Original Article

Treatment with compound *Lactobacillus acidophilus* followed by a tetracycline- and furazolidone-containing quadruple regimen as a rescue therapy for *Helicobacter pylori* infection

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Abstract

Background/Aim: Treatment of *Helicobacter pylori* infections has become more difficult because of increasing antibiotic resistance. We assessed the efficacy and safety of treatment with probiotics followed by a tetracycline- and furazolidone-containing quadruple regimen as rescue treatment for *H. pylori* infection.

Patients and Methods: This retrospective study examined patients with at least two *H. pylori* eradication failures. Patients were given a two-week compound *Lactobacillus acidophilus* (1 g t.i.d.), followed by a quadruple antibiotic regimen (esomeprazole [20 mg b.i.d.] + bismuth potassium citrate [220 mg b.i.d.] + tetracycline [750 mg b.i.d.] + furazolidone [100 mg b.i.d.]) for 10 days as rescue therapy. Eradication was evaluated using the ^{13}C-urea breath test at 4 weeks after the end of therapy, and side effects were recorded.

Results: The records of 50 patients were examined. Four cases experienced treatment failure, and one case received replacement with metronidazole because of allergy to furazolidone. The eradication rate was 92.0% [95% confidence interval (CI): 84.0–98.0%) in intention-to-treat (ITT) analysis and 91.8% (95% CI: 83.7–98.0%) in per protocol (PP) analysis. Side effects (mainly dizziness, dry mouth, and skin rash) occurred in 10 patients, all of which resolved after cessation of antibiotics.

Conclusions: Patients who failed multiple attempts at *H. pylori* eradication may benefit from a treatment with probiotics followed by a tetracycline- and furazolidone-containing quadruple regimen.

Keywords: Efficacy, furazolidone, *Helicobacter pylori*, probiotics, safety, tetracycline

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INTRODUCTION

More than 50% of the world's population currently have gastrointestinal *H. pylori* infections, including an estimated 40 to 60% of Chinese adults.[1] Among patients with *H. pylori* infections, 100% have or will develop chronic active gastritis but fewer than 10% have *H. pylori*-related dyspepsia. A total of 15% to 20% develop peptic ulcers, but less than 1% ultimately develop gastric malignant tumors.[2]

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H. pylori gastritis is defined as an infectious disease,[3] and eradication of *H. pylori* plays an important role in the cure, reversal, and delay of disease onset.

Consensus in China recommends bismuth-containing quadruple regimen (bismuth, PPI, and two kinds of antibiotics) for eradication, and antibiotics with high eradication rates are preferred first.[4] But due to the widespread use of antibiotics for treatment of *H. pylori* infections, antibiotic resistance has increased greatly.[3] In particular, epidemiological data for *H. pylori* in China show high resistance to clarithromycin (20–45%), levofloxacin (20–45%), and metronidazole (40–70%), although the resistance rates to tetracycline, furazolidone, and amoxicillin are all below 5%.[5-7] The increasing resistance of *H. pylori* to antibiotics has led to an increasing rate of failure to eradicate *H. pylori*. Thus, the selection of a safe and effective antibiotic regimen for patients who have failed previous regimens is a major challenge for clinicians.

METHODS

Study population

Patients were retrospectively enrolled by the Department of Gastroenterology, Changhai Hospital from June 2015 to May 2018. All included patients were 18 to 70 years old; positive for the urea breath test at least 4 weeks after last eradication treatment; and experienced at least two *H. pylori* eradication failures. Patients were excluded if they presented with severe comorbidity or a malignant tumor; had a known history of allergy to the drugs in the therapeutic regimen; used nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotic therapy, or bismuth salts up to 4 weeks before study inclusion; or were pregnant or breast-feeding.

All clinical data were collected. Previous eradication regimens and the dates of eradication failures were extracted from the medical records and telephone interviews. This retrospective study was approved by the ethics committee of Shanghai Changhai Hospital (No. CHEC 2017-210). Informed consent was obtained from all the patients.

Protocol

The regimen consisted of compound *Lactobacillus acidophilus* (1.0 g, t.i.d) for 2 weeks, followed by 10 days of esomeprazole (20 mg, b.i.d), bismuth potassium citrate (220 mg, b.i.d), tetracycline (750 mg, b.i.d), and furazolidone (100 mg, b.i.d). According to the manufacturer (Yi Jun Kang®, He Li Pharm. Co. Ltd. China), each probiotic tablet contained 5×10^6 cells of *Lactobacillus acidophilus*, 2.5×10^6 cells of *Streptococcus faecalis*, and 5×10^3 cells of *Bacillus subtilis*. Esomeprazole was taken 30 min before a meal, and all other drugs were taken after meals. All patients were asked to quit smoking and drinking alcohol during the treatment regimen.

Eradication status was evaluated using ^{13}C-UBT, at least 4 weeks after the end of treatment. The result was considered negative if the value was below 4. Adverse effects during treatment were also recorded.

Statistical analysis

All enrolled patients were analyzed using intention-to-treat (ITT) analysis, and all enrolled patients who completed the entire regimen were analyzed using per-protocol (PP) analysis. All the analyses were performed with IBM Statistical Package for the Social Sciences (SPSS) software version 21.0.

RESULTS

General information

We retrospectively examined the records of 50 patients who met the inclusion criteria (17 men and 33 women, mean age: 47.3 years, age range: 29–68 years) [Table 1]. There were five cases with atrophic gastritis, 37 cases with non-atrophic gastritis, eight cases with peptic ulcer [Table 1]. The number of previous treatment failures ranged from 2 to 10 (two times for 28 patients, three times for 12 patients, and four or more times for 10 patients).

Analysis of the antibiotics used in previous regimens [Table 2] indicated that clarithromycin was used in 41 cases, levofloxacin in 32 cases, amoxicillin in 42 cases (six of whom had histories of penicillin allergy), and metronidazole in 30 cases. There was no previous use of tetracycline or furazolidone.

The characteristics of the rescue regimens [Table 3] were also analyzed. Two cases repeated the original regimen, six cases repeated clarithromycin or levofloxacin, three cases repeated metronidazole without dose optimization,

Table 1: General characteristics of patients with refractory *H. pylori* infections

Characteristics		*n* (%)
Total number		50
Sex	Male	17 (34.0)
	Female	33 (66.0)
Endoscopy results	Atrophic gastritis*	5 (10.0)
	Non-atrophic gastritis	37 (74.0)
	Peptic ulcer†	8 (16.0)
No. of treatment failures	2	28 (56.0)
	3	12 (24.0)
	4 or more	10 (20.0)

*Atrophic gastritis: moderate-severe atrophy and (or) intestinal metaplasia.
†Peptic ulcer: gastric ulcer, duodenal ulcer, and (or) compound ulcer

Table 2: Antibiotics previously used to treat *H. pylori* infections

	Clarithromycin	Levofloxacin	Amoxicillin	Metronidazole	Tetracycline	Furazolidone
n (%)	41 (82.0)	32 (64.0)	42 (84.0)	30 (60.0)	0 (0)	0 (0)
Allergy cases	N/A	N/A	6	N/A	N/A	N/A

three cases used antibiotics not in the recommended guidelines (gentamicin, erythromycin, or cefaclor),[4,8] and two cases used clarithromycin- or metronidazole-containing triple therapy without drug sensitivity testing. The 34 (68.0%) other cases met the normalization principle recommended by the *Fifth Chinese National Consensus Report on the Management of Helicobacter pylori Infection* (Refer to previous regimens; do not repeat the original regimen; do not repeat the application of clarithromycin or levofloxacin; optimize dosage when repeatedly using metronidazole; and perform drug sensitivity testing before using clarithromycin- or metronidazole-containing triple therapy).[4]

Eradication rate

Among all 50 patients, there were four failures based on the ^{13}C-UBT and one patient changed to another antibiotic because of an allergy to furazolidone [Table 4]. Thus, the eradication rate was 92.0% in the ITT analysis, and 91.8% in the PP analysis.

Adverse effects

A total of 10 patients experienced adverse effects during treatment [Table 5]. Four cases had mild dizziness, three cases complained of dry mouth, two cases experienced skin rashes, one case complained of loose stools, and one case complained of mild foot pain. All of these adverse effects were mild, did not significantly affect the quality of life, and ended after cessation of the antibiotic regimen. All patients with adverse effects completed their treatments, except for one patient who changed medications because of a skin rash. In addition, all 10 of these patients had negative results for the ^{13}C-UBT.

DISCUSSION

More than 50% of people worldwide are infected with *H. pylori*, a pathogen associated with several human diseases.

Table 3: Previous rescue regimens used to treat *H. pylori* infections

Regimen	A	B	C	D	E	F
n (%)	2 (4.0)	6 (12.0)	3 (6.0)	2 (4.0)	3 (6.0)	34 (68.0)

A: Repeated use of the original regimen; B: Repeated use of clarithromycin or levofloxacin; C: Repeated use of metronidazole without dose optimization; D: Use of clarithromycin- or metronidazole-containing triple therapy without drug sensitivity testing; E: Use of antibiotics not in the recommended guidelines (gentamicin, erythromycin, or cefaclor); F: Use of a regimen meeting the normalization principle recommended by the Fifth Chinese National Consensus Report on the Management of Helicobacter pylori Infection.[4]

Our retrospective study of patients who experienced at least two *H. pylori* eradication failures indicates that 10.0% had atrophic gastritis, 74.0% had non-atrophic gastritis, and 16.0% had peptic ulcers. Eradication of *H. pylori* is considered essential for resolving symptoms of dyspepsia,[9,10] curing peptic ulcer,[11] delaying or reversing the progress of atrophic gastritis,[12] preventing gastric carcinoma,[13,14] and curing or alleviating gastric mucosa-associated lymphoid tissue (MALT) lymphoma.[15] The increased use of antibiotic treatments for *H. pylori* has increased the rates of antibiotic resistance. In particular, *H. pylori* has high resistance to metronidazole, clarithromycin, and levofloxacin in certain geographic regions, but is generally not resistant to amoxicillin, tetracycline, and furazolidone.[5-7] However, metronidazole, clarithromycin, levofloxacin, and amoxicillin are the main antibiotics used to eradicate *H. pylori*.

Among our 50 patients, 82.0% used clarithromycin, 64.0% used levofloxacin, 60.0% used metronidazole, and 84.0% used amoxicillin. We expected that the high utilization rates of clarithromycin, metronidazole, and levofloxacin will lead to further increases in drug resistance and treatment failures. Thus, it was important to choose an effective rescue regimen after the failure of initial treatment. The latest consensus report proposed an *H. pylori* normalization treatment which says: do not repeat the original regimen, do not repeat the application of clarithromycin or levofloxacin, optimize dosage when repeatedly using metronidazole, and perform drug sensitivity testing before using clarithromycin- or metronidazole-containing triple therapy.[4] All of our patients had at least two eradication failures, and only 68.0% of the previous rescue regimens met this normalization principle. The improper clinical use of antibiotics may be a major reason for the repeated eradication failures.

Drug sensitivity testing is recommended for patients with multiple eradication failures,[15] although it is not

Table 4: *H.pylori* eradication rate in patients receiving a 2-week probiotic pretreatment followed by an antibiotic regimen

	n	ITT (95% CI)	PP (95% CI)
Total	50		
Successful	46	92.0 (84.0-98.0)	91.8 (83.7-98.0)
Failure	4		
Change of drug	1		

ITT: Intention-to-treat; PP: Per-protocol

Table 5: Adverse effects in patients receiving a 2-week probiotic pretreatment followed by an antibiotic regimen

	n	% (95% CI)
Loose stool	1	2.0 (0.0-6.0)
Dizziness	4	8.0 (2.0-16.0)
Skin rash	2	4.0 (0.0-10.0)
Foot joint pain	1	2.0 (0.0-6.0)
Dry mouth	3	6.0 (0.0-12.0)
Total	10	20.0 (10.0-32.0)

CI: Confidence interval

widely performed in China due to the high cost and long time needed to obtain results. The European consensus recommends the use of tetracycline- and metronidazole-containing quadruple regimen for rescue treatment of *H. pylori* infection.[16] *H. pylori* in China has a relatively high resistance rate to metronidazole, but a low resistance rate to furazolidone, so multiple consensus statements recommend furazolidone.[8,4] In addition, considering that some patients have amoxicillin allergies, tetracycline and furazolidone are used together as rescue antibiotics.

H. pylori has a low rate of resistance to tetracycline and previous studies reported that tetracycline-containing bismuth quadruple therapy can achieve a high eradication rate.[17-19] The common adverse effects of tetracycline therapy are gastrointestinal symptoms (nausea, emesis, and epigastric discomfort), allergic reactions (papules and erythema), damage to the liver and kidneys, and occasionally hemolytic anemia and certain other rare conditions. Furazolidone is a nitrofuran antibiotic that has strong antibacterial effects against many gram-positive and gram-negative bacteria, can accumulate to high levels in the gastrointestinal tract,[20] and has no cross-resistance to metronidazole.[20,21] Furazolidone has a resistance rate below 1%, and the treatment of *H. pylori* infection with furazolidone generally has a high eradication rate.[22,23] The most common adverse effects of furazolidone are nausea, vomiting, diarrhea, anorexia, skin rash, headache, dizziness, drug fever, and hypotension, although hemolytic anemia, jaundice, and polyneuritis occur occasionally. A comparison of regimens with different doses of furazolidone shows that such side effects are more common when using a 10-day-course and at high doses (200 mg b.i.d.).[24-26] The recommended dose of furazolidone is 100 mg b.i.d., and an increase to 100 mg t.i.d. improves efficacy but decreases safety.[4] The patients in the present study received a furazolidone dose of 100 mg b.i.d. for 10 days.

Relatively, few studies have examined the efficacy and safety of the tetracycline- and furazolidone-containing quadruple regimen for the treatment of refractory *H. pylori*, and there are limited applications in the clinic. Lu *et al*. reported that the eradication rate following 14 days of tetracycline (500 mg, tid)- and furazolidone (100 mg, t.i.d)-containing bismuth quadruple regimen was 96.1% when used as rescue therapy and that the side effects were mainly nausea, abdominal pain, diarrhea, and dizziness.[27] In 2014, Hu *et al*. showed that the eradication rate following 14 days of tetracycline (750 mg, b.i.d)- and furazolidone (100 mg, b.i.d)-containing quadruple regimen was also more than 90% in patients who had initial eradication failure, and that the incidence of side effects (mainly epigastric discomfort, dizziness, drug fever, and skin rash) was 32%.[28]

Chinese and other consensus guidelines suggest that the use of probiotics may reduce some of the adverse effects of antibiotic therapy, by modulating the gastric microenvironment, although it is still controversial whether probiotics reduce the eradication rate of *H. pylori*.[4,15,29] Several meta-analyses of randomized-controlled trials (RCTs)[20,30-32] reported that probiotic supplements reduce the side effects associated with antibiotic-based *H. pylori* eradication therapies, and that there were encouraging results with *Lactobacillus spp.*, *Saccharomyces boulardii*, and *Bacillus clausii*. Other research with different *Lactobacillus* strains, *Bifidobacterium* strains, and *S. boulardii* also reported that these probiotics may have beneficial effects on *H. pylori* eradication.[33,34] In this study, we examined the influence of probiotics on the safety and efficacy of antibiotic therapy by giving patients a 2-week course with compound *L. acidophilus* before beginning the antibiotic regimen. The rate of side effects was found to be 20%, mainly dizziness, dry mouth, and skin rash. Only one patient changed treatment because of a skin rash, and all of the side effects resolved after completion of the antibiotic regimen. Compared with previous studies that did not administer probiotics,[21,22] a significantly lower rate of gastrointestinal discomfort was found, possibly because the prior probiotic treatment regulated gastrointestinal microbiota.

The eradication rate in our patients was 92.0% based on ITT analysis and 91.8% based on PP analysis. We speculate that the high eradication rate in patients who had multiple eradication failures may be due to the addition of the 2-week course of probiotics prior to the quadruple therapy. Probiotics can improve the gastric microenvironment, and decrease *H. pylori* load and activity, thereby increasing the efficacy of subsequent antibiotics.[32,35,36] Most studies examining the use of probiotics in patients with *H. pylori* infections focused on the co-administration of probiotics with antibiotics, and fewer reports have examined the effect of pretreatment with probiotics. Our previous research first reported that the administration of compound *L. acidophilus*

for 2 weeks, either before or after triple therapy, improved the eradication rates.[37] In addition, pretreatment with 2 weeks of *B. infantis* before standard triple therapy increased the eradication rate from 68.9% to 90.5%.[38]

Although our results showed that pretreatment with 2 weeks of probiotics prior to 10-day quadruple therapy was associated with good efficacy and safety in patients with repeated eradication failures, this study was a retrospective, single-center trial without a control group. Thus, it is necessary to develop controlled trials to confirm the benefits of probiotics in patients receiving antibiotic regimens for the treatment of *H. pylori* infections. However, because the eradication rate from tetracycline- and furazolidone-containing quadruple therapy is very high, large samples would be needed to identify a statistically significant difference. In addition, to further analyze the beneficial effects of probiotics on gastric microecology, it is necessary to study gene-level changes in the gastric microbiota following the use of probiotics.

CONCLUSIONS

Patients who have failed multiple *H. pylori* eradication regimens may benefit from pretreatment with probiotics followed by a combined tetracycline- and furazolidone-containing quadruple regimen to achieve a high eradication rate and limited adverse effects.

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Conflicts of interest
There are no conflicts of interest.

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