World Journal of Gastroenterology

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World J Gastroenterol 2024 October 21; 30(39): 4295-4304

DOI: 10.3748/wjg.v30.i39.4295

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of low-dose tetracycline, amoxicillin quadruple therapy in *Helicobacter pylori* infection: A retrospective single center study

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade A, Grade B

P-Reviewer: Farwati R; Zou YT

Received: May 14, 2024

Revised: September 9, 2024

Accepted: September 24, 2024

Published online: October 21, 2024

Processing time: 150 Days and 17.1 Hours

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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) eradication rates have declined with the rise of antibiotic-resistant strains in recent years. Although highly effective with a low prevalence of resistance, standard dose tetracycline is associated with frequent adverse events. The efficacy and safety of low-dose tetracycline as part of tetracycline and amoxicillin-containing bismuth quadruple therapy are not well described.

AIM

To compare the efficacy and safety of low-dose compared to standard dose tetracycline with combined amoxicillin-containing bismuth quadruple therapy in patients with *H. pylori* infection.

METHODS

Consecutive patients with *H. pylori* infection receiving tetracycline, amoxicillin,

proton pump inhibitor, and bismuth for 14 days at Sir Run Run Shaw Hospital (1/2022-6/2023) were evaluated. The low-dose tetracycline group received tetracycline 500 mg twice daily (bid) while the standard dose group received 750 mg bid or 500 mg three times daily (tid). Primary endpoints were *H. pylori* eradication rate and treatment-related adverse events.

RESULTS

The mean age of the 218 patients was 48.7 ± 14.0 years, 120 (55%) were male, and 118 (54.1%) received treatment as primary therapy. Furthermore, 73 (33%) patients received low-dose tetracycline (500 mg bid) and 145 (67%) received standard dose tetracycline including 500 mg tid in 74 (33%) and 750 mg bid in 71 (33%). On intention-to-treat analysis, *H. pylori* eradication rates were 89% [95% confidence interval (CI): 82%-96%] in the 500 mg bid group, 82% (95%CI: 74%-91%) in the 500 mg tid group, and 79% (95%CI: 69%-89%) in the 750 mg bid group without a statistically significant difference (P = 0.25). The incidence of adverse events was lower in the low-dose compared to the standard dose group (12.3% *vs* 31.1% or 23.9%; P = 0.02).

CONCLUSION

Low-dose tetracycline combined with amoxicillin quadruple therapy for 14 days achieved a high eradication rate and fewer adverse events compared to the standard dose tetracycline regimen in patients with *H. pylori* infection.

Key Words: *Helicobacter pylori*; Tetracycline; Amoxicillin; Eradication; Adverse events; Bismuth quadruple therapy

Core Tip: *Helicobacter pylori* (*H. pylori*) eradication rates have declined with the rise of antibiotic-resistant strains in recent years. Although highly effective, the standard dose of tetracycline as part of the *H. pylori* treatment regimen is associated with a high incidence of adverse events. Our results demonstrated that low-dose tetracycline combined with amoxicillin as part of bismuth-containing quadruple therapy can achieve a high eradication rate and fewer adverse events compared to standard dose tetracycline in patients with *H. pylori* infection.

Citation: Zhao YR, Wang XJ, Zhu MJ, Chen AL, Zhang D, Du Q, Kim JJ, Hu WL. Efficacy and safety of low-dose tetracycline, amoxicillin quadruple therapy in *Helicobacter pylori* infection: A retrospective single center study. *World J Gastroenterol* 2024; 30(39): 4295-4304

URL: https://www.wjgnet.com/1007-9327/full/v30/i39/4295.htm

DOI: https://dx.doi.org/10.3748/wjg.v30.i39.4295

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral gram-negative, rod-shaped microaerophilic bacterium with a flagella that colonizes the gastric and duodenal mucosa, triggering a host inflammatory response and resulting in damage to the structure and function of the stomach[1]. *H. pylori* infection is a common chronic infectious disease, associated with a risk of developing peptic ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma[1]. *H. pylori* has infected more than 50% of the global population[2]. Although 80% of infected individuals are asymptomatic, most are accompanied by different degrees of gastritis[2]. Furthermore, approximately 80%-90% of gastric cancer is attributed to *H. pylori* infection worldwide[3,4]. Given that *H. pylori* is regarded as a group I human carcinogen and *H. pylori*-associated gastritis is considered an infectious disease, eradication is highly recommended[5-7].

According to the 2022 Chinese Society of Gastroenterology guidelines on *H. pylori* therapy, bismuth quadruple therapy is strongly recommended as a first-line regimen in primary and rescue therapy, in addition to other society guidelines[6,8-10]. The most commonly used antibiotics include amoxicillin, metronidazole, clarithromycin, tetracycline, and levofloxacin. However, the incidence of treatment failure has risen in recent years given the increased prevalence of *H. pylori* infection resistant to standard antibiotics[11]. Poor adherence and host genetics (CYP2C19 polymorphisms and low gastric pH associated with gene multidrug resistance protein 1, interleukin-1β) also likely contribute to the reasons for failed therapy[12,13]. A meta-analysis of 351 studies showed that resistance rates were 30% for clarithromycin, 61% for metronidazole, 35% for levofloxacin, 4% for tetracycline, and 6% for amoxicillin as primary therapy for *H. pylori* in the Asia-Pacific region[14]. The Maastricht VI/Florence Consensus Report recommended tetracycline and metronidazole-containing bismuth quadruple therapy as first-line treatment[11]. However, the increase in the prevalence of *H. pylori* resistant to metronidazole may impact treatment success[15].

Tetracycline is a broad-spectrum antibiotic produced by actinomycetes that inhibits bacterial reproduction and viability by interfering with protein synthesis through binding reversibly to a pocket in the 30S subunit of bacterial ribosomes containing 16S rRNA[16]. Amoxicillin is a penicillin-type antibiotic that interferes with cell wall synthesis and can exert excellent antibacterial activity during the bacterial multiplication period[17]. Given the low rate (0.4%) of dual-resistance with the combination of tetracycline and amoxicillin[18], quadruple therapy containing the two antibiotics is

highly effective[19-21]. A randomized trial conducted in China showed that tetracycline and amoxicillin-based quadruple therapy achieved high eradication rates of 87.2% and 91.9% on intention-to-treat (ITT) and per-protocol (PP) analyses[22]. However, recommended standard doses of tetracycline [500 mg three or four times daily (tid or qid)] may result in poor adherence and treatment failure given frequent dosing requirements and the high incidence of antibiotic-related adverse events.

In our previous study, low-dose tetracycline [500 mg twice a day (bid)] as a component of tetracycline and furazolidone quadruple therapy for 14 days resulted in a high eradication rate of 92.4%, comparable to standard tetracycline dose regimens, with a lower incidence of adverse events[23]. The aim of the present study was to evaluate the efficacy and safety of low-dose compared to standard dose tetracycline combined with amoxicillin-containing bismuth quadruple therapy for 14 days in achieving *H. pylori* eradication.

MATERIALS AND METHODS

Study design and population

This was a retrospective study conducted in Sir Run Run Shaw Hospital (Hangzhou, China) between January 2022 and June 2023. The study was approved by the Institutional Review Board of Sir Run Run Shaw Hospital, Medical School, Zhejiang University, Hangzhou (SRRSH: 2024-0053). Demographic characteristics including medical co-morbidities (diabetes, hypertension, hyperlipidemia), endoscopic findings, adverse events, treatment history, regimens, and outcomes were collected by reviewing clinical records, and conducting telephone surveys. Consecutive patients > 18 years of age with *H. pylori* infection diagnosed by a positive 13C/14C-urea breath test (UBT) treated with tetracycline and amoxicillin-containing quadruple therapy for 14 days were evaluated. Patients with a history or active gastrointestinal malignancy, previous upper gastrointestinal surgery, severe comorbidities, pregnant or lactating women, or incomplete information were excluded. Repeat 13C/14C-UBT was performed one month after completion of therapy to evaluate eradication.

Study definitions

H. pylori infection was defined by positive 13C/14C-UBT. Eradication was defined as negative on follow-up UBT. Tetracycline and amoxicillin-containing bismuth quadruple therapy was defined by 14 days treatment with tetracycline, amoxicillin, proton pump inhibitor (PPI) and bismuth at different doses and frequencies. Tetracycline was prescribed as 500 mg bid in the low-dose tetracycline group, and 750 mg bid or 500 mg tid in the standard dose tetracycline group, taken 30 minutes after meals. Amoxicillin was given as 1000 mg twice daily in all groups, taken 30 minutes before meals. PPIs including omeprazole, rabeprazole, pantoprazole and vonoprazan were taken bid 30 minutes before meals. Colloidal bismuth pectin or bismuth potassium citrate was also taken bid 30 minutes before meals. Specific drug dosage information was as follows: Omeprazole 20 mg, rabeprazole 10 mg, pantoprazole 40 mg, vonoprazan 20 mg, colloidal bismuth pectin 0.2-0.4 g, and bismuth potassium citrate 0.6 g per dose. Poor adherence was defined as taking less than 80% of the total prescribed doses.

Study endpoints

The primary endpoint of the study was the eradication rate of *H. pylori* in each treatment group by ITT analysis. The secondary endpoints were the frequency of adverse events and adherence rate.

Statistical analysis

All data were analyzed by SPSS version 26.0 software (IBM Corp., United States). Categorical variables were described as numbers and percentages and were analyzed by Pearson χ^2 or Fisher's exact test, as appropriate. Continuous variables were described as mean ± SD, and were analyzed by one-way ANOVA. Multivariate logistic regression model was used to identify independent factors associated with eradication failure. All P values were two-sided and were considered statistically significant when < 0.05.

RESULTS

Demographic data

During the study period, 218 patients with *H. pylori* infection received 14 days of quadruple therapy containing tetracycline, amoxicillin, PPI, and bismuth. The mean age of the patients was 48.7 ± 14.0 years, 120 (55.0%) were male, and 118 (54.1%) received treatment as primary therapy for *H. pylori* infection. Among those who received prior therapy, 74 (33.9%) received one and 26 (11.9%) received two or more *H. pylori* therapies.

Seventy-three (33.5%) patients received low-dose and 145 (66.5%) received standard dose tetracycline including 74 (33.9%) in the 500 mg tid group and 71 (32.6%) in the 750 mg bid group. There were no differences between the three groups in terms of baseline demographic and clinical characteristics including age, gender, smoking history, alcohol drinking history, family history of gastric cancer, hypertension, diabetes, and hyperlipidemia (Table 1). However, the types of PPI and bismuth differed (P < 0.001) among the treatment groups. Prior to therapy, 157 (72.0%) patients received gastroscopy without differences in the diagnosis of chronic gastritis, peptic ulcer, or intestinal metaplasia among the three groups. Finally, a higher proportion of patients received low-dose tetracycline (82.2% *vs* 56.8% and 22.5%, P < 0.001) compared to those who received standard dose tetracycline for primary therapy (Table 1).

Table 1 Demographic and clinical data of patients

Variables	500 mg bid (*n* = 73)	500 mg tid (*n* = 74)	750 mg bid (*n* = 71)	*P* value
Age, mean ± SD	49.2 ± 12.0	50.2 ± 13.9	46.6 ± 15.8	0.348
Age range (years)	20-72	23-72	22-77	
Age, ≤ 50 years	36	35	40	0.523
Sex, male/female	41/32	39/35	40/31	0.899
Family history of gastric cancer	1	2	1	1.000
NSAIDS	2	3	0	0.375
Probiotics	7	2	3	0.202
Smoking	15	16	15	1.000
Alcohol drinking	10	14	13	0.689
Hypertension	17	17	15	0.958
Diabetes	5	6	3	0.694
Hyperlipidemia	1	3	1	0.623
Endoscopy diagnosis				0.600
Gastritis	49	42	36	
Ulcer	14	7	9	
Unknown	10	25	26	
Intestinal metaplasia				0.325
No	40	27	22	
Yes	23	22	23	
Unknown	10	25	26	
Treatment times				< 0.001
1	60	42	16	
2	8	27	39	
≥ 3	5	5	16	
Rescue therapy[1]	13	32	55	
PPI				< 0.001
Omeprazole	2	5	27	
Rabeprazole	66	63	37	
Pantoprazole	1	5	1	
Vonoprazan	4	1	6	
Bismuth				< 0.001
Bismuth potassium citrate	4	27	37	
Colloidal bismuth pectin	69	47	34	

[1]Rescue therapy was defined as patients who had received eradication therapy once or more but failed.

P values were from two-sided comparisons of the differences between the three groups. 500 mg bid: Tetracycline twice daily; 500 mg tid: Tetracycline three times daily; 750 mg bid: Tetracycline twice daily; NSAIDS: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitor.

Eradication rates

Overall, 182 (83.4%) patients achieved successful *H. pylori* eradication (Figure 1). With regard to ITT, *H. pylori* eradication rates were 89.0% in the 500 mg bid group, 82.4% in the 500 mg tid group, and 78.9% in the 750 mg bid group ($P = 0.25$) (Figure 1). Of the 118 patients receiving primary therapy, eradication rates were 90.0%, 88.1%, and 87.5% in the 500 mg bid group, 500 mg tid group and 750 mg bid group, respectively, without statistically significant differences ($P = 0.85$) (Table 2). Of the 100 patients receiving rescue therapy, eradication rates were 84.6%, 75.0%, and 76.4% in the 500 mg bid group, 500 mg tid group and 750 mg bid group, respectively, without statistically significant differences ($P = 0.89$)

Table 2 Treatment times of patients and the eradication rates

	Eradication rate			*P* value
	500 mg bid (*n* = 73)	500 mg tid (*n* = 74)	750 mg bid (*n* = 71)	
All	65, 89.0%	61, 82.4%	56, 78.9%	0.25
Primary therapy	54/60, 90.0%	37/42, 88.1%	14/16, 87.5%	0.85
1 prior therapy	8/8, 100%	22/27, 81.5%	27/39, 69.2%	
≥ 2 prior therapies	3/5, 60.0%	2/5, 40.0%	15/16, 93.8%	
Rescue therapy[1]	11/13, 84.6%	24/32, 75.0%	42/55 76.4%	0.89

[1]Rescue therapy was defined as patients who had received eradication therapy once or more but failed.

P values were from two-sided comparisons of the differences between the three groups. 500 mg bid: Tetracycline twice daily; 500 mg tid: Tetracycline three times daily; 750 mg bid: Tetracycline twice daily.

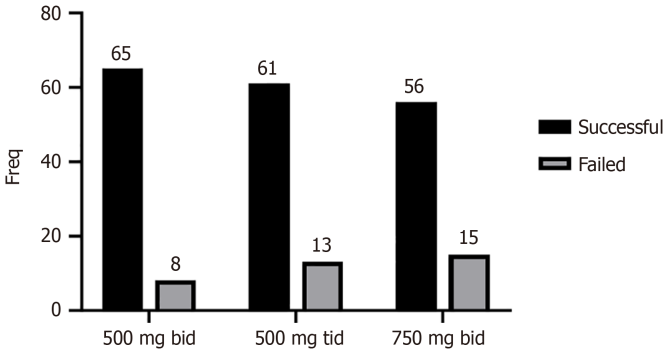

Figure 1 Eradication efficacy of the different groups. 500 mg bid: Tetracycline twice daily; 500 mg tid: Tetracycline three times daily; 750 mg bid: Tetracycline twice daily.

(Table 2).

Failure to complete treatment

Seven (3%) patients failed to complete the prescribed treatment due to adverse events or non-adherence. In the low-dose tetracycline group, one of two patients who failed to complete therapy achieved eradication. In the standard dose tetracycline group, two of five patients who failed to complete therapy achieved eradication, both in the 500 mg tid group (Supplementary Table 1). After excluding 7 patients who failed to complete the prescribed therapy, the overall eradication rates in the 500 mg bid, 500 mg tid, and 750 mg bid group were 90.1%, 83.0%, and 81.1%, respectively, without statistically significant differences (P = 0.30). Of the 115 patients receiving treatment as primary therapy, the eradication rates were 89.8%, 87.8%, and 93.3%, respectively (P = 0.92). Among the 96 patients receiving the treatment as rescue therapy, the eradication rates were 91.6%, 76.6%, and 77.7%, respectively (P = 0.63) (Supplementary Table 1). Patients who received incomplete therapy were less likely to achieve eradication (42.9% *vs* 84.8%, P = 0.047) compared to those who completed therapy (Supplementary Table 2).

Adverse events

Overall, 36 patients (16.5%) suffered from at least one adverse event during the treatment period, with a cumulative number of 49 adverse events (Table 3). The incidence of adverse events was lower in the low-dose tetracycline (12.3% *vs* 31.1% or 23.9%, P = 0.02) compared to the standard dose groups. The most common adverse events were abdominal discomfort (14, 28.6%) followed by nausea (5, 10.2%).

Predictors of eradication failure

On univariate analysis, age, gender, alcohol drinking history, hypertension, diabetes, hyperlipidemia and other demographic characteristics were not associated with failed eradication. However, patients with a family history of gastric cancer (P = 0.02), smoking history (P = 0.007), and those receiving rescue therapy (P = 0.03) were associated with failed eradication (Supplementary Table 3). Multivariate analysis confirmed that patients with a family history of gastric cancer [odds ratio (OR) = 12.4, 95% confidence interval (CI): 1.1-140.6, P = 0.04], smoking history (OR = 2.8, 95%CI: 1.2-6.2, P = 0.01), and those receiving rescue therapy (OR = 2.3, 95%CI: 1.05-4.8, P = 0.04) were associated with failed eradication (Supplementary Table 4).

Table 3 Adverse events in the different treatment groups

Adverse effect	All	500 mg bid (*n* = 73)	500 mg tid (*n* = 74)	750 mg bid (*n* = 71)	*P* value
Total, *n*/*N* (%)[1]	22.5 (49/218)	12.3 (9/73)	31.1 (23/74)	23.9 (17/71)	0.023
Taste distortion	1	0	1	0	
Belching	1	0	1	0	
Loss of appetite	3	0	1	2	
Nausea	5	1	3	1	
Vomiting	4	1	1	2	
Abdominal pain	1	0	1	0	
Bloating	3	0	3	0	
Diarrhea	3	1	0	2	
Skin rash	4	2	1	1	
Fever	3	0	1	2	
Dizziness	3	1	1	1	
Melena	2	0	1	1	
Constipation	2	0	1	1	
Abdominal discomfort[2]	14	3	7	4	

[1]The symptoms of a single adverse event are counted as 1, and a patient may have multiple adverse events.
[2]Abdominal discomfort, but not specified.
P values were from two-sided comparisons of the differences among the three treatment groups. 500 mg bid: Tetracycline twice daily; 500 mg tid: Tetracycline three times daily; 750 mg bid: Tetracycline twice daily. N: Number of total patients; *n*: Number of patients with adverse events.

DISCUSSION

In this single center study evaluating the efficacy and safety of tetracycline combined with amoxicillin, bismuth and PPI quadruple therapy for *H. pylori* infection, the low-dose tetracycline (500 mg bid) regimen achieved a high eradication rate with few adverse events compared to the standard dose tetracycline regimen. The rise in antibiotic resistance is the primary factor leading to the increase in failed *H. pylori* therapy, posing a major public health concern. A high proportion of patients with prior failed therapy harbor antibiotic-resistant *H. pylori* infection. In a randomized trial of 312 patients with *H. pylori* infection who previously failed therapy performed in China, resistance rates of *H. pylori* to metronidazole of 87.8%, clarithromycin 90.2%, levofloxacin 85.4%, amoxicillin 8.3%, and tetracycline 1.0% were observed[24]. Similarly, *H. pylori* resistance rates to metronidazole, clarithromycin, levofloxacin, and amoxicillin tetracycline were 43.2%, 33.9%, 24%, 2.1% and 0%, respectively, in 1050 patients that included more than a quarter who experienced prior treatment failure[25]. Despite the high prevalence of *H. pylori* resistant to metronidazole, clarithromycin, and levofloxacin in both studies, rates of resistance to tetracycline and amoxicillin remained low, even among patients who failed prior therapy. Our study did not show a difference in eradication rates between patients receiving primary or rescue therapy.

Tetracycline, as a common component of bismuth-based quadruple therapy, is an antibiotic that maintains a high resistance barrier to *H. pylori* strains, because three adjacent point mutations (AGA-926 to 928-TTC) are required for the development of resistance. A single or double mutations at these sites result in only low to intermediate levels of resistance[25,26]. Similarly, amoxicillin resistance in *H. pylori* is rare as simultaneous mutations at multiple sites in penicillin-binding proteins associated genes are required to significantly increase the minimal inhibitory concentration[27].

Tetracycline as a component of various treatment regiments remains highly effective against *H. pylori* infection. In a multicenter, randomized trial of 339 patients with *H. pylori* infection naïve to treatment, combination therapy with amoxicillin (1 g bid), tetracycline (500 mg tid), esomeprazole, and colloidal bismuth pectin or bismuth potassium citrate for 14 days demonstrated high eradication rates of 90.5% and 92.3% on ITT analysis[28]. However, given common treatment-related adverse events and the inconvenience of frequent dosing, low-dose tetracycline (500 mg bid) has been evaluated as part of quadruple therapy in *H. pylori* eradication. A prospective, single-center study of 118 patients showed that patients receiving tetracycline 500 mg bid combined with omeprazole, metronidazole, and bismuth subcitrate for 14 days resulted in eradication rates of 95% in the ITT analysis and 98% in the PP analysis, with only 5% experiencing moderate or severe adverse events[29]. Another study evaluating the same regimen showed an eradication rates of 93% in ITT analysis and 97% in PP analysis among 68 patients with previous eradication failure, with only 2 patients suffering moderate adverse events[30]. A simplified low-dose 10 days quadruple therapy containing a formulation of tetracycline 500 mg bid, bismuth salicylate, metronidazole and rabeprazole, showed that the eradication rate could reach 95.1% by PP analysis and 92.9% by ITT analysis, with excellent adherence with minimal adverse events[31]. Although a number of studies have confirmed the high eradication rate of low-dose tetracycline, comparative studies evaluating different doses

of tetracycline are lacking. In our previous study, low-dose tetracycline (500 mg bid) as part of tetracycline and furazolidone quadruple therapy for 14 days demonstrated a similar eradiation rate (92.4% *vs* 93.2% or 92.4%; $P = 0.96$) with a favorable safety profile (15.3% *vs* 32.3% and 29.4%; $P = 0.002$) compared to those who received standard dose tetracycline regimens[23].

In addition to antibiotic resistance, treatment-related adverse events and patient adherence are important factors affecting eradication rates, while age, smoking, CYP2C19 phenotype, diabetes, and use of probiotics are factors that may affect efficacy[32-34]. Multiple dosing and side effects are common causes of poor patient adherence[35]. Although the sample size was small, our study showed that patients with poor adherence were less likely to achieve eradication, consistent with previous studies[27,36-38]. Furthermore, our study demonstrated that smoking increased (OR = 2.8, 95%CI: 1.2-6.2) the odds of failed *H. pylori* therapy. In a meta-analysis evaluating 5538 patients receiving *H. pylori* therapy, patients who smoked were nearly twice more likely to have persistent *H. pylori* infection after treatment compared with non-smokers[32]. The proposed biologic mechanism includes increased gastric acid secretion from smoking leading to impaired mucus secretion and gastric blood flow, thereby reducing local antibiotic delivery[13].

Gut microbiota play an important role in human health, including regulating intestinal inflammation, maintaining human metabolic homeostasis, and regulating the immune system[39]. Dysregulation of the gut microbiota is associated with the development of inflammatory bowel disease, obesity, type 2 diabetes, and other systemic diseases[40]. Studies have shown that *H. pylori* infection can influence the structure, diversity, and biological function of gastric microbiota associated with the incidence of gastrointestinal diseases[41]. However, *H. pylori* therapy with antibiotics may reduce beneficial bacteria, leading to a decrease in microbial diversity, and even increased abundance of potentially pathogenic bacteria[42,43]. In addition, acid suppression with PPI as part of the treatment regimen may also affect gut microbial diversity[44]. However, in a meta-analysis of 1218 patients receiving *H. pylori* therapy, change in gut microbiota appeared transient, largely resolving after a year[45].

Supplemental probiotics in addition to standard antibiotic therapies have been evaluated as treatment for *H. pylori*. Multiple meta-analyses have demonstrated that probiotics (*i.e.*, *Lactobacillus, Saccharomyces boulardii,* and *Bacillus clausii*) reduced treatment-related adverse events and enhanced eradication rates[45,46]. Probiotics may affect the survival of *H. pylori* in the stomach by the synthesis of antibacterial substances (*e.g.*, organic fatty acids, ammonia, H_2O_2), change in local pH, direct competition with *H. pylori* for space and nutrients, influence on *H. pylori* colonization and adhesion, modification of the toxin or its receptors, and immunoregulation[47,48]. Although our study failed to demonstrate the association of probiotic therapy with eradication rate or adverse events, additional high-quality studies are needed.

Our study has limitations related to the retrospective study design. Although the baseline characteristics were generally similar, factors other than the tetracycline dose may have affected study endpoints. For example, differences in the type and dose of bismuth and PPI agents and a higher proportion of patients taking standard dose tetracycline as rescue therapy, may have introduced bias. Furthermore, important information regarding prior *H. pylori* therapy was not consistently available. Finally, evaluation of the effect of low-dose tetracycline regimen on gut microbiota was beyond the scope of the study and was not examined but may be invaluable in future studies.

CONCLUSION

In conclusion, low-dose tetracycline combined with amoxicillin-containing bismuth quadruple therapy achieved a high eradication rate with fewer treatment-related adverse effects compared to standard dose tetracycline quadruple therapy. Given its superior safety profile, low-dose tetracycline may provide an alternate treatment option as a component of the *H. pylori* treatment regimen. High quality randomized trials are needed to validate our findings.

FOOTNOTES

Author contributions: Zhao YR, Zhu MJ, and Hu WL designed the research study; Zhao YR and Wang XJ collected and analyzed the data; Zhao YR wrote the manuscript; Chen AL, Zhang D, and Kim JJ reviewed and edited the manuscript; Zhao YR, Du Q, and Kim JJ revised the manuscript; Hu WL supervised this work. All authors have read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board of Sir Run Run Shaw Hospital, Medical School, Zhejiang University, Hangzhou (Approval No. SRRSH: 2024-0053).

Informed consent statement: Patient consent was waived due the impossibility of identifying patients and the retrospective design of the investigation.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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S-Editor: Wang JJ
L-Editor: Webster JR
P-Editor: Yu HG

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