8.3%)	37 (11.7%)	.341
Intestinal metaplasia	4 (1.3%)	3 (1.0%)	4 (1.3%)	1.000
Gastric polyp	12 (3.8%)	11 (3.5%)	13 (4.1%)	.917
Stomach macular	1 (0.3%)	2 (0.6%)	2 (0.6%)	1.000
Other	17 (5.4%)	8 (2.5%)	8 (2.5%)	.079
Family infection of *H. pylori* (unchecked:no:yes)	177:62:76	174:74:67	175:75:65	.644
Family history of gastric carcinoma	9 (2.9%)	7 (2.2%)	8 (2.5%)	.880
History of antibiotics use in 2 years	169 (53.7%)	162 (51.4%)	161 (51.1%)	.785
Penicillin	128 (40.6%)	112 (35.6%)	110 (34.9%)	.266
Cephalosporin	89 (28.3%)	83 (26.3%)	74 (23.5%)	.391
Ofloxacin	20 (6.3%)	20 (6.3%)	26 (8.3%)	.556
Furazolidone	1 (3.7%)	0	0	1.000
Clarithromycin	6 (1.9%)	6 (1.9%)	7 (2.2%)	.948
Metronidazole/tini-dazole	21 (6.7%)	15 (4.8%)	23 (7.3%)	.391
Tetracycline	3 (1.7%)	0	0	1.000
Others	10 (3.2%)	8 (2.6%)	7 (2.2%)	.759

3 | RESULTS

3.1 | Patients

From April 2021 to January 2022, a total of 1080 subjects were screened for eligibility and 945 subjects were randomly allocated to groups A, B, and C (315 in each group). The trial profile is shown in Figure 1. Among them, 303, 309, and 307 patients completed regimens A, B, and C, respectively, and attended the follow-up 13C/14C-UBT. Two subjects (from groups A and C, respectively) lost to follow-up and 12 subjects (5, 4, and 3 from groups A, B, and C, respectively) refused 13C/14C-UBT. These patients with unclear

TABLE 2 Eradication rate of each group in ITT, mITT and PP analyses

Variables	Group A ESO 20mg Qid AMX 750mg Qid	Group B ESO 40mg Bid AMX 1 g Tid	Group C ESO 20mg Tid AMX 1 g Tid	p-value
ITT	88.6% (279/315)	84.4% (266/315)	86.7% (273/315)	.315
95% CI	84.5%–91.9%	80.0%–88.3%	82.4%–90.2%	
mITT	90.3% (278/308)	85.5% (266/311)	87.8% (273/311)	.197
95% CI	86.4%–93.3%	81.1%–89.2%	83.6%–91.2%	
PP	90.4% (274/303)	85.8% (265/309)	88.3% (271/307)	.202
95% CI	86.5%–93.5%	81.4%–89.5%	84.1%–91.7%	

eradication status were scored as treatment failures in the ITT analysis and excluded from mITT and PP analyses. Eleven subjects (5, 2, and 4 from groups A, B, and C, respectively) took less than 80% of drugs (poor adherence), who were excluded from the PP analysis. The demographic and clinical characteristics of the ITT population are summarized in Table 1. The three groups were comparable with regard to sex, age, body mass index (BMI), place of residence, smoking, drinking, digestive symptoms, endoscopy diagnosis, family infection of *H. pylori*, family history of gastric carcinoma, and antibiotic use in the prior 2 years (*p* > .05). The baseline characteristics of the mITT and PP populations were similar to those of the ITT population (Tables S1 and S2).

3.2 | Eradication rates of *H. pylori* infection

As shown in Table 2, in the ITT analysis, the eradication rates were 88.6% (279/315; 95% CI 84.5%–91.9%), 84.4% (266/315; 95% CI 80.0%–88.3%), and 86.7% (273/315; 95% CI 82.4%–90.2%) for groups A, B, and C, respectively (*p* = .315). The mITT analysis showed that eradication rates were 90.3% (278/308; 95% CI 86.4%–93.3%), 85.5% (266/311; 95% CI 81.1%–89.2%), and 87.8% (273/311; 95% CI 83.6%–91.2%) for groups A, B, and C, respectively (*p* = .197). According to the PP analysis, the eradication rates were 90.4% (273/303; 95% CI 86.5%–93.5%), 85.8% (265/309; 95% CI 81.4%–89.5%), and 88.3% (271/307; 95% CI 84.1%–91.7%) for groups A, B, and C, respectively (*p* = .202). There was no significant difference in eradication rates among the three regimens.

3.3 | Risk factors influencing eradication efficacy

As shown in Table 3, factors influencing the eradication efficacy of three dual therapy regimens were analyzed in the mITT population. History of antibiotics use in 2 years reduced the eradication rate in group B (ESO 40mg Bid, AMX 1 g Tid) patients (ie, 81.4% vs 90.0% in patients with or without history of antibiotics use, *p* = .031). Other factors, such as sex, age, BMI, smoking, drinking, and place of residence, did not influence the efficacy. In addition, adverse events and compliance had no impact on treatment outcomes.

3.4 | Adverse events and compliance

The incidence of adverse events was 13.7% (43/314), 12.7% (40/315), and 12.1% (38/314) in groups A, B, and C, respectively (*p* = .834). Common manifestations included diarrhea, abdominal distension, abdominal pain, nausea, vomiting, constipation, dry mouth, skin rash, headache, dizziness, weakness, etc. (Table 4). The side effects were mainly mild or moderate and gradually disappeared after the completion of treatment. Two subjects from groups B and C showed significant abdominal pain and then recovered after drug withdrawal. No serious adverse events occurred during the study period. There was no significant difference in compliance among three treatment groups: 97.8% (308/315) in group A, 98.7% (311/315) in group B, and 98.1% (309/315) in group C (*p* = .658).

4 | DISCUSSION

The important factors related to eradication success include sensitive antibiotics, good compliance, and high intragastric pH.[18] Among the six antibiotics commonly used for *H. pylori* eradication, the resistance rates to clarithromycin, metronidazole, and levofloxacin are 20%–50%, 20%–70%, and 20%–60%, respectively.[19–21] Increasing antibiotic resistance is a leading cause of *H. pylori* eradication failures by first-line regimens. The high-dose dual therapy, with satisfactory eradication effect, simplified administration, and fewer adverse reactions, has regained attention.[7] Deeper gastric acid suppression and sufficient AMX are crucial factors for the efficacy of dual therapy.[22]

In fact, AMX is a kind of time-dependent semi-synthetic penicillin and excretes within 8h after administration. Frequent administration up to 3 or 4 times a day is needed to maintain plasma concentrations above the minimum inhibitory concentration (MIC). A meta-analysis of PPI-AMX dual therapy showed that 3 grams of AMX daily provided the best effect, but whether given 1 gram three times a day or 750mg four times a day is as yet unknown.[17] Based on previous and present results, AMX 1 gram three times daily had similar effects as 750mg four times daily.[16]

AMX is also a pH-dependent antibiotic, which is more stable in higher intragastric pH environment. *H. pylori* are much more sensitive to AMX when intragastric pH is above 6.[23] Intragastric pH

TABLE 3 Univariate analysis of factors influencing eradication rates in the three treatment groups

The cure rate in subgroups	Group A (n = 308) ESO 20 mg Qid AMX 750 mg Qid	Group B (n = 311) ESO 40 mg Bid AMX 1 g Tid	Group C (n = 311) ESO 20 mg Tid AMX 1 g Tid
Gender			
Male	127/143 (88.8%)	126/145 (86.9%)	124/145 (85.5%)
Female	151/165 (91.5%)	140/166 (84.3%)	149/166 (89.8%)
p-value	.425	.522	.255
Age			
<35 years	97/107 (90.7%)	82/98 (83.7%)	76/86 (88.4%)
35–50 years	98/108 (90.7%)	109/124 (87.9%)	103/119 (86.6%)
>50 years	83/93 (89.2%)	75/89 (84.3%)	94/106 (88.7%)
p-value	.925	.621	.872
BMI, kg/m^2			
<25	215/234 (91.9%)	207/243 (85.2%)	210/235 (89.4%)
≥25	63/74 (85.1%)	59/68 (86.8%)	63/76 (82.9%)
p-value	.088	.743	.135
Digestive symptoms			
Yes	197/222 (88.7%)	186/217 (85.7%)	188/216 (87.0%)
No	81/86 (94.2%)	80/94 (85.1%)	85/95 (89.5%)
p-value	.148	.889	.546
Smoking			
Yes	49/55 (89.1%)	60/69 (87.0%)	63/67 (94.0%)
No	229/253 (90.5%)	206/242 (85.1%)	210/244 (86.1%)
p-value	.747	.703	.078
Drinking			
Yes	53/60 (88.3%)	64/74 (86.5%)	61/69 (88.4%)
No	225/248 (90.7%)	202/237 (85.2%)	212/242 (87.6%)
p-value	.575	.789	.858
Family population			
<3	47/55 (85.5%)	52/63 (82.5%)	63/70 (90.0%)
≥3	231/253 (91.3%)	214/248 (86.3%)	210/241 (87.1%)
p-value	.185	.450	.520
Place of residence			
Suburban area	36/40 (90.0%)	34/41 (82.9%)	39/44 (88.6%)
Urban area	242/268 (90.3%)	232/270 (85.9%)	234/267 (87.6%)
p-value	1.000	.611	.852
Family infection of H. pylori			
Yes	66/73 (90.4%)	55/66 (83.3%)	54/65 (83.1%)
No	57/61 (93.4%)	64/73 (87.7%)	63/74 (85.1%)
p-value	.524	.467	.740
Family history of gastric carcinoma			
Yes	8/8 (100%)	5/7 (71.4%)	7/8 (87.5%)
No	270/300 (90.0%)	261/304 (85.9%)	266/303 (87.8%)
p-value	.736	.597	1.000
History of antibiotics use in 2 years			
Yes	150/166 (90.4%)	131/161 (81.4%)	140/159 (88.1%)
No	128/142 (90.1%)	135/150 (90.0%)	122/152 (86.5%)
p-value	.948	.031	.692

(Continues)

TABLE 3 (Continued)

The cure rate in subgroups	Group A (n = 308) ESO 20 mg Qid AMX 750 mg Qid	Group B (n = 311) ESO 40 mg Bid AMX 1 g Tid	Group C (n = 311) ESO 20 mg Tid AMX 1 g Tid
Side effect			
Yes	40/45 (88.9%)	32/40 (80.0%)	32/39 (82.1%)
No	238/263 (90.5%)	234/271 (86.3%)	241/272 (88.6%)
p-value	.949	.287	.346
Compliance			
Good	274/303 (90.4%)	265/309 (85.8%)	271/307 (88.3%)
Poor	4/5 (80.0%)	1/2 (50.0%)	2/4 (50.0%)
p-value	.984	.671	.120

value is closely related to the type, dosage, and frequency of PPI. Higher dose or shorter interval of PPI administration can overcome the influence of cytochrome P450 2C19 (CYP2C19) gene polymorphism and achieve sufficient acid inhibition.[24,25] In fact, CYP2C19 mainly affects the eradication effect of *H. pylori* infection by influencing PPI pharmacokinetics and pharmacodynamics.[26] Compared with first-generation PPIs, ESO has an improved pharmacokinetic profile with regards to CYP2C19 genotype, and CYP2C19 polymorphisms have less influence. Hong et al[26] reported that ESO (20 mg Qid) was not affected by the CYP2C19 gene polymorphism. Nevertheless, the high dose and frequency of PPI usage might increase the cost of treatment and the number of missed doses. In this study, compliance to all three regimens was around 98%. Such good compliance may be related to the regular follow-up and timely medication guidance for all subjects during treatment. The proportion of patients missing more than 10% of the total medication was 6.3%, 3.5%, and 3.8% in groups A, B, and C, respectively (p = .169). A four-times-daily regimen may increase more missed doses in real world.

Can dual therapy be further optimized while still maintaining satisfactory eradication rate? In 2019, a study found an ITT eradication rate of 92.5% with 14-day dual therapy using ESO (40 mg Bid) and AMX (1 g Tid).[27] Sapmaz et al[28] reported that three times daily rabeprazole (20 mg Tid) combined with AMX (750 mg Tid) also achieved satisfactory results. Thus, we used two optimized ESO administrations in this trial: ESO 40 mg Bid or 20 mg Tid, both of which would maintain relatively higher intragastric pH theoretically.

The findings of this study are as follows. First, there was no significant difference among the three groups in terms of eradication rate, safety, and compliance. Both of these optimized dual therapies are effective treatment options for *H. pylori* infection. However, the eradication rate by the ITT analysis in regimen B (ESO 40 mg Bid plus AMX 1 g Tid) was 84.4% (<85%), which may be due to the fact that ESO "increased dose" is not as effective as "increased frequency".[24] Therefore, the regimen C (ESO 20 mg plus AMX 1 g Tid) is highly recommended. Second, risk factors influencing the treatment success were extensively analyzed, and only the history of antibiotics use in 2 years was found to reduce the effect of regimen B (ESO 40 mg Bid plus AMX 1 g Tid). Zhou et al[29] showed that

previous antibiotic use or exposure was associated with the antibiotic resistance of *H. pylori*. It is suggested that the eradication rate was more easily influenced by the history of antibiotics use under inadequate acid suppression. Third, the overall incidence of adverse reactions was 12.8% (121/943) and there was no significant difference among the three groups. In our previous study, the incidence of adverse reactions was as high as 28.1% in the bismuth-containing quadruple therapy.[16] It is suggested that these dual regimens have less adverse reactions compared with bismuth-containing quadruple therapy. Diarrhea, abdominal distension, and nausea were the most frequently observed adverse events. Fourth, although patient compliance was as high as 98% in the three groups, eradication failed in four patients with poor compliance. In addition to simplifying treatment protocols, patient education about taking all the pills on time is extremely important.

This study was a large-sample (945) and multi-center randomized controlled trail. We confirmed that these two optimized dual therapies (ESO 40 mg Bid or 20 mg Tid plus AMX 1 g Tid for 14 days) were as effective and safe as the classical dual therapy (ESO 20 mg plus AMX 750 mg Qid for 14 days). Additionally, the present study is the first one to compare AMX-PPI dual therapies at different doses and frequency of administration. Dual therapy is supposed to be recommended as first-line treatment, and comparative studies among different regimens are still needed.

There were some limitations in the present study. First, this study was an open-label clinical trial rather than a double-blind one, and bias is inevitable. Hence, these findings still need to be further verified in randomized controlled double-blind trials. Second, due to experimental conditions and feasibility in clinical practice, we did not test for antibiotic sensitivity, 24-intragastric pH, and the CYP2C19 genotypes during the treatment. These shortcomings prevented us from evaluating the degree of gastric acid inhibition and the efficacy of optimized dual therapy in resistant strains. Third, our findings do not apply to subjects who are allergic to penicillin or AMX because AMX is the only antibiotic used in all regimens in our study. Fourth, our study was limited to the treatment-naive population. It is unclear whether the treatment-experienced population is suitable for dual therapy. Further clinical studies are required for optimized dual therapy, including novel potassium-competitive acid blocker such as vonoprazan.

TABLE 4　Adverse events and compliance in the three treatment groups

Safety and compliance	Group A (n = 314) ESO 20 mg Qid AMX 750 mg Qid	Group B (n = 315) ESO 40 mg Bid AMX 1 g Tid	Group C (n = 314) ESO 20 mg Tid AMX 1 g Tid	p-value
Patients with adverse events	43 (13.7%)	40 (12.7%)	38 (12.1%)	.834
Mild	38 (12.1%)	37 (11.7%)	34 (10.8%)	.876
Moderate	5 (1.6%)	2 (0.6%)	3 (1.0%)	.452
Severe	0	1 (0.3%)	1 (0.3%)	1.000
Variety of adverse events				
Diarrhea	11 (3.5%)	9 (2.9%)	8 (2.5%)	.772
Abdominal distension	7 (2.2%)	7 (2.2%)	8 (2.5%)	.953
Abdominal pain	8 (2.5%)	6 (1.9%)	4 (1.3%)	.506
Nausea	3 (1.0%)	9 (2.9%)	7 (2.2%)	.224
Vomiting	0	1 (0.3%)	0	1.000
Constipation	5 (1.6%)	3 (1.0%)	3 (1.0%)	.750
Dry mouth	4 (1.3%)	2 (0.6%)	3 (1.0%)	.656
Skin rash	1 (0.3%)	1 (0.3%)	1 (0.3%)	1.000
Headache	1 (0.3%)	5 (1.6%)	2 (0.6%)	.293
Dizziness	2 (0.6%)	1 (0.3%)	1 (0.3%)	.851
Weakness	3 (1.0%)	0	1 (0.3%)	.135
Others	3 (1.0%)	4 (1.3%)	3 (1.0%)	1.000
Discontinued drugs because of adverse events	1 (0.3%)	2 (0.6%)	1 (0.3%)	1.000
Good compliance	308 (97.8%)	311 (98.7%)	309 (98.1%)	.658

5 | CONCLUSION

In conclusion, we demonstrated that two optimized dual regimens (ESO 40 mg Bid plus AMX 1 g Tid or ESO 20 mg Tid plus AMX 1 g Tid for 14 days) were as equally effective and safe as a classical dual regimen (ESO 20 mg plus AMX 750 mg Qid for 14 days) in *H. pylori*-infected treatment-naive patients. AMX and PPI high-dose dual therapy can be optimized by appropriately reducing the frequency of PPI and AMX administration.

AUTHOR CONTRIBUTIONS

Study design: Ying-Ying Han, Pei-Yuan Li; Patient recruitment and acquisition of data: Yun-Lian Hu, Hui Long, Ya Lin, Qiong He, Wei-Gang Chen, Xiang-Wu Ding, Lin Zhou, Ping An, Fen Wang, Zhen-Yu Zhang; Data interpretation, statistical analysis, and manuscript editing: Ying-Ying Han, Pei-Yuan Li. All authors reviewed the manuscript and approved the final version of this report.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

ORCID

Fen Wang https://orcid.org/0000-0002-1387-1126
Pei-Yuan Li https://orcid.org/0000-0002-6300-1460

REFERENCES

1. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology.* 2017;153(2):420-429.
2. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut.* 2017;66(1):6-30.
3. Crowe SE. *Helicobacter pylori* infection. *N Engl J Med.* 2019;380(12):1158-1165.
4. Malfertheiner P. *Helicobacter pylori* treatment for gastric cancer prevention. *N Engl J Med.* 2018;378(12):1154-1156.
5. Leja M, Axon A, Brenner H. Epidemiology of *Helicobacter pylori* infection. *Helicobacter.* 2016;21(Suppl 1):3-7.
6. Fallone CA, Chiba N, van Zanten SV, et al. The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology.* 2016;151(1):51-69.e14.

7. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol.* 2017;112(2):212-239.

8. Liu WZ, Xie Y, Lu H, et al. Fifth Chinese National Consensus Report on the management of *Helicobacter pylori* infection. *Helicobacter.* 2018;23(2):e12475.

9. Zhang W, Chen Q, Liang X, et al. Bismuth, lansoprazole, amoxicillin and metronidazole or clarithromycin as first-line *Helicobacter pylori* therapy. *Gut.* 2015;64(11):1715-1720.

10. Xie C, Lu NH. Review: clinical management of *Helicobacter pylori* infection in China. *Helicobacter.* 2015;20(1):1-10.

11. Sugimoto M, Uotani T, Sahara S, et al. Efficacy of tailored *Helicobacter pylori* eradication treatment based on clarithromycin susceptibility and maintenance of acid secretion. *Helicobacter.* 2014;19(4):312-318.

12. Arslan N, Yılmaz Ö, Demiray-Gürbüz E. Importance of antimicrobial susceptibility testing for the management of eradication in *Helicobacter pylori* infection. *World J Gastroenterol.* 2017;23(16):2854-2869.

13. Kuo YT, Liou JM, El-Omar EM, et al. Primary antibiotic resistance in *Helicobacter pylori* in the Asia-Pacific region: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2017;2(10):707-715.

14. Zhu YJ, Zhang Y, Wang TY, 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;13:1756284820937115.

15. Yang X, Wang JX, Han SX, Gao CP. High dose dual therapy versus bismuth quadruple therapy for *Helicobacter pylori* eradication treatment: a systematic review and meta-analysis. *Medicine (Baltimore).* 2019;98(7):e14396.

16. Guan JL, Hu YL, An P, et al. Comparison of high-dose dual therapy with bismuth-containing quadruple therapy in *Helicobacter pylori*-infected treatment-naive patients: an open-label, multicenter, randomized controlled trial. *Pharmacotherapy.* 2022;42(3):224-232.

17. Gao CP, Zhang D, Zhang T, et al. PPI-amoxicillin dual therapy for *Helicobacter pylori* infection: an update based on a systematic review and meta-analysis. *Helicobacter.* 2020;25(4):e12692.

18. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut.* 2010;59(8):1143-1153.

19. Thung I, Aramin H, Vavinskaya V, et al. Review article: the global emergence of *Helicobacter pylori* antibiotic resistance. *Aliment Pharmacol Ther.* 2016;43(4):514-533.

20. Hu Y, Zhu Y, Lu NH. Primary antibiotic resistance of *Helicobacter pylori* in China. *Dig Dis Sci.* 2017;62(5):1146-1154.

21. Shetty V, Lamichhane B, Tay CY, et al. High primary resistance to metronidazole and levofloxacin, and a moderate resistance to clarithromycin in *Helicobacter pylori* isolated from Karnataka patients. *Gut Pathog.* 2019;11:21.

22. Bayerdörffer E, Miehlke S, Mannes GA, et al. Double-blind trial of omeprazole and amoxicillin to cure *Helicobacter pylori* infection in patients with duodenal ulcers. *Gastroenterology.* 1995;108(5):1412-1417.

23. Scott D, Weeks D, Melchers K, Sachs G. The life and death of *Helicobacter pylori*. *Gut.* 1998;43(Suppl 1):S56-S60.

24. Sugimoto M, Shirai N, Nishino M, et al. Rabeprazole 10 mg q.d.s. decreases 24-h intragastric acidity significantly more than rabeprazole 20 mg b.d. or 40 mg o.m., overcoming CYP2C19 genotype. *Aliment Pharmacol Ther.* 2012;36(7):627-634.

25. Yang JC, Lin CJ, Wang HL, et al. High-dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* infection. *Clin Gastroenterol Hepatol.* 2015;13(5):895-905.e5.

26. Hong J, Shu X, Liu D, et al. Antibiotic resistance and CYP2C19 polymorphisms affect the efficacy of concomitant therapies for *Helicobacter pylori* infection: an open-label, randomized, single-centre clinical trial. *J Antimicrob Chemother.* 2016;71(8):2280-2285.

27. Yu L, Luo L, Long X, et al. High-dose PPI-amoxicillin dual therapy with or without bismuth for first-line *Helicobacter pylori* therapy: a randomized trial. *Helicobacter.* 2019;24(4):e12596.

28. Sapmaz F, Kalkan IH, Atasoy P, Basyigit S, Guliter S. A non-inferiority study: modified dual therapy consisting higher doses of rabeprazole is as successful as standard quadruple therapy in eradication of *Helicobacter pylori*. *Am J Ther.* 2017;24(4):e393-e398.

29. Zhou JJ, Shi X, Zheng SP, et al. Efficacy of bismuth-based quadruple therapy for eradication of *Helicobacter pylori* infection based on previous antibiotic exposure: a large-scale prospective, single-center clinical trial in China. *Helicobacter.* 2020;25(6):e12755.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Han Y-Y, Long H, Lin Y, et al. Optimized dual therapy for treatment-naive patients of *Helicobacter pylori* infection: A large-scale prospective, multicenter, open-label, randomized controlled study. *Helicobacter.* 2022;27:e12922. doi: 10.1111/hel.12922