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Identifying the best regimen for primary eradication of Helicobacter pylori: analysis of 240 cases

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Abstract

The treatment regimen for the eradication of *Helicobacter pylori* may be best when therapy is susceptibility guided. However, it is unrealistic to use a strategy based on susceptibility testing to prioritize therapy for every patient in China. Empirical therapy of *H. pylori* is still widely used. The study was designed to discuss the best first-line treatment regimen depending on empirical therapy. The focal point of the study was the optimal length of the therapy. Also, the selection of antibiotics was discussed in the article. This was a prospective, randomized, non-inferiority trial. *H. pylori*-infected patients who have no previous eradication therapy were randomly assigned to the following: 20 mg of rabeprazole, 1000 mg of amoxicillin, 500 mg of clarithromycin, and 220 mg of bismuth potassium citrate (BACPPI), administered twice a day for 10 or 14 days. The efficacy, side effects, and remission rate of clinical symptoms were determined. A total of 240 subjects were included in the study. The eradication rate with 14 and 10 days was essentially identical in both intention-to-treat (90.83% [95% CI, 86%–96%] vs. 87.50% [95% CI, 82%–93%]) and per-protocol (94.78% [95% CI, 91%–99%] vs. 92.11% [95% CI, 87%–97%]) analyses. Loss of appetite and belching symptoms were significantly better in the BACPPI-10 group than those in the control group after treatment. Side effects were generally mild and similar between groups. Our results showed that a 10-day amoxicillin–clarithromycin-containing bismuth quadruple therapy may be recommended for the primary empirical treatment of *H. pylori* infection in Beijing, China.

KEYWORDS
bismuth quadruple therapy, efficacy, *Helicobacter pylori*, primary eradication

1 | INTRODUCTION

The treatment regimen for the eradication of *Helicobacter pylori* (*H. pylori*) should be susceptibility guided. Unfortunately, susceptibility-guided therapy for every patient in China is unrealistic because *H. pylori* infect an estimated 50% of the population of China (Cheng et al., 2009; Nagy et al., 2016), which means that the number of patients requiring treatment is approximately 700 million. Besides, susceptibility testing is completed only in large urban hospitals where the conditions are permitted. It is unrealistic to use

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a strategy based on susceptibility testing to prioritize therapy for every patient. Moreover, from the social perspective, susceptibility-guided therapy increases the financial burden to both families and societies. Hitherto, the empirical therapy of *H. pylori* is still widely used as the first-line treatment in most Chinese hospitals. The regimen to be chosen through the experience should have the appropriate balance of safety, efficacy, and society's health-care costs. Based on the analysis of 240 cases, the study was designed to discuss the best first-line treatment regimen depending on empirical therapy in China. The focal point of the study was the optimal length of the therapy. Also, the selection of antibiotics was discussed in the article.

2 | SUBJECTS AND METHODS

2.1 | Study design and subjects

This was a prospective, randomized, non-inferiority trial conducted from May 2018 to January 2020 at Peking University First Hospital and Peking University International Hospital, China.

The sample size was calculated using the Power Analysis and Sample Size software. We used alpha and beta cutoffs of 2.5% (0.025) and 20% (0.2), respectively. The estimated eradication rate for the control group was 91% (31/34) in the preliminary experiment. Acceptable success rates have often been defined as 80% or more on an intention-to-treat (ITT) basis. Thus, we accepted a difference of equal to or <11% between the two groups as an equivalent result. The ratio between the control and experimental groups is 1:1. The calculated sample size without dropouts was calculated as 107 completed patients per group and increased to approximately 119 allowing for a 10% dropout rate.

At baseline, the patients were interviewed by medical staff to evaluate for inclusion and exclusion. All patients provided informed consent to participate in the study. Thereafter, they were randomly assigned to one of two treatment groups in a 1:1 ratio according to a computer-generated randomization list. These patients were subject to follow-up evaluations to assess therapeutic compliance and the occurrence of adverse events. *H. pylori* and therapeutic outcome detections were performed 4 weeks after treatment.

2.2 | Inclusion criteria

Patients between ages 18 and 65 years who had at least one positive test within half a month from the rapid urease test, histology, culture, ^{14}C-urea breath test (^{14}C-UBT), or^{13}C-urea breath test (^{13}C-UBT) were eligible for enrollment. Every patient in the study met the indications for *H. pylori* eradication allowed by the treatment guidelines (Liu, et al., 2018).

2.3 | Exclusions

The exclusion criteria were as follows: first, patients with a history of previous *H. pylori* eradication, gastrectomy, severe diseases (e.g., heart, liver, and kidney dysfunctions), psychosis, severe neurosis, or malignancy and pregnancy or lactating women; second, patients with peptic ulcer and symptoms with an unclear cause including diarrhea, abdominal pain, and constipation; third, patients who received antibiotics, proton pump inhibitors (PPIs), or histamine-2 blockers during the 4 weeks before enrollment or have a history of repeated or long-term use of macrolide antibiotics; and fourth, patients with an allergy to penicillin or contraindication to the study drugs.

2.4 | Treatment regimens

Patients were treated with 20 mg of rabeprazole, 1000 mg of amoxicillin, 500 mg of clarithromycin, and 220 mg of bismuth potassium citrate (BACPPI), all twice daily. The treatment period of the experimental group was 10 days, while that of the control group was 14 days. PPIs and bismuth were administered half an hour before a meal, while antibiotics were administered after the meal. All patients were asked to quit drinking during and in the 2 weeks after the end of the treatment.

2.5 | Outcome assessment

The primary outcome of the study was the *H. pylori* eradication rate in relation to treatment duration (i.e., BACPPI-14 vs. BACPPI-10). The secondary outcomes were the prevalence of adverse events, adherence, cost, and remission rate of clinical symptoms.

Eradication status was evaluated by ^{13}C-UBT(UBTs; UCBT Kit, Atom High Tech), which was performed at least 4 weeks after the end of treatment. The test was performed after an overnight fast. Patients were only allowed to drink water during the test. A baseline breath sample was obtained by blowing through a disposable plastic straw into a 20-ml container, and a capsule containing 75 mg of ^{13}C-urea was given to patients with 100 ml of water. Another breath sample was collected after 30 min. The baseline and 30-min breath samples were assayed with a mass spectrometer. The test was considered negative if the difference between the baseline sample and the 30-min sample bellowed 4.0 units. All patients were asked to stop taking PPIs and histamine-2 blockers for at least 2 weeks before ^{13}C-UBT.

Interviews at the outpatient clinic were arranged before, at the end of, and one month after treatment. Patients were interviewed for the presence/absence and severity/frequency of gastrointestinal symptoms (De Luca et al., 2004). Severity was measured on a 3-point scale. The frequency was also recorded on a 3-point scale. A symptom index (severity × frequency) measuring dyspepsia was calculated for the main symptoms (De Luca et al., 2004). Responsiveness

was assessed by comparing the mean symptom index before, at the end of, and one month after appropriate therapy.

2.6 | Tolerability and compliance

Patients who were informed of the common side effects of the drugs were asked to record these symptoms during treatment. Adverse events were assessed by research staff with a predefined case report form. After completion of therapy, compliance was evaluated by counting the number of recycled drugs. Actual dose taken/expected dose <80% was considered to be low compliance. Patients with poor compliance were excluded from the per-protocol (PP) analysis.

2.7 | Statistics

The statistical analysis was performed using SPSS (version 21 for Windows). The eradication rates of *H. pylori* infection in the two groups were calculated using both ITT and PP analyses. Categorical data were analyzed using the chi-square test. The severity and frequency of symptoms between groups were analyzed using the Mann–Whitney *U* test. The severity and frequency of symptoms within groups were compared using the Wilcoxon signed-rank test. The significance level was set at $p < 0.05$.

3 | RESULTS

3.1 | Patients

A total of 240 patients were recruited, including 111 women and 129 men, of whom 120 were randomly assigned to the BACPPI-14 treatment group and 120 in the BACPPI-10 treatment group (Table 1). Characteristics including gender, age, and baseline of main symptoms before treatment were similar in both groups (Tables 1 and 3).

3.2 | Eradication of *H. pylori* infection

Among 240 patients, seven dropped out of the treatment after 3–7 days because of side effects. Four patients who lost to follow-up were not included in the PP analysis. A total of 115 patients in the BACPPI-14 group and 114 in the BACPPI-10 group completed the study as prescribed (Figure 1 and Table 2).

The PP eradication rate was 109 of 115 (94.78%; 95% confidence interval [CI], 91%–99%) with the quadruple therapy BACPPI for 14 days and 105 of 114 (92.11%; 95% CI, 87%–97%), with the BACPPI for 10 days (Table 2). The ITT eradication rate was 109 of 120 (90.83%; 95% CI, 86%–96%) in the BACPPI-14 group and 105 of 120 (87.50%; 95% CI, 82%–93%) in the BACPPI-10 group (Table 2). Neither of them had a statistically significant difference ($p > 0.05$).

TABLE 1 Baseline characteristics for the two groups of patients

Characteristic	BACPPI-14	BACPPI-10	*p*-value
No. of patients	120	120	
Male/female	68/52	61/59	0.365
Mean age (year)	48.11 ± 12.39	45.89 ± 12.92	0.176

BACPPI-14 = bismuth quadruple therapy for 14 days.
BACPPI-10 = bismuth quadruple therapy for 10 days.

3.3 | Changes in patients' symptoms

The main clinical symptoms (epigastric pain, upper abdominal discomfort, loss of appetite, and belching) of both groups were relieved significantly at the end of and one month after treatment. It showed that eradication therapy was beneficial in the relief of dyspeptic symptoms. Loss of appetite and belching symptoms were significantly better in the BACPPI-10 group than those in the control group after treatment (Table 3). However, the remission rates of the four main symptoms were judged to be equivalent one month after treatment (Table 3).

3.4 | Patient compliance and side effects

The most common side effects in both groups were skin rash, diarrhea, abdominal distention, and nausea. Seven patients with negative penicillin skin test stopped taking the study drugs after 3–7 days because of reported drug eruption. The skin of the patients returned to normal after 2–7 days without any additional treatment. Eight patients developed diarrhea, and four of them received treatment with intestinal probiotics. Other complications were mild and went into remission without any treatment. The frequency of adverse effects was 6.7% (8/120) in patients treated with the quadruple therapy BACPPI for 10 days and 11.7% (14/120) in those treated with the longer treatment. For the most common side effects, the incidence rates were similar in both groups ($p = 0.18$). However, the 14-day plan may have increased the risk of adverse events. In the 14-day group, there were six patients with diarrhea, two of which occurred on days 11–14, and two patients with diarrhea occurred on days 5–10 with symptoms worsening on days 11–14. At 11–14 days of treatment,nausea worsened in 3 patients but had no effect on diet, 2 of whom had abdominal discomfort. one patient had palpitations. The overall tolerability was good.

Good compliance was achieved in 115 of 120 patients (95.83%) in the BACPPI-14 group and 114 of 120 patients (95.00%) in the BACPPI-10 group. There was no difference in compliance between the two groups.

4 | DISCUSSION

As a class I carcinogen of gastric cancer, *H. pylori* is the devil pathogen infecting approximately 50% of the world's population

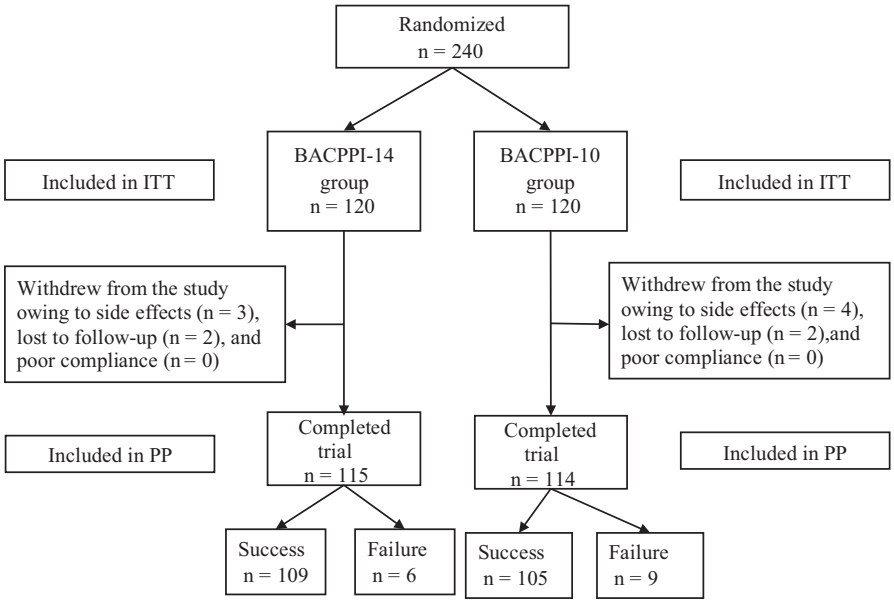

FIGURE 1 Trial profile. ITT, intention to treat; PP, per protocol

TABLE 2 Intervention status of patients enrolled in the trial

Status	BACPPI-14	BACPPI-10	*p*-value
Received standard intervention as allocated	120	120	
Withdrew from study	3	4	
Lost to follow-up	2	2	
Completed trial	115	114	
Treatment failures	6	9	
Cure rate ITT	109/120 (90.83%)	105/120 (87.50%)	0.406
95% CI	86-96	82-93	
Cure rate PP	109/115 (94.78%)	105/114 (92.11%)	0.413
95% CI	91-99	87-97	

Note: Data are n/N (%) for proportional data.

Abbreviations: CI, confidence interval; ITT, intention to treat; PP, per protocol.

(Peleteiro et al., 2014; Smith et al., 2019). Accordingly, the infection rate of *H. pylori* in Chinese adults is reported as high as 40%–60% (Nagy et al., 2016). The overall incidence of gastric cancer in China is also high, and emerging evidence has shown that the eradication of *H. pylori* may reduce the risk of gastric cancer (Ford et al., 2014; Pan et al., 2016; Zhou et al., 2020). However, the extensive treatment of *H. pylori* infection with antibiotics has increased its resistance rates, which lead to a compromise in the efficacy (Cheng et al., 2007; Fagoonee & Pellicano, 2019; Gao et al., 2010; Liu, et al., 2018). Treatment failure has become an issue of concern.

The acquisition of antibiotic resistance is the most common cause of eradication failure (Zou et al., 2020). In China, the rate of *H. pylori* resistance to different antibiotics is generally high, with a clear difference among regions and populations (Ji et al., 2016; Liu et al., 2019; Tong et al., 2015; Zhang et al., 2015). The duration of treatment of *H. pylori* was increased from 7 to 14 days, but the eradication rate was still less than 80% in some regions (Cheng et al., 2007; Gao et al., 2010; Liu, et al., 2018), while a high eradication rate (more than 90%) was achieved by three types of first-line 7-day triple therapies in others (Tong et al., 2015). Compared with patients who had failed the previous treatment, those who have no previous eradication therapy had a significantly higher eradication rate and lower resistance rates for metronidazole, clarithromycin, and levofloxacin (Liu et al., 2019). It is important to choose a treatment plan that is coincident with the status of the area.

Currently, the commonly used antibiotics for the eradication of *H. pylori* include amoxicillin, metronidazole, clarithromycin, levofloxacin, furazolidone, and tetracycline (Liu, et al., 2018). The average antibiotics resistance rates in Beijing were 0.3% (amoxicillin), 37.2% (clarithromycin), 1.7% (furazolidone), 63.9% (metronidazole), 1.2% (tetracycline), 50.3% (levofloxacin), and 61.9% (moxifloxacin), as in most parts of China (Gao et al., 2010; Hu et al., 2017). Although furazolidone and tetracycline are effective antibiotics, they have several side effects and are always not available (Chen et al., 2016; Zhang

TABLE 3 Comparison of the four-symptom mean measurement.

Symptoms	BACPPI-14	BACPPI-10
Epigastric pain*		
Baseline symptoms	2.44 ± 3.25	2.44 ± 3.27
After the treatment	1.10 ± 1.52	1.05 ± 1.47
One month after the treatment	0.51 ± 0.97	0.47 ± 0.91
Upper abdominal discomfort*		
Baseline symptoms	1.54 ± 2.80	1.41 ± 2.69
After the treatment	0.71 ± 1.29	0.42 ± 0.77
One month after the treatment	0.39 ± 0.80	0.27 ± 0.61
Loss of appetite*		
Baseline symptoms	2.00 ± 2.76	1.88 ± 2.82
After the treatment#	1.50 ± 1.98	0.59 ± 0.81
One month after the treatment	0.53 ± 0.91	0.31 ± 0.50
Belching*		
Baseline symptoms	2.09 ± 3.02	2.19 ± 3.21
After the treatment#	1.57 ± 1.95	0.61 ± 0.81
One month after the treatment	0.46 ± 0.84	0.25 ± 0.44

#$p < 0.05$. Loss of appetite and belching symptoms were significantly different between the two groups after the treatment.

*$p < 0.05$, significant differences in after the treatment symptoms versus baseline symptoms and one month after the treatment symptoms vs. baseline symptoms.

et al., 2014, 2020; Zhuge et al., 2018). China's food and drug agency announced in 2018 (no. 43 of 2018) that the drug label of furazolidone would be revised across the nation due to the health risk it posed to multiple organ systems, making it clear that furazolidone could only be used for the treatment of refractory *H. pylori* infection. The increased dosage of metronidazole improved the eradication rates in high metronidazole resistance areas but increased the frequency of the side effects at the same time (Ji & Lu, 2018). The regimen containing levofloxacin is not recommended to be used as the first-line treatment because of its low eradication efficacy (Malfertheiner et al., 2017). Amoxicillin and clarithromycin may be more commonly used relatively with their low side effects rate and good availability. However, the clarithromycin resistance rates are high in China, the triple treatment has lost some efficacy, and the eradication rate has been <80% in most parts of China (Liu, et al., 2018; Wang et al., 2014). Bismuth is one of the few antimicrobials to which resistance does not develop and easily available in China (Lu et al., 2013; Sun et al., 2010). The most recent data show that adding bismuth to triple therapy may increase the cure rates of resistant strains by 30%–40% (Dore et al., 2016; Lu et al., 2013). A study from Shanghai where clarithromycin resistance was high achieved 97.4% (95% CI, 93.8%–100%) PP and 93.7% (95% CI, 88.3%–99.0%) ITT with bismuth, clarithromycin, amoxicillin, and PPI quadruple therapy for 14 days (Sun et al., 2010). Studies in China identified bismuth-containing quadruple therapy that was highly effective despite the high prevalence of resistance to metronidazole, fluoroquinolones, and macrolides (Liang et al., 2013; Lu et al., 2013; Sun et al., 2010). The guideline named "national consensus for the treatment of *Helicobacter pylori* and related symptoms based integrative traditional Chinese and western medicine" recommends that the regimen used in the first-line treatment should not only achieve a high eradication rate but also be safe and acceptable for the greatest number of people (Hu & Zhang, 2018). Amoxicillin–clarithromycin-containing bismuth quadruple therapy is the appropriate regimen that can conform to all the guidelines and standards described earlier. What matters now, however, is the optimal length of the therapy.

Seven types of first-line 14-day bismuth-containing quadruple therapies are recommended by the current consensus in China (Liu, et al., 2018). *H. pylori* infects an estimated 50% of the population of China (Cheng et al., 2009; Nagy et al., 2016). It means that over half of the Chinese population may have to be treated with the long course of multi-antibiotic treatments. Whether the duration of therapy should be 14 days is debatable, especially for patients who have no previous eradication therapy. No rationale for choosing a length of bismuth-containing quadruple therapy has been established. The study was designed to discuss the optimal length of bismuth-containing quadruple therapy to reduce the use of unnecessary antibiotics. The efficacy and safety of 10- and 14-day bismuth quadruple therapy in patients who have no previous eradication therapy were compared in the study.

However, in Beijing where clarithromycin resistance was high, this study achieved 92.11% (95% CI, 87%–97%) PP and 87.50% (95% CI, 82%–93%) ITT with bismuth, clarithromycin, amoxicillin, and PPI quadruple therapy for 10 days. The main clinical symptoms of both groups were relieved significantly at the end of and one month after treatment, which showed that eradication therapy was beneficial in the relief of dyspeptic symptoms. Similar results were obtained in several trials that assessed the potential role of *H. pylori* eradication in improving dyspeptic symptoms. A meta-analysis of randomized controlled studies with 12-month follow-up also confirmed that *H. pylori* eradication therapy was associated with improvement of dyspeptic symptoms, which was consistently demonstrated in the Asian, European, and American populations (Zhao et al., 2014). Bismuth quadruple therapy administered for 10 days was not inferior to the 14-day treatment in terms of efficacy that clinical symptoms were significantly better and adverse events were less frequent. Fourteen-day therapies are costly and uncomfortable for the patients and have an increased risk of side effects. Patients who have a history of repeated or long-term use of macrolide antibiotics were excluded from the study to achieve good results. It may be quite helpful to ask the history of antibiotic administration before treatment if a drug resistance test could not be carried out. Also, other possible reasons that both groups could achieve a relatively high eradication rate included the following: First, medicines were taken only as directed, at the right time, and excellent compliance was achieved; second, patients were followed up regularly, and the data were reliable. Some studies had come to similar conclusions to ours. Bismuth quadruple therapy containing

tetracycline and metronidazole remained highly effective (i.e., ≥95% PP and >90% ITT) despite reducing the duration from 14 to 10 days (Dore et al., 2011). However, the ten-day hybrid regimen could not achieve an acceptable eradication rate. The 14-day hybrid regimen seems to be an acceptable option for *H. pylori* eradication in Iran (Metanat et al., 2015). More research needs to be done on the optimal duration of the different treatment options.

Our study had limitations. Susceptibility data were lacking in this study. However, the goal was not to test whether this combination could provide excellent results in a difficult-to-treat population but identify the best strategy for a population that has no previous eradication therapy in China where the empirical therapy of *H. pylori* is still widely used. Antibiotic resistance to commonly used anti- *H. pylori* drugs in Beijing has increased remarkably, making Beijing an ideal site to identify regimens that remain effective despite widespread antimicrobial resistance (Cheng et al., 2009; Zhu et al., 2020). Perhaps, Beijing's experience can be replicated across the country, but more research is needed.

In conclusion, the results in both groups were highly effective despite widespread antimicrobial resistance. Bismuth quadruple therapy administered for 10 days was not inferior to the 14-day treatment in terms of efficacy. Fourteen-day therapies are costly and uncomfortable for the patients and have an increased risk of side effects. Besides, their ability to overcome clarithromycin resistance has not been established. Therefore, in this population who has no previous eradication therapy, 10-day amoxicillin–clarithromycin-containing bismuth quadruple therapy may be recommended in China, and individualized therapy should be considered if the patient is believed very likely to have a strain resistant to clarithromycin.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Yao Chen: Data curation (lead); Formal analysis (lead); Investigation (equal); Software (lead); Writing-original draft (lead); Writing-review & editing (supporting). **Qingyi Liu:** Data curation (supporting); Formal analysis (supporting); Investigation(equal); Resources(supporting). **Fulian Hu:** Conceptualization (lead); Data curation (supporting); Investigation (supporting); Project administration (lead); Supervision (lead); Writing-review & editing (lead). **Jizheng Ma:** Data curation (supporting); Investigation (supporting); Resources (equal).

ETHICS STATEMENT

This study was approved by the Ethics Committee of Peking University International Hospital (grant number 2018-066BMR) and conducted according to the principles of the Declaration of Helsinki and standards of Good Clinical Practice.

DATA AVAILABILITY STATEMENT

All primary data obtained in this study excluding information related to participant identities are available in supplementary table at Zenodo: https://doi.org/10.5281/zenodo.4029619.

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