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Original Article

Efficacy assessment of diverse antibiotic combinations in bismuth quadruple regimens and risk factors for *Helicobacter pylori* eradication: a retrospective single-center study in China

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Abstract: Objectives: To evaluate the efficacy of various antibiotic combinations in bismuth quadruple therapy for *H. pylori* eradication. Methods: This study involved a retrospective analysis of data collected from a single medical center in Beijing, China. A cohort of patients was enrolled with *H. pylori* infection that underwent 14-d bismuth quadruple therapy (antibiotics, omeprazole, and bismuth) and received a test for cure between January 2020 and December 2023. Patient demographics and therapeutic regimens were meticulously compiled and subsequently categorized into five groups based on antibiotic combinations used: amoxicillin-clarithromycin, amoxicillin-levofloxacin, amoxicillin-doxycycline, clarithromycin-levofloxacin, and clarithromycin-doxycycline. The eradication rates were then calculated and compared across these distinct regimens. Results: This study evaluated a cohort of 575 patients, comprising 261 males and 314 females. A significant majority of patients, 76.3% (n=439), received a treatment regimen comprising amoxicillin and clarithromycin. The amoxicillin-levofloxacin combination was administered to 8.5% (n=49) of the patients. A smaller proportion, 1.7% (n=10), were treated with an amoxicillin-doxycycline regimen. Furthermore, 8.9% (n=51) of the patients received a clarithromycin-levofloxacin regimen, while 4.5% (n=26) were treated with a combination of clarithromycin and doxycycline. Patients treated with the amoxicillin-doxycycline-based regimen exhibited significantly higher eradication rates than other regimens (70.0% *vs* 65.4%, 32.7%, 54.9%, and 42.3%, respectively; P=0.001). Furthermore, the results indicated that risk factors such as smoking and alcohol consumption had a significant impact on the eradication rates (all P<0.01). Conclusion: This study reveals significant differences in the eradication rates of various antibiotic combinations for *H. pylori* infection. Of particular note is that the amoxicillin-doxycycline-based regimen outperformed other antibiotic combinations, with a considerably higher eradication rate. This provides vital insight to inform clinical decision-making in the treatment of *H. pylori*.

Keywords: *Helicobacter pylori*, quadruple therapy, antibiotic combinations, bismuth, eradication rate

Introduction

Helicobacter pylori (*H. pylori*) infection is one of the most prevalent chronic bacterial infections in humans, affecting approximately 50% of the global population [1]. In general, the infection rates in regions such as Africa, Asia, and Latin America are higher than in Europe [2]. Eradication of *H. pylori* is essential for the treatment of these diseases, including gastritis, peptic ulcer disease, and early-stage lymphoma of mucosal-associated lymphoid tissue [3]. In 2014, the World Health Organization (WHO) also recommended the eradication of *H. pylori* as a preventive strategy against gastric cancer [4]. This recommendation serves to highlight the pivotal role that *H. pylori* eradication plays in public health, particularly in areas where infection and gastric cancer rates are high.

The triple therapy, which comprises a proton pump inhibitor (PPI) and amoxicillin in combination with either clarithromycin or metronidazole, is typically recommended treatment for *H. pylori* eradication [5]. Nevertheless, the efficacy of

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triple therapy in eradicating *H. pylori* has declined significantly from over 90% in the 1990s to less than 70% currently [6]. The eradication effect of *H. pylori* treatment has decreased owing to the growing prevalence of antimicrobial resistance. Consequently, bismuth-based quadruple therapy, which introduces bismuth into the standard triple regimen, is now recommended as the preferred first-line treatment. This approach has demonstrated high success rates in eliminating *H. pylori*, including strains that are resistant to conventional antibiotics [7, 8]. The eradication rates for *H. pylori* therapies are declining, primarily due to the limited availability of antimicrobial susceptibility testing, which is not widely accessible in much of China. Consequently, antibiotic regimens are often selected empirically, further complicating effective treatment strategies.

Currently, antibiotic therapy is the most effective and commonly used treatment against *H. pylori* infection [9]. The efficacy of antibiotics in treating *H. pylori* is significantly limited by the highly acidic environment of the human stomach [10]. Antibiotics that exhibit resistance to acidic conditions and possess strong bactericidal properties, such as clarithromycin and amoxicillin, are preferred for treating *H. pylori* infections [11]. Proton pump inhibitors (PPIs) enhance the effectiveness of antibiotic treatment for *H. pylori* by inhibiting gastric acid secretion [12]. Omeprazole, a first-generation PPI, has a well-established history of clinical efficacy in the treatment of various conditions, including peptic ulcer, gastroesophageal reflux disease (GERD), acute gastric mucosal lesions, and stress ulcers [13]. Despite numerous studies that claim one PPI is superior to another, consensus indicates that PPIs are more similar than different [14]. Previous research has shown that omeprazole at a 20 mg dose remains comparably effective to newer PPIs such as esomeprazole (30 mg), lansoprazole (30 mg), pantoprazole (40 mg), rabeprazole (20 mg), and dexlansoprazole (30 mg) in the acute treatment of reflux oesophagitis and in preventing its recurrence [15]. This serves to illustrate the continued relevance and efficacy of omeprazole in the management of these conditions, despite the introduction of newer medications.

Bismuth plays a pivotal role in quadruple therapy for *H. pylori* eradication, acting as a protective barrier for the gastric mucosa [16]. Research indicates that the incorporation of bismuth into a 14-day triple therapy regimen enhances the eradication rates of *H. pylori*, even in the presence of high antimicrobial resistance [17, 18]. A variety of antibiotics, including amoxicillin, clarithromycin, levofloxacin, and doxycycline, are utilized in clinical settings. However, it remains uncertain whether therapeutic regimens that incorporate these distinct combinations of antibiotics achieve comparable rates of *H. pylori* eradication.

The lack of comprehensive, large-scale data on *H. pylori* eradication represents a significant obstacle to the development of effective, applicable treatment guidelines. Furthermore, the potential correlations between demographic characteristics and the failure of *H. pylori* eradication require further investigation. To address these issues, we conducted a retrospective study evaluating the efficacy of various antibiotic combinations in *H. pylori* eradication regimens. Specifically, our study examined the effectiveness of bismuth quadruple regimens that combine different antibiotics (amoxicillin, clarithromycin, levofloxacin, and doxycycline) with omeprazole and bismuth. The aim of this study is to provide robust evidence that will guide the optimization of antibiotics-bismuth quadruple regimens in *H. pylori* infection treatment.

Material and methods

Ethical approval

This retrospective study was conducted in accordance with the Declaration of Helsinki and the guidelines of the Consolidated Standards of Reporting Trials (CONSORT). The study protocol was approved by the Institutional Ethics Board of the Civil Aviation General Hospital, Beijing, China (No. 2023-L-K-22). The trial was registered in the Chinese Clinical Trials Registration (www.chictr.org.cn) with the registration number ChiCTR2400079647.

Sample collection and grouping

In this study, we initially collected data from 3432 cases of *H. pylori* infected patients from the gastroenterology department of our hospital between January 2020 and December 2023. The dataset, compiled from patients'

Table 1. The SFDA approval number and usage of different drugs in this study

Drug	SFDA approval number	Usage
Amoxicillin	H14021834	1000 mg, b.i.d, p.o
Clarithromycin	H20059139	500 mg, b.i.d, p.o
Levofloxacin	H20040091	200 mg, b.i.d, p.o
Doxycycline	H20030627	100 mg, b.i.d, p.o
Omeprazole	H20150023	20 mg, b.i.d, p.o
Bismuth capsules	H20093592	220 mg, b.i.d, p.o

Abbreviations: SFDA, Chinese State Food and Drug Administration; Omeprazole, omeprazole and sodium bicarbonate capsules; Amoxicillin, amoxicillin capsules; Clarithromycin, clarithromycin tablets; Doxycycline, doxycycline hyclate enteric-coated capsules; Levofloxacin, levofloxacin tablets; Bismuth capsules, colloidal bismuth pectin capsules.

medical records, included a number of critical variables, such as age, gender, treatment regimens, results of the urea breath test (UBT), and endoscopic findings.

The inclusion criteria were as follows: (1) Availability of complete general, clinical, and prescription records; (2) Confirmation of *H. pylori* infection status before treatment using the urea breath test; (3) Patients received quadruple therapy for *H. pylori* infection according to the standard antibiotic combinations and dosages; (4) Duration of treatment lasted 14 day; (5) The eradication status *of H. pylori* was confirmed by urea breath test 4 weeks after the end of treatment. The exclusion criteria were as follows: (1) Patients who were lost to follow-up or changed their therapy regimen; (2) Therapies that included other drugs, such as probiotics and/or Chinese traditional medicines; (3) Patients who were aged below 18 or over 70 years.

Following the application of the aforementioned criteria, 575 patients diagnosed with *H. pylori* who were undergoing omeprazole-based quadruple therapy were selected for the study. These patients were subsequently divided into five groups based on different antibiotic combinations: amoxicillin-clarithromycin group (n=439), amoxicillin-levofloxacin group (n=49), amoxicillin-doxycycline group (n=10), clarithromycin-levofloxacin group (n=51), and clarithromycin-doxycycline group (n=26). The treatment duration for all groups was consistently 14 days. Details of the different drugs used in the study, including their SFDA approval number and usage, are presented in **Table 1**.

H. pylori eradication standard

The primary outcome of this study was determined by the eradication rate of *H. pylori*. Secondary outcomes included the identification of risk factors that contribute to the failure of eradication. Following the completion of the antibiotic quadruple regimen therapy, treatment was halted for at least 4 weeks. Patients were then retested using the urea breath test. A negative result indicated successful *H. pylori* eradication, while a positive result was considered an eradication failure. The eradication rate for each group was calculated by dividing the number of patients with negative test results by the total number of patients in that group.

Statistical analysis

Continuous variables were reported as means with standard deviations, while categorical variables were expressed as frequencies and proportions (percentages). For parametric data analysis, the student's *t*-test was employed. T Categorical data comparisons were conducted using either the chi-squared test or Fisher's exact test, depending on the data distribution. Logistic regression models were utilized to identify independent factors associated with successful *H. pylori* eradication, and these models were used to calculate adjusted odds ratios (AORs) with their corresponding 95% confidence intervals (CIs). All statistical analyses were performed using the SPSS 25.0 (IBM Corp., Armonk, NY, USA). A *P* value of less than 0.05 was considered statistically significant.

Results

Basic characteristics of enrolled patients

The clinical characteristics are presented in **Table 2**. A total of 575 outpatients with positive *H. pylori* infection were enrolled in this study. The mean age in the positive and negative group was 46.43±16.13, 42.42±14.21, respectively. Out of these patients, *H. pylori* was successfully eradicated in 349 patients, resulting in an overall eradication rate of 60.7%.

Table 2. Baseline characteristics of study cohort

Characteristics	Total (n=575)	Positive (n=226)	Negative (n=349)	*P* value
Age (mean ± SD)		46.43±16.13	42.42±14.21	0.002
Gender				
Male	261 (45.4)	108 (47.8)	153 (43.8)	0.353
Female	314 (54.6)	118 (52.2)	196 (56.2)	
Smoking history				
No	482 (83.8)	166 (73.5)	316 (90.5)	<0.001
Yes	93 (16.2)	60 (26.5)	33 (9.5)	
Drinking history				
No	497 (86.4)	175 (77.4)	322 (92.3)	<0.001
Yes	78 (13.6)	51 (22.6)	27 (7.7)	
Endoscopy diagnosis				
Chronic superficial gastritis	430 (74.8)	157 (69.5)	273 (78.2)	0.013
Chronic atrophic gastritis	53 (9.2)	32 (14.2)	21 (6.0)	
Gastroduodenal polyps	41 (7.1)	13 (5.8)	28 (8.0)	
Reflux oesophagitis	22 (3.8)	11 (4.9)	11 (3.2)	
Gastroduodenal ulcer	20 (3.5)	10 (4.4)	10 (2.9)	
Others	9 (1.6)	3 (1.3)	6 (1.7)	

Negative indicated *Helicobacter pylori* eradication and positive was considered eradication failure. Others included nine cases of gastric xanthoma, three of acute erosive/hemorrhagic gastritis, and six of duodenitis.

Table 3. Comparison of eradication rates after eradication

Group	Total (n=575)	Positive (n=226)	Negative (n=349)	Eradication rate (%)	χ^2	*P* value
Amoxicillin + Clarithromycin	439 (76.3)	152 (67.3)	287 (82.2)	65.4	24.949	0.001
Amoxicillin + Levofloxacin	49 (8.5)	33 (14.6)	16 (4.6)	32.7		
Amoxicillin + Doxycycline	10 (1.7)	3 (1.3)	7 (2.0)	70.0		
Clarithromycin + Levofloxacin	51 (8.9)	23 (10.2)	28 (8.0)	54.9		
Clarithromycin + Doxycycline	26 (4.5)	15 (6.6)	11 (3.2)	42.3		

P values were obtained from the comparisons of the proportion between groups using χ^2 statistic.

Significant differences were observed between the groups in demographic characteristics such as age, smoking history, and drinking history (all $P<0.01$). All patients underwent gastroscopy, revealing diagnoses of chronic superficial gastritis (74.8%), chronic atrophic gastritis (9.2%), gastroduodenal polyps (7.1%), reflux esophagitis (3.8%), and gastroduodenal ulcer (3.5%). Notable differences were also detected in the prevalence of these conditions among the groups ($P<0.05$).

H. pylori eradication rate of each quadruple regimen

The *H. pylori* eradication rates for each treatment group are detailed in **Table 3**. The eradication rates for the amoxicillin-clarithromycin, amoxicillin-levofloxacin, amoxicillin-doxycycline, clarithromycin-levofloxacin, and clarithromycin-doxycycline groups were 65.4%, 32.7%, 70.0%, 54.9%, and 42.3%, respectively. Unfortunately, none of the groups achieved an eradication rate of 80.0% or higher. Notably, the amoxicillin-doxycycline group exhibited a slightly higher eradication rate compared to other groups. However, the clinical significance of this finding remains unclear and warrants further investigation, particularly given the small sample size of this group.

Risk factors of H. pylori eradication failure

Stepwise logistic regression analyses were conducted to identify factors associated with eradication failure. Statistically significant associa-

Table 4. Multivariate analyses for risk factors of eradication failure

Variable	*β*	Wald	AOR	95% CI	*P* value
Age	-0.008	1.543	0.992	0.979-1.005	0.214
Smoking history					
No			Reference		
Yes	-0.932	11.677	0.394	0.231-0.672	0.001
Drinking history					
No			Reference		
Yes	-0.892	8.251	0.410	0.223-0.753	0.004
Antibiotic combinations					
Amoxicillin + Clarithromycin			Reference		
Amoxicillin + Levofloxacin	-1.415	17.959	0.243	0.126-0.467	<0.001
Amoxicillin + Doxycycline	-0.217	0.095	0.805	0.202-3.210	0.758
Clarithromycin + Levofloxacin	-0.333	1.111	0.717	0.386-1.331	0.292
Clarithromycin + Doxycycline	-0.791	3.350	0.453	0.194-1.058	0.067

Abbreviations: AOR, Adjusted odds ratio; CI, Confidence interval.

tions were found for smoking and drinking history. As shown in **Table 4**, having a smoking history (AOR=0.394, 95% CI: 0.231-0.672) and drinking history (AOR=0.410, 95% CI: 0.223-0.753) were identified as risk factor of eradication failure, with both differences were statistical significance (all $P<0.01$). When setting the amoxicillin plus clarithromycin regimen as the reference, the regimen containing amoxicillin plus levofloxacin was associated with a significantly higher risk of eradication failure (AOR= 0.243, 95% CI: 0.126-0.467; $P<0.01$).

Discussion

H. pylori infection is a well-established risk factor for the development of gastric ulcers and gastric carcinoma [19]. Extensive research has demonstrated the pivotal role of eradicating *H. pylori* infection in mitigating the risk of gastric cancer and peptic ulcers, reducing the incidence of secondary primary gastric cancer, and lowering mortality rates associated with gastric cancer [20]. Consequently, it is imperative that patients receive timely and appropriate treatment aimed at *H. pylori* eradication in order to prevent the development of peptic ulcers and their associated complications.

The treatment of *H. pylori* infection typically involves a combination of antibiotics with a broad-spectrum activity, including amoxicillin, metronidazole, clarithromycin, levofloxacin, furazolidone, and tetracycline [21]. It is, however, important to note that the eradication regimens that have been endorsed by numerous international guidelines are primarily empirical in nature [3]. As a meta-analysis study has highlighted that the existing evidence does not provide sufficient grounds to discourage the use of empirical regimens in clinical practice or to endorse susceptibility-guided treatment as the primary therapeutic approach, until susceptibility testing is further refined and made globally accessible [22]. Despite these insights, identifying an optimal therapy to combat *H. pylori* infection remains a significant challenge. This challenge is further compounded by the rapid increase in antimicrobial resistance, which significantly hampers successful eradication efforts. Additionally, factors such as patient compliance and environmental influences play a role, but antibiotic resistance stands out as a primary cause of treatment failure. Incorporating bismuth into triple therapy regimens has demonstrated the potential to enhance cure rates even in the face of high levels of antimicrobial resistance. Studies have demonstrated that the incorporation of bismuth can result in a notable 30-40% increase in the success of resistance treatment strategies [23]. Nonetheless, the increasing resistance to clarithromycin and levofloxacin can significantly compromise the efficacy of adapted quadruple therapy, making it difficult to achieve success rate of 90% or higher.

The data from this study indicates that all five quadruple regimens exhibited unsatisfactory eradication rates (below 80%), even though

prescription was in strict accordance with guidelines. One potential explanation for this discrepancy is that the prevalence of *H. pylori* resistance to antibiotics has increased over recent years. The average antibiotic resistance rates in Beijing are 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 [24]. The main reason for eradication failure is antibiotic resistance, with the abuse of antibiotics significantly increases the resistance of *H. pylori* [25]. In China, due to the high level of resistance of *H. pylori* to antibiotics, the Chinese guidelines recommend a 14-day treatment to eradicate *H. pylori*. However, the eradication rate remains below 80% in some regions [26]. It is of paramount importance to select a treatment plan that is in alignment with the antibiotic resistance status of the specific region.

Currently, the commonly used antibiotics for the eradication of *H. pylori* include amoxicillin, metronidazole, clarithromycin, levofloxacin, furazolidone, and tetracycline. Our research and previous studies [27, 28] have indicated that regimens containing levofloxacin are not recommended as first-line treatments due to their low efficacy in eradicating *H. pylori*. Amoxicillin and clarithromycin are the antibiotics most frequently employed in practice due to their favorable side effect profile and high accessibility. Bismuth is one of the few antimicrobials that does not develop resistance and is readily available in China [26]. The results of our study indicate that 76.3% of patients accepted the amoxicillin-clarithromycin quadruple regimen, with an eradication rate of 65.4%. A study conducted in Shanghai, China, where clarithromycin resistance was high, achieved impressive eradication rates of 97.4% per protocol (PP) and 93.7% intention-to-treat (ITT) with a bismuth, clarithromycin, amoxicillin, and proton PPI quadruple therapy for 14 days [29]. The high eradication rate can be attributed to several factors, including strict adherence to medication guidelines, excellent patient compliance, and regular follow-up, which collectively ensure reliable data.

The phenomenon of penicillin-induced allergy remains a significant obstacle to the eradication of *H. pylori*. Doxycycline is a second-generation tetracycline antibiotic with a similar range of medications to that of amoxicillin, which could theoretically replace amoxicillin for the treatment of *H. pylori* [30]. A 14-day doxycycline-containing (100 mg bid) bismuth quadruple regimen has been found to achieve approximately 93.8% eradication, with far fewer side effects (11.6%) than the tetracycline group (31.0%) in the first-line treatment [31]. In the present study, the eradication rate of the amoxicillin-doxycycline quadruple therapy was 70.0%, which was superior to that of all other groups. Doxycycline has not been widely employed for the eradication of *H. pylori*, resulting in a paucity of studies in this area [32]. It is recommended that the use of doxycycline in first-line treatment for *H. pylori* infection be expanded, particularly in patients allergic to penicillin in antibacterial therapy.

A number of factors, including antibiotic susceptibility, the extent of acid secretion inhibition (related to PPI, dose, and eradication regimens), environmental factors such as smoking, and patient compliance, can significantly influence the effectiveness of *H. pylori* eradication [33, 34]. Research has demonstrated that tobacco carcinogens can directly damage gastric mucosa, perpetuating *H. pylori* infections and reducing eradication effectiveness. Furthermore, when analyzed jointly, smoking and drinking habits can better predict *H. pylori* eradication outcomes than analyzing them individually [35-37]. This study identifies a significant relationship between smoking and drinking habits and *H. pylori* eradication rates, thereby underscoring the influence of these lifestyle habits on the success of eradication treatment.

Despite the insightful findings of our study, several limitations must be acknowledged. Firstly, we were unable to monitor patient compliance. The extent to which patients adhere to their medication regimen has a significant impact on the eradication rate of *H. pylori*, regardless of the treatment regimen employed. Patients who demonstrate high levels of compliance tend to exhibit significantly higher eradication rates compared to those who exhibit low levels of compliance [38]. Secondly, excluding patients who met the exclusion criteria may limit the generalizability of our findings to a broader population. The relatively limited number of patients in our study further underscores

the need for additional clinical studies exploring different antibiotic combinations for *H. pylori* infection treatment. Thirdly, while we successfully established the efficacy of different antibiotic combinations in bismuth quadruple regimens, timely monitoring of side effects was not feasible. Additionally, due to limited data in our hospital information system, we could not provide a more detailed baseline characteristic outline of the included patients.

Finally, as a retrospective, single-center study with limited groups regarding antibiotic combinations and treatment duration, our findings are not exhaustive. Therefore, we anticipate future large-scale, prospective clinical trials to validate the efficacy and safety of different antibiotic combinations in bismuth quadruple regimens and to optimize the duration of *H. pylori* eradication treatment further.

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Disclosure of conflict of interest

None.

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