Outcomes of furazolidone- and amoxicillin-based quadruple therapy for *Helicobacter pylori* infection and predictors of failed eradication

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Retrospective Study

Outcomes of furazolidone- and amoxicillin-based quadruple therapy for *Helicobacter pylori* infection and predictors of failed eradication
Abstract

AIM
To evaluate the outcomes of furazolidone- and amoxicillin-based quadruple therapy for treatment of Helicobacter pylori (H. pylori) infection and identify predictors of failed eradication.

METHODS
Patients with H. pylori infection treated with furazolidone, amoxicillin, bismuth, and proton pump inhibitor therapy (January 2015 to December 2015) who received the 13C-urea breath test > 4 wk after treatment were evaluated. Demographic and clinical data including prior H. pylori treatment attempts, medication adherence, alcohol and cigarette consumption during therapy, and treatment-related adverse events were recorded by reviewing medical records and telephone surveys. H. pylori eradication rates for overall and subgroups were evaluated. Multivariate analysis was performed to identify independent predictors of failed H. pylori eradication.

RESULTS
Of the 992 patients treated and retested for H. pylori infection, the overall eradication rate was 94.5% [95% confidence interval (CI): 94.1%-95.9%]. H. pylori eradication rate of primary therapy was 95.0% (95%CI: 93.5%-96.5%), while that of rescue therapy was 91.3% (95%CI: 86.8%-95.8%). Among the 859 patients who completed the study protocol, 144 (17%) reported treatment-related adverse events including 24 (3%) leading to premature discontinuation. On multivariate analysis, poor medication adherence [adjusted odds ratio (AOR) = 6.7, 95%CI: 2.8-15.8], two or more previous H. pylori treatments (AOR = 7.4, 95%CI: 2.2-24.9), alcohol consumption during therapy (AOR = 4.4, 95%CI: 1.5-12.3), and possibly smoking during therapy (AOR = 1.9, 95%CI: 0.9-4.3) were associated with failed H. pylori eradication.

CONCLUSION
Furazolidone- and amoxicillin-based quadruple therapy for H. pylori infection in an area with a high prevalence of clarithromycin resistance demonstrated high eradication rates as primary and rescue therapies with a favorable safety profile. Patient education targeting abstinence from alcohol during therapy and strict medication adherence may further optimize H. pylori eradication.

Key words: Helicobacter pylori; Furazolidone; Quadruple regimen; Side effects; Eradication

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Core tip: This study examined the outcomes of furazolidone- and amoxicillin-based quadruple therapy as both primary and rescue therapies for Helicobacter pylori (H. pylori) infection in nearly a thousand patients.

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Detailed data on adverse events and factors associated with failed H. pylori eradication were evaluated. Furazolidone- and amoxicillin-based quadruple therapy demonstrated a high H. pylori eradication rate exceeding 90% with a favorable safety profile in a real-world setting. Abstinence from alcohol during therapy and strict medication adherence may further optimize eradication. The results validate updated guidelines recommending furazolidone-based quadruple therapy as a first-line treatment for H. pylori infection in areas with a high prevalence of clarithromycin resistance.

INTRODUCTION
Helicobacter pylori (H. pylori) is a common pathogen associated with the development of peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. The prevalence of H. pylori infection exceeds 50% worldwide, with a higher prevalence in developing countries[1,2]. Effective eradication of H. pylori by a combination of antimicrobial and acid suppressive therapies reduces the risk of recurrent peptic ulcers and possible gastric cancer[3,4]. However, with the emergence of antibiotic-resistant H. pylori strains, traditional triple therapies have become increasingly ineffective, with some studies reporting eradication rates as low as 50%-60%. Selecting optimal therapies for antibiotic-resistant H. pylori infection has become a global public health priority.

Furazolidone is a monoamine oxidase inhibitor and nitrofurantoin-type antibiotic commonly used in Asia. Compared to high rates of resistance observed with clarithromycin, metronidazole, and levofloxacin, H. pylori strains resistant to furazolidone remain uncommon[5-8]. However, early animal studies demonstrating increased adverse events have limited widespread application of furazolidone in the treatment of H. pylori infection[9-11]. Given the high prevalence of H. pylori strains resistant to clarithromycin and metronidazole observed in recent studies, international guidelines recommend bismuth containing quadruple regimens that include amoxicillin, furazolidone or tetracycline for rescue therapies[12-14]. Furthermore, updated Chinese and international guidelines recommended furazolidone, amoxicillin, bismuth, and proton pump inhibitor (PPI) quadruple therapy as a first-line regimen option for H. pylori infection[15].

Although a number of studies with limited sample size have shown that furazolidone-based quadruple therapy is a viable treatment option, there is a lack of large, randomized controlled trials to support its efficacy. This study aimed to evaluate the outcomes of furazolidone-based quadruple therapy for H. pylori infection in an area with a high prevalence of clarithromycin resistance and to identify predictors of failed eradication.
size demonstrate high efficacy of furazolidone- and amoxicillin-based quadruple therapy for treatment of \( H. pylori \) infection, data on the adverse events, particularly impacting treatment course, are not well described\[16\]. Furthermore, predictors of failed \( H. pylori \) eradication other than the choice of regimen or poor medication adherence are largely unknown\[16,21\]. Given the high prevalence of clarithromycin-resistant \( H. pylori \) infection observed at our center, furazolidone- and amoxicillin-based quadruple therapy has been adopted as a first-line therapy for treatment of \( H. pylori \) since 2013. Therefore, we performed a retrospective study of patients who received furazolidone- and amoxicillin-based quadruple therapy for treatment of \( H. pylori \) at our center. The aim of our study was to evaluate the efficacy and safety of furazolidone- and amoxicillin-based quadruple therapy as primary and rescue therapies for \( H. pylori \) infection and also to identify predictors of failed \( H. pylori \) eradication.

**MATERIALS AND METHODS**

**Study population**

Patients diagnosed with \( H. pylori \) infection at Sir Run Run Shaw Hospital (Hangzhou, China) from January 2015 to December 2015 who received furazolidone- and amoxicillin-based quadruple therapy and had a follow-up \( ^{13} \)C-urea breath test (\( ^{13} \)C-UBT) > 4 wk after the completion of therapy were evaluated. All patients who received one of two forms of direct \( H. pylori \) testing available at our center (\( ^{13} \)C-UBT or gastric biopsy) were searched, and pharmacy records were examined to identify patients who received furazolidone- and amoxicillin-based quadruple therapy. All patients aged \( \geq 18 \) years who received repeat \( H. pylori \) breath test > 4 wk after treatment were eligible for the study. Patients who lacked repeat \( H. pylori \) testing to evaluate for eradication status or received therapies other than furazolidone- and amoxicillin-based quadruple therapy were excluded. Medical records including endoscopy, pathology, \( ^{13} \)C-UBT, and pharmacy records were reviewed to characterize the clinical course before and after treatment of \( H. pylori \) infection. After the follow-up breath test, all patients were seen in an outpatient visit and contacted for a detailed telephone survey. The protocol was approved by the Ethics Committee of Sir Run Run Shaw Hospital prior to initiating the study.

**Treatment**

Per hospital clinical pathway since 2013, all patients with \( H. pylori \) infection without contraindications to penicillin, furazolidone, bismuth, or proton pump inhibitor were treated with furazolidone, amoxicillin, bismuth, and PPI for 10-14 d unless specified by the clinician. Patients were treated with furazolidone 100 mg, amoxicillin 1 g, proton pump inhibitor (esomeprazole 20 mg, rabeprazole 10 mg, pantoprazole 40 mg, lansoprazole 30 mg, or omeprazole 20 mg), and colloidal bismuth pectin (200 mg to 400 mg); all were taken twice a day. Patients were instructed to take antibiotics immediately after meals but take PPI and bismuth 30 min before meals. Four weeks after the completion of treatment, all patients were recommended to obtain a follow-up \( ^{13} \)C-UBT and an outpatient consultation.

**Data collection**

Baseline data including age, gender, smoking status, alcohol status, and educational levels at the time of \( H. pylori \) testing as well as all prior \( H. pylori \) treatment attempts were recorded by reviewing medical records and telephone surveys. Endoscopy and \( H. pylori \) breath test reports were reviewed to obtain information on the date and indication and/or diagnosis for \( H. pylori \) testing. Data on \( H. pylori \) treatment regimens and duration were obtained by reviewing electronic pharmacy records. Data including medication adherence, potential treatment-related adverse events (dizziness, headache, fatigue, fever, anorexia, nausea, vomiting, diarrhea, constipation, abdominal discomfort or pain, bitter taste, skin rash/pruritus, weight loss, dysphagia, dyspnea, blurred vision, and myalgia), as well as smoking and tobacco status before and during treatment were collected at the time of repeat \( H. pylori \) testing, outpatient consultation, or by a follow-up phone survey. In order to evaluate \( H. pylori \) resistance pattern, available \( H. pylori \) culture and antibiotic susceptibility data at the center between January 2013 and December 2014 were also collected.

**Definitions and outcomes**

The primary endpoint of the study was \( H. pylori \) eradication rate. Secondary endpoints were treatment-related adverse events and predictors of eradication failure. The primary endpoint was also analyzed by subgroups by patients receiving primary or rescue therapy and those with or without adverse events. Potential treatment-related adverse events were expressed as proportion of individuals experiencing a specific side effect and any side effects. Predictors of eradication failure including demographic (age, gender, and educational level), clinical (number of previous treatment and indication/diagnosis of \( H. pylori \) testing), and treatment-related factors (PPI type, bismuth dose, treatment duration, medication adherence, smoking during treatment, and alcohol use during treatment) were evaluated. The number of previous \( H. pylori \) infection treatment was categorized as none, one, or \( \geq 2 \) prior treatment attempts. Smoking status was defined as non-smoker; abstinence during therapy, and smoking during therapy. Alcohol use was defined as non-alcohol user, abstinence during therapy, and alcohol use during therapy. Educational levels were categorized by years of education (< 7, 7-9, 10-12, 13-16, or \( \geq 16 \) years). Poor adherence to \( H. pylori \) treatment was defined as patient reporting < 80% adherence of prescribed therapy\[22\]. Severe adverse event was defined as treatment-related.
adverse event necessitating discontinuation of therapy within 10 d.

Statistical analysis
Sociodemographic and outcome data were described using number and frequency for categorical variables and mean and standard deviation for continuous variables. Eradication rates between different groups were compared using the \( \chi^2 \) test. Initially, potential factors associated with failed eradication was evaluated by using a \( \chi^2 \) test or Fisher’s exact test. Afterwards, variables associated with failed eradication were included in a multiple logistic regression model to evaluate for predictors of failed eradication. All statistical analyses were performed using IBM SPSS Statistics V22.0 software. Two-sided \( P \)-values < 0.05 were considered significant.

RESULTS
During the one-year study period, 992 patients were treated with furazolidone- and amoxicillin-based quadruple therapy and received the \(^{13}\)C-UBT > 4 wk after eradication (Table 1). The mean age of the patients was 46.7 ± 12.4 years, 501 (50.5%) were male, and 259 (26.1%) were treated for indication of peptic ulcers. Furthermore, 842 (84.9%) patients had no prior \( H. pylori \) treatment, 127 (12.8%) had one prior treatment, and 23 (2.3%) had ≥ 2 prior treatments. Nine hundred and seventy-one (97.9%) and 21 (2.1%) patients were prescribed a 14-d regimen and a 10-d regimen, respectively. \( H. pylori \) culture and antibiotic susceptibility study available from 2013–2014 (\( n = 52 \)) showed clarithromycin-resistant strains in 9 (17.3%), levofloxacin-resistant strains in 20 (38.5%), metronidazole-resistant strains in 38 (73.1%), furazolidone-resistant strains in 2 (3.8%), and none with amoxicillin-resistant strains (Supplementary Table 1).

### H. pylori eradication rate
Of the 992 patients, 859 completed the study protocol. The overall eradication rate was 94.5% (95%CI: 94.1%-95.9%). \( H. pylori \) eradication rates were 95.0% (95%CI: 93.5%-96.5%) and 91.3% (95%CI: 86.8%-95.8%) for primary and rescue therapies, respectively. Among those who completed the follow-up, patients who did not experience medication-related adverse events had a higher eradication rate (95.5% vs 90.3%, mean difference = 5.2%, 95%CI: 0.7%-11.7%) compared to those who experienced any reported adverse events (Table 2).

### Treatment-related adverse events
Of the 859 patients who completed the study, 144 (16.8%) experienced one or more treatment-related adverse events (Table 3). The common adverse events including abdominal pain in 39 (4.5%), nausea in 20 (2.3%), dizziness in 11 (1.3%), fatigue in 11 (1.3%), anorexia in 13 (1.5%), and skin rash/pruritus in 18 (2.1%) were reported. Twenty-four (2.8%) patients experienced severe treatment-associated adverse events necessitating premature discontinuation of intended therapy including 10 (1.2%) who completed < 10 d of treatment. Skin rash/pruritus (\( n = 3, 0.4\% \)) was the most common severe treatment-related adverse event.

### Predictors of failed \( H. pylori \) eradication
On univariate analysis, the number of previous \( H. pylori \) treatment (78.3%-95.0%, \( P = 0.002 \)), smoking status (88.2%-95.6%, \( P = 0.004 \)), alcohol status (79.4%-95.5%, \( P < 0.001 \)), and poor \( H. pylori \) treatment adherence (77.5% vs 96.2%, \( P < 0.001 \)) were associated with failed \( H. pylori \) eradication (Table 4). Multivariate analysis demonstrated that ≥ 2 prior \( H. pylori \) treatment attempts (AOR = 7.4; 95%CI: 2.2-24.9, \( P = 0.001 \)) compared to no treatment, and poor adherence (AOR = 6.7; 95%CI: 2.8-15.8, \( P < 0.001 \)) compared to acceptable adherence were associated with failed \( H. pylori \) eradication. Furthermore, alcohol use during treatment compared

| Variable | Information |
|----------|-------------|
| Age (mean age ± SD) | 46.7 ± 12.4 |
| Gender | Male 501 (50.5%) Female 491 (49.5%) |
| Smoking history | 199/859 (23.2%) |
| Alcohol intake history | 231/859 (26.9%) |
| Educational level | < 7 yr 164 (16.5) 7-9 yr 249 (25.1) 10-12 yr 197 (19.9) 13-16 yr 229 (23.1) > 16 yr 20 (2.0) Unknown 133 (13.4) |
| Diagnosis | Functional dyspepsia 478 (48.2) Peptic ulcers 259 (26.1) Erosive esophagitis 69 (7.0) Other sources of upper GI bleeding 5 (0.5) Gastric tumors 6 (0.6) Asymptomatic gastritis 75 (7.6) \(^{13}\)C-UBT positive during health checkup 100 (10.1) |
| Number of previous \( H. pylori \) treatment(s) | None 842 (84.9) One 127 (12.8) Two or more 23 (2.3) |
| PPI type | Esomeprazole 264 (26.6) Rabeprazole 224 (22.6) Pantoprazole 435 (43.9) Other PPIs 69 (7.0) |
| Bismuth dose | 400 mg per day 213 (21.5) 600 mg per day 391 (39.4) 800 mg per day 388 (39.1) |
| Duration of regimen | 14-d regimen 971 (97.9) 10-d regimen 21 (2.1) |

Gi: Gastrointestinal; PPI: Proton pump inhibitor; \(^{13}\)C-UBT: \(^{13}\)C-urea breath test.
to non-alcohol user (AOR = 4.4; 95%CI: 1.5-12.3, P = 0.008), but not alcohol users abstinent during treatment (AOR = 1.0; 95%CI: 0.4-2.3, P = 1.00), was associated with failed H. pylori eradication. Finally, smoking during treatment demonstrated a trend towards failed H. pylori eradication (AOR = 1.9; 95%CI: 0.9-4.3, P = 0.10) compared to non-smokers. Age, gender, educational level, PPI type, bismuth dose, therapy duration, and the indication for treatment were not associated with failed H. pylori eradication.

**DISCUSSION**

In this single-center study evaluating furazolidone- and amoxicillin-based quadruple therapy for H. pylori infection in an area with a high prevalence of clarithromycin resistance, the eradication rates were high at > 90% for both primary and rescue therapies. Furthermore, treatment-related adverse events were infrequent with fewer than 3% requiring treatment discontinuation. Poor adherence to prescribed therapy, two or more prior eradication attempts, and concurrent alcohol use during treatment were associated with failed eradication.

The rise in the prevalence of antibiotic-resistant H. pylori strains has led to increased treatment failure with traditional triple therapies[2,10,23]. In recognition of high global prevalence of clarithromycin- and/or metronidazole-resistant H. pylori infection, the updated Maastricht V/Florence Consensus Report emphasized that bismuth quadruple or non-bismuth quadruple, concomitant therapies (PPI, amoxicillin, clarithromycin, and a nitroimidazole) are now the treatment of choice in regions with high (> 15%) clarithromycin resistance while bismuth quadruple therapies are recommended in regions with high dual resistance to clarithromycin and metronidazole (> 15%)[18]. Furthermore, the guidelines recommended that clarithromycin should be avoided and a combination of antibiotics with high barrier to resistance (amoxicillin, tetracycline, furazolidone, and rifabutin) should be selected. The Fifth Chinese National Consensus Report recommended furazolidone, amoxicillin, bismuth, and PPI quadruple therapy as one of the first-line regimens for H. pylori therapy given that estimated resistance to clarithromycin and metronidazole exceeds 20% and 40%, respectively, in China[20].

Our results from a real-world experience demonstrated that furazolidone- and amoxicillin-based quadruple therapy achieved a 95% H. pylori eradication rate which is within the higher range of all eradication rates reported in the literature[14]. Although older studies mostly containing furazolidone as a component of substandard regimens (inadequate duration or absence of PPI) reported a low pooled-eradication rate of 76%, our findings are consistent with recent studies reporting high eradication rates of 85%-95% in combination with 14 d of amoxicillin[24-26]. For example, in a randomized study of 424 patients with H. pylori infection from Shanghai comparing four different bismuth-based quadruple therapies (amoxicillin, tetracycline, metronidazole, or furazolidone) as rescue therapies, furazolidone-containing regimens had a higher eradication rate (93.4% vs 85.9%; mean difference = 7.6%, 95%CI: 1.4%-13.8%) compared to non-furazolidone-containing regimens per intent to treat (ITT)[24]. Furthermore, a multicenter prospective study that included 180 patients with H. pylori-positive duodenal ulcer allocated to amoxicillin 1 g, furazolidone 100 mg, rabeprazole 10 mg, and bismuth 220 mg twice a day for 10 d demonstrated an eradication rate of 86% per ITT[26]. In another randomized controlled study comparing different durations and doses of furazolidone, 40 patients receiving furazolidone 200 mg to 300 mg per day with amoxicillin, PPI, and bismuth for 2 wk as rescue therapies led to an eradication rate of 88% per ITT[25]. Finally, a retrospective study of 27 United States patients receiving furazolidone-containing non-bismuth quadruple therapy for 2 wk demonstrated a high eradication rate of 97% per ITT[9]. The eradication rate of 95% in our study is remarkable, especially given that 15% of patients have experienced prior treatment failure.

The high eradication rates of H. pylori with furazolidone- and amoxicillin-containing quadruple therapy in our study may be related to several factors. First, two antibiotics (furazolidone and amoxicillin) with the highest barrier to resistance were included in the treatment regimen. With the exception of Iran where furazolidone-resistant H. pylori is common (5% to 22%), the reported resistance rates in China, Vietnam, and United States are consistently < 5%[2,11,23,27-30]. A recent local study examining 545 H. pylori cultures obtained from children showed absence of furazolidone-resistant H. pylori, consistent with the low (4%) resistance rate shown at our center[29]. In addition to the low prevalence of furazolidone-resistant H. pylori (< 5%), amoxicillin as the backbone of eradication therapy continues to have the lowest prevalence of H. pylori resistance reported globally (< 1%-2%) and in China (< 5%). Second, bismuth

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**Table 2** Helicobacter pylori eradication rates with furazolidone- and amoxicillin-based quadruple therapy: Overall and by subgroup % (95%CI)

| Variable                  | n/N     | Eradication rate |
|---------------------------|---------|-----------------|
| Overall                   | 935/992 | 94.5 (94.1-95.9) |
| Primary                   | 800/842 | 95.0 (93.5-96.5) |
| Rescue                    | 137/150 | 91.3 (86.8-95.8) |
| Adverse events¹           |         |                 |
| Without                   | 683/715 | 95.5 (94.0-97.0) |
| With                      | 130/144 | 90.3 (85.5-95.1) |

¹Patients who completed the study protocol were divided into two groups: with or without adverse events during therapy. Eradication rates of two groups were calculated and the difference between the two groups was analyzed. Eradication rates were higher among patients without (mean difference = 5.2%, 95%CI: 0.7%-11.7%, P = 0.01) compared to those with adverse events during therapy. n: Number of successful eradication; N: Number of total patients.
that has been shown to improve treatment eradication rate by 30%-40% in areas with a high prevalence of *H. pylori* resistance was routinely added in our study\[^{31}\]. Third, almost all (98%) patients received a 14-d regimen and none of the patients were prescribed < 10 d of intended therapy. Although the results are inconsistent, a systematical review of 75 studies demonstrated that longer duration of therapy improves eradication and 14 d of treatment have been recommended by updated guidelines\[^{18,32,33}\]. Finally, selection bias favoring higher eradication rate is possible among population returning for confirmatory *H. pylori* testing.

Our study demonstrated that adverse events occurred in 17% (95%CI: 14.3%-19.3%) of the cohort with premature discontinuation of therapy occurring in 2.8% (95%CI: 1.7%-3.9%). The adverse events (abdominal discomfort, dizziness, nausea, fatigue, anorexia, rash, and pruritus) observed in our study were mild and non-specific, similar to other studies evaluating furazolidone-containing regimens\[^{34}\]. Furthermore, all side effects resolved after the completion or withdrawal of therapy without any documented events of severe hepatotoxicity or kidney injury. Although the incidence of adverse events with furazolidone-containing *H. pylori* regimen is common (18%-33%)\[^{16,25}\], the incidence of adverse events associated with furazolidone-containing regimen is not elevated compared to amoxicillin-based triple or tetracycline and metronidazole-based quadruple therapy\[^{46}\]. A Chinese meta-analysis of 788 patients also demonstrated no difference in the incidence of adverse events between furazolidone-containing quadruple therapy compared to other quadruple therapy regimens as rescue therapies (14.1% vs 13.8%; OR = 1.04, 95%CI: 0.7-1.6)\[^{35}\]. The incidence of furazolidone-associated adverse events is dose-dependent and severe among those treated with high- (400 mg per day) compared to low-dose furazolidone (200 mg per day), longer duration, and co-therapy with bismuth. Low-dose furazolidone studies generally demonstrate a low incidence of adverse events of < 20%\[^{36-39}\]. Although the eradication rate in patients with adverse events was lower (90.3% vs 95.5%, mean difference = -5.2%, 95%CI: -0.7% to -11.7%) compared to those without adverse events in our study, the overall eradication rate remained high at > 90%.

Furazolidone is a synthetic nitrofuran that has been widely used as an antibiotic to treat enteric infections globally. The carcinogenetic effects of furazolidone suggested in early animal studies\[^{12-15,40}\] have remained speculative in clinical settings. Furazolidone is a category 3 agent and considered unclassifiable in regards to carcinogenicity in humans\[^{41}\]. Despite being a widely used antibiotic in Asia for more than two decades, teratogenicity or carcinogenicity in humans has yet to be reported despite close scrutiny\[^{42}\]. Furazolidone is currently not available in the United States due to the lack of a commercial market\[^{43}\]. The abandonment of furazolidone-based therapy of finite duration due to concerns of side effects may be misguided\[^{42}\]. Our current study of nearly 1000 patients demonstrating a favorable safety profile supports the use of low-dose furazolidone-based quadruple therapy for *H. pylori* infection.

Multivariate analysis demonstrated that poor adherence (AOR = 6.7, 95%CI: 2.8-15.8), multiple treatment (AOR = 7.4, 95%CI: 2.2-24.9), alcohol

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**Table 3.** Adverse events of furazolidone- and amoxicillin-based quadruple therapy (n = 859) n (%)  

| Adverse event | Number | Severe | Impact on treatment | Eradication |
|---------------|--------|--------|---------------------|-------------|
| Abdominal discomfort | 39 (4.5) | - | 2 stopped prior to completion (10, 12 d) | 38 (97.4) |
| Dizziness | 11 (1.3) | 2 (0.2) | 4 stopped prior to completion (7, 10, 12 d); 1 experienced dizziness after drinking alcohol and stopped prior to completion (10 d); 1 took 50% medicine | 10 (90.9) |
| Nausea (with/without vomiting) | 20 (2.3) | - | 1 took 75% medicine | 16 (80.0) |
| Fatigue | 11 (1.3) | 1 (0.1) | 1 stopped prior to completion (12 d); 1 changed to traditional Chinese medicine during therapy (7 d) | 9 (81.8) |
| Anorexia | 13 (1.5) | - | 1 took 80% medicine | 13 (100) |
| Skin rash/ pruritus | 18 (2.1) | 3 (0.4) | 4 stopped prior to completion (4, 7, 10, 11 d); 2 changed to other regimens during therapy (2, 10 d); 1 took half of amoxicillin and all other drugs | 15 (83.3) |
| Fever | 2 (0.2) | 2 (0.2) | 2 stopped prior to completion (7, 9 d) | 2 (100) |
| Diarrhea | 9 (1.1) | 1 (0.1) | 1 stopped prior to completion (less than 7 d) | 8 (88.9) |
| Constipation | 3 (0.4) | - | - | 3 (100) |
| Flatulence | 2 (0.2) | - | - | 2 (100) |
| Muscle pain or spasm (shoulder/back) | 3 (0.4) | - | - | 1 (33.3) |
| Acid regurgitation | 1 (0.1) | - | - | 1 (100) |
| Abdominal pain | 4 (0.5) | 1 (0.1) | 2 stopped prior to completion (7,10 d) | 4 (100) |
| Weight loss | 3 (0.4) | - | - | 3 (100) |
| Bitter taste/dry throat | 2 (0.2) | - | 1 took 75% medicine | 2 (100) |
| Belching | 1 (0.1) | - | - | 1 (100) |
| Chest congestion | 1 (0.1) | - | - | 1 (100) |
| Heartburn | 1 (0.1) | - | - | 1 (100) |
| Total | 144 (16.8) | 10 (1.2) | 24 (2.8) | 130 (90.3) |
use (AOR = 4.4, 95%CI: 1.5-12.3), and possibly smoking (AOR = 1.9, 95%CI: 0.9-4.3) during therapy were associated with failed \textit{H. pylori} eradication. As expected and consistent with previous findings, poor adherence defined by taking < 80% of the prescribed therapy and history of multiple treatment failures defined by \( \geq 2 \) treatment attempts had more than 6-fold and 7-fold increased risks of treatment failure, respectively\cite{44,45}. Concurrent alcohol, but not alcohol abstinence during therapy, compared to non-alcohol use increased the odds of treatment failure in our study. Although the reason is unclear, concurrent alcohol use with furazolidone may lead to increased adverse events that may impact adherence to therapy. Smoking has been previously associated with decreased \textit{H. pylori} eradication rate with proposed reasons including adverse impact on adherence, decreased gastric mucosal blood flow, increased gastric acidity, and altered PPI metabolism\cite{46,47}.

Our findings have clinical implications. Rather than pathogen-associated factors, host-associated factors were primary determinants of successful eradication of \textit{H. pylori} with furazolidone- and amoxicillin-containing quadruple therapy. Furthermore, excluding prior treatment failure, other predictors can potentially be modified during the treatment course to optimize the eradication rate. Our findings highlight the role of physician-patient communication, emphasizing the importance of adherence to prescribed therapy and alcohol cessation during therapy to optimize \textit{H. pylori} eradication.

The strength of our study is the evaluation of a large patient population in a "real-world" setting examining furazolidone- and amoxicillin-containing quadruple therapy as both primary and rescue regimens. Furthermore, detailed data of adverse events as well as evaluation of factors associated with failed \textit{H. pylori} eradication were analyzed. Finally, our study showed that furazolidone- and amoxicillin-based quadruple therapy led to a high eradication rate regardless of furazolidone dose (\textit{i.e.}, 200 mg per day), bismuth dose, or PPI type previously raised as potential factors for successful \textit{H. pylori} eradication.

### Table 4  Univariate and multivariate analyses for predictors of failed \textit{Helicobacter pylori} eradication

| Factor | n/N (%) | \( P \) value\textsuperscript{1} | OR (95\%CI) | \( P \) value\textsuperscript{2} |
|--------|---------|-----------------|-------------|-----------------|
| **Age (yr)** | | | | |
| < 60 | 781/827 (94.4) | 0.96 | - | - |
| \( \geq 60 \) | 156/165 (94.5) | 0.24 | - | - |
| **Gender** | | | | |
| Male | 469/501 (93.6) | 0.24 | - | - |
| Female | 468/491 (95.3) | 0.29 | - | - |
| **Education\textsuperscript{3}** | | | | |
| < 7 yr | 150/164 (91.5) | 0.29 | - | - |
| 7-9 yr | 237/249 (95.2) | - | - | - |
| 10-12 yr | 187/197 (94.9) | 7.4 (2.2-24.9) | 0.001 |
| 13-16 yr | 219/229 (95.6) | - | - | - |
| > 16 yr | 20/20 (100) | - | - | - |
| **Number of previous \textit{H. pylori} treatment(s)** | | | | |
| None | 800/842 (95.0) | 0.002 | Reference | - |
| One | 119/127 (93.7) | 1.2 (0.5-2.7) | 0.73 |
| Two or more | 18/23 (78.3) | 7.4 (2.2-24.9) | 0.001 |
| **Diagnosis** | | | | |
| Functional dyspepsia | 453/478 (94.8) | 0.49 | - | - |
| Peptic ulcers | 245/259 (96.6) | - | - | - |
| Erosive esophagitis | 67/69 (97.1) | - | - | - |
| Other sources of upper GI bleeding | 4/5 (80.0) | - | - | - |
| Gastric neoplasm | 6/6 (100.0) | - | - | - |
| Asymptomatic gastritis | 68/76 (90.7) | - | - | - |
| 13C-UBT positive during health checkup | 94/100 (94.0) | - | - | - |
| **PPI type** | | | | |
| Esomeprazole | 253/264 (95.8) | 0.42 | - | - |
| Rabeprazole | 209/224 (93.3) | - | - | - |
| Pantoprazole | 408/435 (93.8) | - | - | - |
| Other PPIs | 67/69 (97.1) | - | - | - |
| **Bismuth** | | | | |
| 400 mg per day | 204/213 (95.8) | 0.4 | - | - |
| 600 mg per day | 371/391 (94.9) | - | - | - |
| 800 mg per day | 362/388 (93.3) | - | - | - |
| **Duration of regimen** | | | | |
| 10 d | 19/21 (90.5) | 0.33 | - | - |
| 14 d | 918/971 (94.5) | - | - | - |
| **Adherence\textsuperscript{2}** | | | | |
| Took 80% medicine or more | 782/819 (95.5) | < 0.001 | Reference | - |
| Took less than 80% medicine | 31/40 (77.5) | 6.7 (2.8-15.8) | < 0.001 |
| **Smoking\textsuperscript{3}** | | | | |
| Non-smoker | 631/660 (95.6) | 0.004 | Reference | - |
| Abstinence during therapy | 77/80 (96.3) | 0.7 (0.2-2.7) | 0.65 |
| Smoking during therapy | 105/119 (88.2) | 1.9 (0.9-4.3) | 0.10 |
| **Alcohol\textsuperscript{3}** | | | | |
| Non-alcohol user | 600/628 (95.5) | < 0.001 | Reference | - |
| Abstinence during therapy | 186/197 (94.8) | 1.0 (0.4-2.3) | 1.00 |
| Alcohol use during therapy | 27/34 (79.4) | 4.4 (1.5-12.3) | 0.008 |

\textsuperscript{1}Univariate analysis; \textsuperscript{2}Data analyzed only for patients who completed the study protocol (n = 859). \textit{n}: Number of successful eradication; \textit{N}: Number of total patients; GI: Gastrointestinal; PPI: Proton pump inhibitor; \textsuperscript{13}C-UBT: \textsuperscript{13}C-urea breath test.
Our study has limitations. Our findings may not be generalizable in areas with highly variable H. pylori-resistant patterns or no access to furazolidone. Future studies evaluating the efficacy of furazolidone- and amoxicillin-based quadruple therapy in areas other than Iran or China may be invaluable. Furthermore, H. pylori culture and sensitivity were not performed in all enrolled patients. However, H. pylori antibiotic sensitivity data available in a subset of patients in our study paralleled findings from two recent large studies from the same region\cite{29,40}. Finally, the analysis of patients who completed repeat evaluation of H. pylori after treatment may lead to bias in the interpretation of the results.

In conclusion, furazolidone- and amoxicillin-based quadruple therapy in a region with high clarithromycin resistance demonstrated high eradication rates as primary and rescue therapies with favorable safety profiles. Patient education targeting abstinence from alcohol and strict medication adherence may further optimize H. pylori eradication.

# Research Background

With the increase of antibiotic resistance of Helicobacter pylori (H. pylori) worldwide, traditional triple therapies have become increasingly ineffective. Selecting optimal therapies for antibiotic-resistant H. pylori infection has become an important global public health priority.

# Research Motivation

Although studies with limited sample size demonstrate high efficacy of furazolidone-based quadruple therapy for treatment of H. pylori, data on the impact of adverse events and predictors of failed H. pylori eradication are not well described. Furthermore, evaluating efficacy and safety of furazolidone- and amoxicillin-based quadruple therapy for H. pylori and identifying predictors of failed eradication in a large patient population are lacking.

# Research Objectives

The aim of the study was to evaluate the outcomes of furazolidone- and amoxicillin-based quadruple therapy for treatment of H. pylori and identify predictors of failed eradication. Furazolidone- and amoxicillin-containing quadruple therapy demonstrated a high eradication rate exceeding 90% both as primary and rescue therapies with a favorable safety profile. Patient education targeting abstinence from alcohol use during therapy and strict medication adherence may further optimize H. pylori eradication. The results provided robust evidence for using furazolidone- and amoxicillin-containing quadruple therapy as a first-line therapy for H. pylori infection in areas with a high prevalence of clarithromycin resistance.

# Research Methods

Patients with H. pylori infection who were treated with furazolidone- and amoxicillin-based quadruple therapy and received 14C-urea breath test > 4 wk after treatment from January 2015 to December 2015 were evaluated. Patient data including sociodemographic data, prior treatment attempts, medication adherence, and treatment-related adverse events were obtained by reviewing medical records and conducting telephone surveys. H. pylori eradication rates for overall and subgroups, treatment-related adverse events, and independent predictors of failed H. pylori eradication were evaluated.

# Research Results

Furazolidone- and amoxicillin-based quadruple therapy demonstrated a high eradication rate exceeding 90% as both primary and rescue therapies. Fewer than 3% of patients reported treatment-related adverse events leading to premature discontinuation. Poor medication adherence, previous H. pylori treatments, and alcohol consumption during therapy were associated with failed H. pylori eradication. These findings suggest that furazolidone- and amoxicillin-based quadruple therapy with proper patient education could optimize treatment of H. pylori infection in regions with high resistance to clarithromycin. Evaluating the efficacy of furazolidone- and amoxicillin-based quadruple therapy in areas other than China may be invaluable in future studies.

# Research Conclusions

Furazolidone- and amoxicillin-based quadruple therapy demonstrated high eradication rates as both primary and rescue therapies for H. pylori infection with a favorable safety profile in areas with a high rate of clarithromycin resistance. Abstinence from alcohol and strict medication adherence during therapy may further optimize H. pylori eradication. These findings validate updated guidelines recommending furazolidone-containing quadruple therapy as a first-line regimen for treatment of H. pylori infection in populations with a high rate of clarithromycin resistance.

# Research Perspectives

Selecting optimal treatment for H. pylori infection is important in regions with a high rate of resistance to clarithromycin. Targeted patient education may further optimize H. pylori eradication. Future studies confirming the high efficacy of furazolidone- and amoxicillin-based quadruple therapy in areas other than China may be invaluable.

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