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.\(^1,2\)

In several conference consensuses,\(^3-5\) 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.\(^4\)

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%,\(^6-11\) mainly due to the increasing resistance to clarithromycin.\(^12-14\) 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.\(^15\)

Currently, a rescue regimen consisting of a PPI, a bismuth salt, metronidazole and tetracycline is still recommended by the Maastricht III Consensus.\(^16\) However, the successful eradication rate for H. pylori using this method has been demonstrated to be unstable and varies from 37% to 95%\(^16,17\). 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 13C 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
positive results of rapid urease test, histology and 13C 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, H2-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 \textit{H. pylori} infection failed to be eradicated with standard first-line triple therapy (PU/GU: 17/8) 25 (17/8) 12 (8/4) 13 (9/4) 0.76

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful eradication</td>
<td>29</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>At least one adverse event</td>
<td>5</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>43</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>Successful eradication rate*</td>
<td>72.50 (56.11–85.40)</td>
<td>64.10 (47.38–78.80)</td>
<td>0.42</td>
</tr>
<tr>
<td>PP (95% CI)</td>
<td>67.44 (51.46–80.92)</td>
<td>59.52 (43.28–74.37)</td>
<td>0.45</td>
</tr>
<tr>
<td>ITT (95% CI)</td>
<td>11.62 (3.89–25.08)</td>
<td>30.95 (17.62–47.09)</td>
<td>0.03</td>
</tr>
<tr>
<td>Adverse event rate (95% CI)*</td>
<td>6.98 (1.46–19.06)</td>
<td>7.14 (1.50–19.48)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*A data is presented in percent. PP: per-protocol analysis; ITT: intention-to-treat analysis

RESULTS

A total of 85 patients whose \textit{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 \textit{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
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. 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. 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*, 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. Tetracyclines are known to have side effects such as gastrointestinal symptoms, paediatric tooth discolouration, candidiasis, photosensitivity reactions, pigmentation changes and central nervous system effects. However, the adverse event profiles of doxycycline may not be identical to those of tetracycline. 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.

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. 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. 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. 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, 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. 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 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


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

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Group A: 2, Group B: 5</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Group A: 1, Group B: 2</td>
</tr>
<tr>
<td>Constipation</td>
<td>Group A: 0, Group B: 1</td>
</tr>
<tr>
<td>Headache</td>
<td>Group A: 1, Group B: 2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Group A: 2, Group B: 5</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Group A: 2, Group B: 4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Group A: 0, Group B: 1</td>
</tr>
</tbody>
</table>

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