

# Doxycycline-based quadruple regimen versus routine quadruple regimen for rescue eradication of *Helicobacter pylori*: an open-label control study in Chinese patients

Zhenhua Wang<sup>1,2</sup>, MD, Shuming Wu<sup>1,2</sup>, MD, PhD

**INTRODUCTION** This study aimed to compare the efficacy and safety of quadruple therapy containing doxycycline and routine quadruple therapy for *Helicobacter (H.) pylori* rescue eradication in patients who had failed the one-week triple therapy.

**METHODS** Patients who failed the first-line eradication therapy were allocated into two groups. Group A patients (n = 43) were administered esomeprazole 20 mg, bismuth potassium citrate 220 mg, amoxicillin 1 g and doxycycline 100 mg, all bid for ten days, while Group B patients (n = 42) were administered esomeprazole 20 mg bid, bismuth potassium citrate 220 mg bid, metronidazole 400 mg bid and tetracycline 750 mg q.6h, for ten days. The results of *H. pylori* eradication were assessed with <sup>13</sup>C urea breath test four weeks after the therapy, and the side effects were recorded.

**RESULTS** A total of 85 patients (average age 46.9 years) were enrolled in the study. Successful eradication rate for *H. pylori* was 72.5% in Group A and 64.1% in Group B, with no significant difference between the two groups. 11.6% (5/43) of patients from group A and 31.0% (13/42) from group B reported at least one adverse event. The adverse events of all 18 patients disappeared after the therapy ceased.

**CONCLUSION** Quadruple therapy containing doxycycline is as effective as routine quadruple therapy for *H. pylori* rescue eradication. The regimen is well tolerated by most patients and causes fewer adverse events than routine quadruple therapy. Hence, it may be recommended as a suitable alternative *H. pylori* rescue regimen in China.

Keywords: doxycycline, *Helicobacter pylori*, quadruple therapy, rescue therapy  
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## INTRODUCTION

*Helicobacter (H.) pylori* infection has been confirmed as a key risk factor for developing peptic ulcers, chronic active gastritis, gastric cancer and type B low-grade mucosa-associated lymphoma.<sup>(1,2)</sup> In several conference consensuses,<sup>(3-5)</sup> *H. pylori* eradication was recommended to prevent peptic ulcer recurrence and gastric cancer. A seven-day triple regimen using a proton pump inhibitor (PPI), amoxicillin and clarithromycin is the dominant first-line *H. pylori* eradication therapy in China, in accordance with the Maastricht III Consensus.<sup>(4)</sup> Although this regimen has been demonstrated to be effective in many clinical trials, the failure rate for *H. pylori* eradication varies from 10% to 23%,<sup>(6-11)</sup> mainly due to the increasing resistance to clarithromycin.<sup>(12-14)</sup> Therefore, patients who fail the one-week triple therapy require another effective rescue regimen. The efficacy of this new rescue regimen would depend on the choice of an antibiotic that faces low resistance.<sup>(15)</sup> Currently, a rescue regimen consisting of a PPI, a bismuth salt, metronidazole and tetracycline is still recommended by the Maastricht III Consensus.<sup>(4)</sup> However, the successful eradication rate for *H. pylori* using this method has been demonstrated to be unstable and varies from 37% to

95%.<sup>(16,17)</sup> The side effects of quadruple therapy may lead to poorer compliance, which would further decrease its efficacy. Moreover, the routine quadruple therapy (PPI, bismuth salt, tetracycline and metronidazole) is impractical in China due to the unavailability of tetracycline. Therefore, we have designed an open-label controlled study to evaluate the efficacies of a new rescue therapy regimen consisting of PPI, bismuth salt, doxycycline and amoxicillin, and to compare its results with those of routine quadruple therapy for *H. pylori* eradication after failure of the standard first-line therapy.

## METHODS

This was an open-label controlled study conducted from April 2010 to March 2011. Patients whose *H. pylori* infection failed to be eradicated with standard first-line triple therapy (either amoxicillin- or metronidazole-based) were alternately allocated to quadruple therapy containing doxycycline and routine quadruple therapy. Informed written consent was obtained from all patients before their participation in the trial. Failure of *H. pylori* eradication after standard first-line triple therapy was established by at least two

<sup>1</sup>Division of Gastroenterology & Hepatology, Shanghai Jiao-Tong University School of Medicine Renji Hospital, Shanghai Institute of Digestive Disease, Shanghai, Republic of China, <sup>2</sup>Key Laboratory of Gastroenterology & Hepatology, Ministry of Health (Shanghai Jiao-Tong University), Shanghai, Republic of China.

**Correspondence:** Dr Wu Shuming, Director, Division of Gastroenterology & Hepatology, Shanghai Jiao-Tong University School of Medicine, Renji Hospital, 145 Middle Shandong Rd, Shanghai 200001, Republic of China. zhenhuaw@sjtu.edu.cn

**Table I. Patient characteristics at baseline.**

Characteristic	Total	Group A	Group B	p-value
No. of patients	85	43	42	0.88
Age* (yrs)	46.89 ± 11.32	47.65 ± 11.28	46.07 ± 11.39	0.52
Male gender	39	21	18	0.58
Gastritis	60	31	29	0.76
Ulcer (PU/GU)	25 (17/8)	12 (8/4)	13 (9/4)	0.76

Note: The two groups were comparable in number of patients, age, gender and endoscopic findings.

\*Data is presented as mean ± standard deviation.

PU: peptic ulcer; GU: gastric ulcer

**Table II. Comparison of *H. pylori* eradication, adverse event and patient default rates between the two treatment groups.**

Outcome	No. of patients		p-value
	Group A	Group B	
Successful eradication	29	25	-
At least one adverse event	5	13	-
Lost to follow-up	3	3	-
Total no. of patients	43	42	-
Successful eradication rate*			
PP (95% CI)	72.50 (56.11–85.40)	64.10 (47.18–78.80)	0.42
ITT (95% CI)	67.44 (51.46–80.92)	59.52 (43.28–74.37)	0.45
Adverse event rate (95% CI)*	11.62 (3.89–25.08)	30.95 (17.62–47.09)	0.03
Default rate (95% CI)*	6.98 (1.46–19.06)	7.14 (1.50–19.48)	0.98

\*Data is presented in percent.

PP: per-protocol analysis; ITT: intention-to-treat analysis

positive results of rapid urease test, histology and <sup>13</sup>C urea breath test (UBT). Patients with co-existing serious illnesses (hepatic, cardiorespiratory, renal diseases, insulin-dependent diabetes mellitus and neoplastic diseases) and patients who were taking PPIs, H<sub>2</sub>-receptor antagonists or antibiotics in the four weeks preceding the enrolment were excluded from the study. Patients < 18 years of age, those with previous gastric surgery and those who were allergic to any of the drugs applied in the study were also excluded.

A total of 85 Chinese patients aged 18–70 years (39 male and 46 female), for whom *H. pylori* eradication failed with standard first-line triple therapy containing either amoxicillin or metronidazole, were divided into two groups. Group A patients (n = 43) received esomeprazole 20 mg bid, bismuth potassium citrate 220 mg bid, amoxicillin 1 g bid and doxycycline 100 mg bid for ten days, while Group B patients (n = 42) received esomeprazole 20 mg bid, bismuth potassium citrate 220 mg bid, metronidazole 400 mg bid and tetracycline 750 mg q.6h for ten days. Patients were evaluated with the UBT at least four weeks after *H. pylori* eradication treatment. Antibiotics, bismuth-containing drugs and antacid agents were not allowed during the four weeks preceding the UBT. Successful eradication of *H. pylori* was confirmed by a negative UBT. At the end of the trial, we assessed the treatment compliance and side effects.

The successful eradication rate of *H. pylori* was assessed with 95% confidence interval (CI) on the basis of intention-to-treat and per-protocol analyses. Patients who defaulted follow-up or did not complete the trial due to severe side effects were

considered as treatment failures and excluded from the per-protocol analysis. The differences in baseline data, successful eradication rate, adverse event rate and default rate between the two groups were compared by paired *t*-test, chi-square test and Fisher's exact test. A p-value < 0.05 was considered statistically significant.

## RESULTS

A total of 85 patients whose *H. pylori* infection failed to be eradicated with standard first-line triple therapy were enrolled in our study and assigned to either Group A or B. Six patients were excluded from the per-protocol analysis due to poor compliance (n = 3) and default from follow-up (n = 3). The clinical characteristics of patients at baseline are summarised in Table I. The two groups had comparable age, gender and endoscopic findings. All patients completed the trial, except for three patients who did not receive UBTs after eradication therapy (Group A: 2; Group B: 1) and another three who stopped therapy due to severe side effects (Group A: 1; Group B: 2). The success rate for *H. pylori* eradication with per-protocol analysis was 72.5% in Group A and 64.1% in Group B. The intention-to-treat successful eradication rate was 67.4% in Group A (30/44) and 59.5% in Group B (24/41) (Table II). There was no significant difference in the successful eradication rates between the two groups.

A total of eight adverse events occurred in Group A and 20 in Group B (Table III). 11.62% (5/43) of patients in Group A and 30.95% (13/42) patients in Group B reported at least one adverse event. Group A had significantly fewer

**Table III. Types of adverse events in the two treatment groups.**

Adverse event	No. of patients	
	Group A	Group B
Nausea	2	5
Diarrhoea	1	2
Constipation	0	1
Headache	1	2
Abdominal pain	2	5
Anorexia	2	4
Dizziness	0	1

patients with adverse events than Group B ( $\chi^2 = 4.75$ ,  $p = 0.0292$ ). The most frequent adverse event was nausea. One patient from Group A withdrew from the eradication treatment due to abdominal pain, while two patients in Group B discontinued treatment due to nausea. The adverse events of all 18 patients disappeared on cessation of therapy.

## DISCUSSION

Eradication of *H. pylori* is a key step in preventing the recurrence of peptic ulcer and the occurrence of gastric cancer.<sup>(4)</sup> Gastric cancer is the top neoplasm disease in China. Hence, more attention should be paid to the diagnosis of *H. pylori* and its eradication. The combination of PPI plus bismuth, tetracycline and metronidazole has been recommended as the optimal second-line therapy by the Maastricht III Consensus.<sup>(4)</sup> However, routine quadruple therapy is not feasible in China due to several reasons. First, tetracycline is unavailable in many areas of China. Second, in China, there is a high prevalence (80%) of metronidazole resistance in *H. pylori*,<sup>(18)</sup> which is primarily responsible for eradication failure. Finally, nausea as an adverse event is common in metronidazole therapy, which decreases treatment compliance.

Doxycycline, a synthetic antibiotic in the tetracycline class, was first developed in 1967. Compared with the original tetracycline, doxycycline has a simpler dosing schedule and is more easily absorbed with food.<sup>(19)</sup> Tetracyclines are known to have side effects such as gastrointestinal symptoms, paediatric tooth discolouration, candidiasis, photosensitivity reactions, pigmentation changes and central nervous system effects.<sup>(19,20)</sup> However, the adverse event profiles of doxycycline may not be identical to those of tetracycline.<sup>(21)</sup> A multicentre study conducted in China in 2005 found that the resistance rate of *H. pylori* was 75.6% for metronidazole and 2.7% for amoxicillin.<sup>(18)</sup>

After taking into consideration factors such as bacterial resistance, antibiotic safety and ease of prescription, we designed a quadruple therapy consisting of doxycycline and amoxicillin in order to investigate the efficacy and safety of *H. pylori* rescue eradication. Although the efficacy of quadruple therapy containing doxycycline was found to be superior to that of routine quadruple therapy in our study, the difference was not statistically significant, and thus, our results would need to be confirmed by larger trials. Despite this, we have found quadruple

therapy containing doxycycline to demonstrate satisfactory safety and compliance, which is more important in clinical practice in China.

In an Iranian study, *H. pylori* was successfully eradicated from 41 out of 60 (68%) patients with the following regimen – doxycycline 100 mg bid, co-amoxiclav 625 mg tid, and omeprazole 20 mg bid for a duration of two weeks, suggesting that doxycycline could be useful in first-line *H. pylori* eradication.<sup>(22)</sup> As a synthetic antibiotic in the tetracycline class, doxycycline has attracted much attention as a possible agent for *H. pylori* rescue eradication. Cammarota et al treated 94 patients whose *H. pylori* infection persisted after undergoing both first and second-line current treatments.<sup>(23)</sup> Of these, 89 patients whose *H. pylori* isolates were found to be susceptible to tetracycline were treated with a one-week quadruple drug combination containing doxycycline 100 mg bid, amoxicillin 1,000 mg bid, bismuth salt 120 mg bid, and omeprazole 20 mg bid. The quadruple regimen eradicated *H. pylori* in 81 of the 89 patients treated.<sup>(23)</sup> The results obtained in this study confirmed that quadruple therapy containing doxycycline may constitute an effective third-line option for treatment due to the low estimated rate of resistance to tetracycline (5%). In our study, the successful rescue eradication rate of *H. pylori* was similar to that obtained by the first-line rescue regimen in the Iranian study,<sup>(20)</sup> thus suggesting that *H. pylori* is sensitive to doxycycline, even after first-line eradication attempt has failed. Second-line rescue regimen selection depends on the initial regimen used, as re-treatment with the same regimen is not recommended.<sup>(4)</sup> It is suggested that the assessment of antibiotic sensitivity to *H. pylori* is necessary only after failure of a second treatment attempt. Hence, quadruple therapy containing doxycycline is thought to be a suitable second-line empiric rescue treatment that conforms to the Maastricht III Consensus<sup>(4)</sup> and clinical practice.

There are two limitations that warrant caution when extrapolating the results of the current study. First, the patients were assigned to the two groups alternately rather than in a random order. Second, the number of patients in each group was relatively small. Despite these limitations, we have found quadruple therapy containing doxycycline to be at least as effective as routine quadruple therapy for *H. pylori* rescue eradication in China. The regimen was well tolerated by most of our patients and caused fewer adverse events than routine quadruple therapy. Therefore, it may be recommended as a suitable alternative *H. pylori* rescue regimen in China.

## REFERENCES

1. Suerbaum S, Michetti P. Helicobacter pylori infection. N Engl J Med 2002; 347:1175-86.
2. Fuccio L, Zagari RM, Eusebi LH, et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? Ann Intern Med 2009; 151:121-8.
3. Talley NJ, Fock KM, Moayyedi P. Gastric Cancer Consensus conference recommends Helicobacter pylori screening and treatment in asymptomatic persons from high-risk populations to prevent gastric cancer. Am J Gastroenterol 2008; 103:510-4.

4. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut* 2007; 56:772-81.
5. Chey WD, Wong BC, Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 2007; 102:1808-25.
6. Huang AH, Sheu BS, Yang HB, et al. Impact of *Helicobacter pylori* antimicrobial resistance on the outcome of 1-week lansoprazole-based triple therapy. *J Formos Med Assoc* 2000; 99:704-9.
7. Zanten SJ, Bradette M, Farley A, et al. The DU-MACH study: eradication of *Helicobacter pylori* and ulcer healing in patients with acute duodenal ulcer using omeprazole based triple therapy. *Aliment Pharmacol Ther* 1999; 13:289-95.
8. Sheu BS, Wu JJ, Lo CY, et al. Impact of supplement with *Lactobacillus*- and *Bifidobacterium*-containing yogurt on triple therapy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2002; 16:1669-75.
9. Bazzoli F, Pozzato P, Rokkas T. *Helicobacter pylori*: the challenge in therapy. *Helicobacter* 2002; 7 suppl 1:43-9.
10. Georgopoulos SD, Ladas SD, Karatapanis S, et al. Effectiveness of two quadruple, tetracycline- or clarithromycin-containing, second-line, *Helicobacter pylori* eradication therapies. *Aliment Pharmacol Ther* 2002; 16:569-75.
11. Peitz U, Sulliga M, Wolle K, et al. High rate of post-therapeutic resistance after failure of macrolide-nitroimidazole triple therapy to cure *Helicobacter pylori* infection: impact of two second-line therapies in a randomized study. *Aliment Pharmacol Ther* 2002; 16:315-24.
12. Agudo S, Alarcón T, Cibrelus L, et al. High percentage of clarithromycin and metronidazole resistance in *Helicobacter pylori* clinical isolates obtained from Spanish children. *Rev Esp Quimioter* 2009; 22:88-92.
13. O'Connor A, Taneike I, Nami A, et al. *Helicobacter pylori* resistance to metronidazole and clarithromycin in Ireland. *Eur J Gastroenterol Hepatol* 2010; 22:1123-7.
14. Chang WL, Sheu BS, Cheng HC, et al. Resistance to metronidazole, clarithromycin and levofloxacin of *Helicobacter pylori* before and after clarithromycin-based therapy in Taiwan. *J Gastroenterol Hepatol* 2009; 24:1230-5.
15. Mégraud F, Lamouliatte H. Review article: the treatment of refractory *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2003; 17:1333-43.
16. Gisbert JP, Pajares JM. Review article: *Helicobacter pylori* "rescue" regimen when proton pump inhibitor-based triple therapies fail. *Aliment Pharmacol Ther* 2002; 16:1047-57.
17. Wong WM, Gu Q, Chu KM, et al. Lansoprazole, levofloxacin and amoxicillin triple therapy vs. quadruple therapy as second-line treatment of resistant *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2006; 23:421-7.
18. Chinese *Helicobacter pylori* Research Group, Chinese Society of Gastroenterology. Prevalence of *Helicobacter pylori* resistance to antibiotics and its influence on the treatment outcome in China: A multicenter clinical study. *Weichang Bingxue* 2007; 12:525-30.
19. Barza M, Schiefe RT. Antimicrobial spectrum, pharmacology and therapeutic use of antibiotics. Part 1: tetracyclines. *Am J Hosp Pharm* 1977; 34:49-57.
20. Casado MJ. Doxycycline in respiratory tract infections. Report of a retrospective study in Spain during the winter 1972-1973. *Chemotherapy* 1975; 21 (Suppl 1):76-90.
21. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther* 2005; 27:1329-42.
22. Taghavi SA, Jafari A, Eshraghian A. Efficacy of a new therapeutic regimen versus two routinely prescribed treatments for eradication of *Helicobacter pylori*: a randomized, double-blind study of doxycycline, co-amoxiclav, and omeprazole in Iranian patients. *Dig Dis Sci* 2009; 54:599-603.
23. Cammarota G, Martino A, Pirozzi G, et al. High efficacy of 1-week doxycycline- and amoxicillin-based quadruple regimen in a culture-guided, third-line treatment approach for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2004; 19:789-95.

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