Furazolidone, amoxicillin, bismuth and rabeprazole quadruple rescue therapy for the eradication of Helicobacter pylori

Hong Cheng, Fu-Lian Hu

AIM: To compare the efficacy and side effect profiles of three furazolidone and amoxicillin-based quadruple rescue therapies for the eradication of Helicobacter pylori (H. pylori).

METHODS: Patients who failed in the H pylori eradication therapy for at least one course were randomly allocated into three groups. Group A received rebaprazole 10 mg + amoxicillin 1 g + furazolidone 100 mg, and bismuth subcitrate 220 mg, twice daily for 1 wk; group B received the same regimen of group A but for 2 wk; and group C received the same regimen of group B, but furazolidone was replaced by furazolidone 100 mg three times daily. To record the side effect profiles at the end of the treatment, H pylori eradication was assessed with 13C-urea breath test 4 wk after therapy.

RESULTS: Sixty patients were enrolled including 28 males, and 20 patients in each group. The average age of the patients was 49.2 years, ranging from 18 to 84 years. H pylori eradication rates with per-protocol analysis were 82%, 89% and 90% in the three groups, respectively. Side effects were found in 11 patients, including mild dizziness, nausea, diarrhea and increased bowel movement. None of the 11 patients needed treatment for their side effects.

CONCLUSION: One- or two-week furazolidone and amoxicillin-based quadruple rescue therapy with a low dose furazolidone (100 mg bid) for the eradication of H pylori is effective. Extending the antibiotic course to 14 d could improve the eradication rates.

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Key words: Helicobacter pylori; Rescue therapy; Quadruple therapy; Furazolidone; Low dose

Peer reviewers: Frank I Tovey, OBE, ChM, FRCS, Honorary Research Fellow, Department of Surgery, University College London, London, United Kingdom; Anthony TR Axon, Professor, Department of Gastroenterology, Infirmary At Leeds, Room 190a, Clarendon Wing, the General Infirmary at Leeds Great George Street, Leeds LS1 3ex, United Kingdom

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INTRODUCTION

Helicobacter pylori (H pylori) infection is associated with many upper gastrointestinal diseases, such as chronic gastritis, peptic ulcer, gastric carcinoma and mild malignant mucosa-associated lymphoid tissue lymphoma (MALToma). During recent years, the efficacy of the first-line therapy including proton pump inhibitors plus two antibiotics seems to have decreased, and several studies have reported intention-to-treat eradication rates lower than 75%[1-3] and even lower than 50%[4,5]. The resistance to antibiotics is the main cause of H pylori treatment failure. A multicenter study conducted in China in 2005 showed that the resistant rates of H pylori were 27.4% for clarithromycin, 75.6% for metronidazole and 2.7% for amoxicillin[6]. Many patients needed to receive rescue therapy for the eradication of H pylori after first- or second-line therapies. The combination of metronidazole, tetracycline, bismuth, and proton pump inhibitor are currently considered standard rescue regimens for the treatment of H pylori infection[7]. However, metronidazole resistance is a rising problem worldwide, particularly in developing countries, such as China, which limits the usefulness of this drug.

Furazolidone, a monoamine oxidase inhibitor, has broad antibacterial activity based on interference with bacterial enzymes. It has already been used to treat peptic ulcer disease for many years in China, before H pylori was discovered[8,9]. Furazolidone emerged as an agent for H pylori eradication regimens due to its low cost and prevalence of resistant strains in China.
The consensus of reports of China in 2005[10] and 2007[11] all recommended that furazolidone should be used for \textit{H pylori} eradication treatment. A large multicenter study in China showed that a combination of omeprazole plus furazolidone and amoxicillin as the first-line regimen had an intention-to-treat \textit{H pylori} eradication rate of 86\%, compared to 69\% for omeprazole plus clarithromycin and metronidazole[12]. However, in another study in China, the intention-to-treat eradication rate of omeprazole-furazolidone-amoxicillin regimen as the rescue regimen was only 52\%[13]. The aim of this pilot study was to compare the efficacy and side effect profiles of three different furazolidone and amoxicillin-based quadruple rescue therapies for the eradication of \textit{H pylori}.

### MATERIALS AND METHODS

**Subjects**

This prospective clinical trial was conducted in Peking University First Hospital. Patients who failed in the eradication of \textit{H pylori} for at least one course were invited to participate in this open-label pilot study. Informed written consent was obtained from all patients participating in the trial.

Patients younger than 18 years of age, and who presented with severe comorbidity, who were pregnant or lactating, with a known history of allergy to the study drugs, and patients who had used proton pump inhibitors, \textit{H} receptor blockers, antibiotics, or bismuth salts up to 4 wk before the study were all excluded.

**Treatment regimen**

Patients were randomly allocated into three groups. Group A received rebaprazole 10 mg, amoxicillin 1 g, furazolidone 100 mg, and bismuth subcitrate 220 mg, twice daily each, for 1 wk; group B received the same regimen as group A but for 2 wk; and group C received the same regimen of group B but furazolidone was replaced by furazolidone 100 mg three times daily. Antibiotics were prescribed after meals whereas rabeprazole and bismuth were administered before meals. Patients were advised to maintain the treatment even with minor adverse effects. No other medication was allowed until the end of the treatment.

**Assessment**

Patients were evaluated using the $^{13}$C-urea breath test at least 4 wk after \textit{H pylori} eradication treatment. Antimicrobials, bismuth-containing drugs and acid-reducing agents were not allowed during the 4 wk preceding the $^{13}$C-urea breath test. The eradication of \textit{H pylori} was defined as a negative urea breath test.

The patient compliance and treatment-related side effects were assessed at the end of the treatment. Side effects were graded as mild if they did not interfere with daily activities of the patients, moderate if they interfered with daily activities to some extent and severe if daily activities became impossible.

### Statistical analysis

Continuous variables were expressed by calculation of the mean and standard deviation. The \textit{H pylori} eradication rate was assessed based on intention-to-treat and per-protocol analysis. The 95\% confidence intervals (95\% CI) were also calculated for both intention-to-treat and per protocol analysis and the eradication rate. The patients, who were lost to follow-up or could not complete the treatment course because of severe side effects, were considered as treatment failures and excluded in the per-protocol analysis. The Chi-square test and Fisher’s exact test were used to compare the differences between the three study groups in terms of baseline data, eradication rate and side effects. $P < 0.05$ was considered significant.

### RESULTS

Sixty patients were enrolled in this study including 28 males, with 20 patients in each group. All of the patients had undergone endoscopy examination before they received \textit{H pylori} eradication at the first time. The average age of the patients was 49.1 years, ranging from 18 to 84 years. Two patients had already undergone three treatments, 42 and 16 had undergone one and two, respectively. There was no predominance regarding the baseline characteristics of the patients (Table 1).

All the patients finished the treatment, but four of them did not receive the \textit{H pylori} eradication of \textit{H pylori} during the second or third courses because of severe side effects, were considered as treatment failures and excluded in the per-protocol analysis. The 95\% confidence intervals (95\% CI) were also calculated for both intention-to-treat and per protocol analysis and the eradication rate. The patients, who were lost to follow-up or could not complete the treatment course because of severe side effects, were considered as treatment failures and excluded in the per-protocol analysis. The Chi-square test and Fisher’s exact test were used to compare the differences between the three study groups in terms of baseline data, eradication rate and side effects. $P < 0.05$ was considered significant.

### DISCUSSION

The eradication of \textit{H pylori} is the main objective in the treatment of peptic ulcer[14,15]. The Masstricht III consensus report concluded that eradication of \textit{H pylori} has the potential to reduce the risk of gastric cancer development; moreover, the optimal time to eradicate \textit{H pylori} is before pre-neoplastic lesions (atrophy and intestinal metaplasia) are present[7]. Gastric carcinoma is common in China. So \textit{H pylori} infection is a major public health problem, for which treatment should be provided when patients are diagnosed. The ideal therapy for \textit{H pylori} infection should achieve a high cure rate of $> 90\%$ on per protocol analysis and $> 80\%$ on intention-to-treat analysis, should be simple and well tolerated, and should be easy to comply with and cost-effective[16]. The combination of proton pump inhibitor plus bismuth, tetracycline and metronidazole has been
recommended as optimal second-line therapy by several guidelines on the management of *H pylori* infection\[^7\]. However, metronidazole resistance is largely responsible for treatment failure. The prevalence of metronidazole resistance for *H pylori* is about 80% in China\[^6\]. The best rescue treatment remains to be defined.

Furazolidone is a broad-spectrum nitrofuran, active against Gram-negative and positive bacteria and protozoa by inhibiting bacterial enzymes, and it has poor oral absorption\[^17\]. Strains resistant to furazolidone are rare and have no cross-resistance to metronidazole\[^18\]. Furthermore, its potential to develop resistance is low\[^19\]. Several studies have shown the efficacy of regimens containing a high-dose furazolidone (200 mg, *b.i.d.*) as the therapy in patients with *H pylori* infection\[^20-22\]. The study of Fakheri *et al.* showed that low-dose furazolidone (100 mg, *b.i.d.*) based triple and quadruple rescue regimens do not yield acceptable success rates\[^23\]. We have reported that a pilot study of rabeprazole, bismuth, furazolidone and amoxicillin as rescue treatment of *H pylori* infection after failure for at least one course of eradication has intention-to-treat and per-protocol eradication rates of 70% and 82% for 1 wk in the group treated with furazolidone (100 mg, *b.i.d.*), 85% and 89% for 2 wk in the group with furazolidone (100 mg, *b.i.d.*), and 90% and 90% for 2 wk in the group with furozolidone (100 mg, *t.i.d.*), respectively. Our study is different from Fakheri *et al.*, as a regimen which is useful in one area may not be effective in another area. Management of first- or second-line *H pylori* eradication failures has become a challenge. In one study, a *H pylori* eradication rate of 69% was obtained after treatment with a 7-d association of bismuth, high-dose furazolidone (200 mg, *b.i.d.*), amoxicillin and a

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### Table 1 Baseline characteristics of patients (mean ± SD)

| Group | No. of patients | Age (yr) | Male | Gastritis | Ulcer (DU/GU) | Smoking | Drinking |
|-------|-----------------|----------|------|-----------|---------------|---------|----------|
| A     | 20              | 49.3 ± 15.2 | 8    | 11        | 8 (7/1)       | 6       | 3        |
| B     | 20              | 49.9 ± 21.5 | 12   | 13        | 9 (8/1)       | 6       | 5        |
| C     | 20              | 48.1 ± 9.3  | 8    | 12        | 7 (7/0)       | 6       | 3        |
| Total | 60              | 49.1 ± 15.8 | 28   | 36        | 24            | 18      | 9        |

**χ² value** - - 2.14 0.42 0.42 0.00 0.89

**P value** - - > 0.05 > 0.05 > 0.05 > 0.05 > 0.05

### Table 2 *H pylori* eradication rates among three treatment groups

| Group | Eradication | Non-eradication | Lost | Total | Eradication rate\(^a\) (PP, %) (95% CI, %) | Eradication rate\(^b\) (ITT, %) (95% CI, %) |
|-------|-------------|-----------------|------|-------|------------------------------------------|------------------------------------------|
| A     | 14          | 3               | 3    | 20    | 82 (57-96)                               | 70 (46-88)                               |
| B     | 17          | 2               | 1    | 20    | 89 (67-99)                               | 85 (62-97)                               |
| C     | 18          | 2               | 0    | 20    | 90 (68-99)                               | 90 (68-99)                               |
| Total | 48          | 7               | 4    | 60    | 87 (78-96)                               | 80 (79-90)                               |

\[^a\]χ² = 0.59, \(P > 0.05\); \[^b\]χ² = 2.89, \(P > 0.05\).

### Table 3 *H pylori* eradication rates in relation to course of previous treatment

| Times of failure | Eradication | Non-eradication | Lost | Total | Eradication rate\(^a\) (PP, %) (95% CI, %) | Eradication rate\(^b\) (ITT, %) (95% CI, %) |
|------------------|-------------|-----------------|------|-------|------------------------------------------|------------------------------------------|
| 1                | 35          | 5               | 2    | 42    | 88 (73-96)                               | 83 (74-96)                               |
| 2                | 13          | 1               | 2    | 16    | 93 (66-100)                              | 81 (54-96)                               |
| 3                | 1           | 1               | 0    | 2     | 50 (1-99)                                | 50 (1-99)                                |
| Total            | 48          | 7               | 4    | 60    | 87 (78-96)                               | 80 (70-90)                               |

\[^a\]χ² = 2.94, \(P > 0.05\); \[^b\]χ² = 1.42, \(P > 0.05\).

### Table 4 Side-effect profile of patients \(^n\) (%)

| Side effects          | Group A | Group B | Group C | Total |
|-----------------------|---------|---------|---------|-------|
| Nausea                | 2       | 1       | 2       | 5 (8.3)|
| Diarrhea              | 1       | 1       | 1       | 3 (5.0)|
| Bowed movement increasing | 0   | 1       | 1       | 2 (3.3)|
| Dizziness             | 0       | 0       | 2       | 2 (3.3)|
| Headache              | 0       | 0       | 1       | 1 (1.7)|
| Asthenia              | 1       | 0       | 0       | 1 (1.7)|
| Total episodes        | 4       | 3       | 7       | 14 (23.3)|
| Total patients\(^c\)  | 2 (10)  | 3 (15)  | 6 (30)  | 11 (18.3)|

Two patients got two kinds of side effects in group A and group C, respectively; \[^c\]χ² = 2.89, \(P > 0.05\).
proton-pump inhibitor for patients with peptic ulcer who failed to respond to other eradication regimens \[24\]. In another study, a similar eradication rate (63%, intention-to-treat) was achieved with a rescue treatment of a 7-d quadruple regimen with omeprazole, bismuth, tetracycline, and high-dose furazolidone (200 mg, b.i.d.) \[25\]. Currently, a standard third-line therapy is lacking, and several guidelines recommend a culture to select proper treatment according to microbial sensitivity to antibiotics for these patients \[7,11\]. However, cultures are often carried out only in research centers. It is a common practice to select a rescue therapy according to experience, especially in China. In this study, the intention-to-treat eradication rates were 73%, 81% and 50% for the patients who failed in \( H \ pylori \) eradication for one, two or three courses, respectively. Although, without information of microbial sensitivity to antibiotics, it has been shown that furazolidone-(100 mg, b.i.d. or t.i.d.) and amoxicillin-based quadruple rescue therapy was highly effective in the population of this region. \( H \ pylori \) eradication can be achieved in most patients, even when antibiotic susceptibility is not tested.

Furazolidone presents some side effects, especially gastrointestinal ones \[17\]. Several studies showed that side effects were very common (more than 20%) in the patients who received treatment with furazolidone-based regimens \[11\], especially with high-dose furazolidone of 200 mg b.i.d. \[24,25\]. A major problem with furazolidone at high doses is the high rate of severe side effects. Most of these effects are related to its role as a monoaminoxidase inhibitor and include fever, rash and severe abdominal pain. Such side effects may lead to the discontinuation of treatment in some patients \[11\]. In this study, the occurrence of side effects was 18.3%, and no intolerable side effects leading to early discontinuation of treatment were found. The most common side effects were nausea and diarrhea. Although the side effects were more frequent after extending the treatment course and adding furazolidone, this difference was not significant among different treatment groups.

The weakness of this study is that although set up as a controlled trial, the number of patients in each arm was small. Further studies should be done to conclude whether the increased dose of furazolidone or the longer period of treatment is helpful.

In conclusion, our study shows that the association of rabeprazole, bismuth, amoxicillin, and low-dose furazolidone is a valuable rescue treatment for patients who failed to respond to the first- or second-line \( H \ pylori \) eradication in China. Lower doses of furazolidone could decrease the incidence of side effects, but this strategy can also lead to a lower eradication rate. However, extending the antibiotic course to 14 d could improve eradication rates, despite a greater likelihood of side effects. The regimens are well tolerated by most patients. These are effective, cheap and safe options for salvage therapy of \( H \ pylori \) positive patients, and may be recommended as good alternative choice regimens in the eradication of \( H \ pylori \) in the population with high metronidazole resistance.

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### COMMENTS

**Background**

*Helicobacter pylori* (\( H \ pylori \)) infection is associated with many upper gastrointestinal diseases. The prevalence of \( H \ pylori \) resistant to antibiotics was increased with the spreading of \( H \ pylori \) eradication. Many patients needed to receive rescue therapy for the eradication of \( H \ pylori \) after first- or second-line therapies.

**Research frontiers**

Furazolidone-based regimens for the eradication of \( H \ pylori \) are low in cost. Lower doses of furazolidone could decrease the incidence of side effects. Not many studies have been performed to evaluate the efficacy of low-dose furazolidone-based quadruple regimens for treatment of \( H \ pylori \) infection.

**Innovations and breakthroughs**

This study provides further evidence of the efficacy and tolerability of low-dose furazolidone-based quadruple regimens in China.

**Applications**

Low-dose furazolidone-based quadruple regimens may be useful rescue therapies for \( H \ pylori \) eradication due to their low cost, low resistance rate and relatively minor side effects, especially in developing countries such as China.

**Peer review**

Furazolidone has been used for the eradication of \( H \ pylori \) for many years, but here it has been used as a component of quadruple rescue therapy. This has been reported less frequently. In this series of three groups of 20 patients, in which \( H \ pylori \) eradication therapy had failed to respond to at least one previous treatment regimen, each group was treated with one of three regimens of quadruple therapy containing furazolidone (either in different doses or for a different time), and the results were highly successful. Side effects from furazolidone are the main disadvantage of this drug, but when used in small doses as in this study, side effects were relatively minor. For the above reasons this is a useful publication.

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