

Clinical Outcomes of Standard Triple Therapy Plus Probiotics or Concomitant Therapy for *Helicobacter pylori* Infection

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Background/Aims: The efficacy of standard triple therapy (STT) in treating *Helicobacter pylori* infection has decreased. Many investigators have attempted to increase the eradication rate. We investigated the outcomes of concomitant therapy (CT) and STT combined with probiotics (STP) as a first-line treatment for *H. pylori* infection. **Methods:** We reviewed the medical records of 361 patients who received either STP (n=286) or CT (n=75). The STP group received STT combined with a probiotic preparation for 1 week. The CT group received STT and metronidazole for 1 week. **Results:** The intention-to-treat and per-protocol eradication rates were 83.6% (95% confidence interval [CI], 79.0 to 87.7) and 87.1% (95% CI, 81.2 to 89.7) in the STP group and 86.7% (95% CI, 78.7 to 93.3) and 91.4% (95% CI, 83.6 to 97.1) in the CT group (p=0.512 and p=0.324), respectively. The frequency of adverse effects was higher in the CT group (28.2%) than in the STP group (12.8%) (p=0.002). **Conclusions:** STP and CT are encouragingly efficacious as first-line treatments for *H. pylori* infection. Therefore, adding probiotics to STT may be a feasible option to avoid side effects. (**Gut Liver 2018;12:165-172**)

Key Words: *Helicobacter pylori*; Probiotics; Metronidazole

INTRODUCTION

Helicobacter pylori is a gram-negative, flagellated bacterium that is often found on the luminal surface of the gastric epithelium. It is well known as the main cause of gastritis, gastroduodenal ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.¹ In South Korea, the rate of *H. pylori* infection is 59.6%, which is higher than that in Western countries.² Furthermore, gastric cancer is one of the most common cancers

in South Korea, in contrast with other countries.^{2,3} To prevent gastric cancer, it is useful to eradicate *H. pylori* infection. In this regard, standard triple therapy (STT), a combination treatment that involves a proton-pump inhibitor (PPI), amoxicillin, and clarithromycin, is the most commonly recommended first-line therapy.^{4,5}

In recent years, the efficacy of STT for *H. pylori* eradication has decreased. The most important cause of this decrease may be resistance to antibiotics, especially to clarithromycin.⁶ To circumvent this decrease in the eradication rate of STT, various methods have been considered; for instance, some clinicians have added probiotics or metronidazole to the STT.^{7,8}

Most specifically, concomitant therapy (CT) is a non-bismuth quadruple-based therapy wherein patients are treated using omeprazole, metronidazole, amoxicillin, and clarithromycin for 5 to 7 days. Previous studies have demonstrated that CT has better results than STT.⁹⁻¹¹ In South Korea, it is standard practice to use CT for 7 or 14 days.¹² However, the country is known to have a high rate of antibiotic resistance. Specifically, resistance rates against clarithromycin, amoxicillin, and metronidazole in 2011 to 2012 isolates were 16.0%, 2.1%, and 56.3%, respectively, and antibiotic resistance is increasing rapidly.¹³ In addition, eradication rates are affected by patient compliance as well as antibiotic resistance. Metronidazole induces several side effects, particularly gastrointestinal symptoms. Patients receiving metronidazole have complained of nausea, vomiting, headache, and metallic taste.¹⁴ Such serious side effects can cause low patient compliance. For this reason, to avoid the side effects associated with CT for *H. pylori* infection, supplementation of probiotics to STT has been more recently used as an alternative. However, it is unclear whether probiotic supplementation is efficacious in *H. pylori* treatment. In the present study, we aimed to compare eradication rates and adverse events between CT and STT plus

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probiotic treatment for first-line *H. pylori* eradication. In addition, several types of probiotics are used recently. Subgroup analysis was performed in the STT combined with a probiotic (STP) group owing to the possibility of differences in outcomes depending on the type of probiotics.

We compared CT including metronidazole which has an increased antibiotic resistance rate and more side effects, with STP which is generally known to be safe and beneficial.

MATERIALS AND METHODS

1. Study population

We reviewed the medical records of patients who had been prescribed either STP or CT for *H. pylori* eradication at Incheon Sarang Hospital between March 2013 and February 2014. All patients were at least 18 years old, and none had ever received treatment for *H. pylori* infection. This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of Incheon Sarang Hospital (reg. no. 2015-02). The informed consent was waived.

The exclusion criteria were as follows: (1) the use of an H₂ receptor antagonist; (2) prescription of PPI or antibiotics in the previous 4 weeks; (3) use of a nonsteroidal anti-inflammatory drug in the 2 weeks before the ¹³C-urea breath test; (4) advanced gastric cancer; (5) previous gastric surgery; (6) systemic illness, such as chronic renal disease, or liver cirrhosis; (7) pregnancy; (8) age <18 years; or (9) insufficient data.

2. Study design

We reviewed the medical records of 361 patients who received either STP (n=286) or CT (n=75) for *H. pylori* eradication. The STP group received standard-dose PPI (rabeprazole, 20 mg), clarithromycin (500 mg), amoxicillin (1 g), and a probiotic preparation twice daily for 1 week. The probiotic bacterial culture used were either *Bacillus subtilis* combined with *Streptococcus*

faecium (STP-I) or freeze-dried *Lactobacillus casei* var. *rhamnosus* (STP-II). The CT group received a standard-dose PPI (rabeprazole, 20 mg), clarithromycin (500 mg), amoxicillin (1 g), and metronidazole (500 mg) twice daily for 1 week. Four weeks after the treatment period, the patients underwent a ¹³C-urea breath test to confirm *H. pylori* eradication.

The primary outcome of this study was the *H. pylori* eradication rate using either STP or CT. Treatment compliance and side effects were also assessed.

3. Diagnosis of *H. pylori* infection

H. pylori infection was defined as a positive result on histologic evaluation or the rapid urease test. Specimens were obtained through endoscopic biopsy, fixed with formalin, and confirmed with Giemsa staining. The rapid urease test was interpreted to be positive if the color of the gel changed to pink or red after 24 hours at room temperature.

4. ¹³C-urea breath test

An initial breath sample was obtained after a 4-hour fast, wherein 100 mg of ¹³C-urea powder (UBiTkkit; Otsuka Pharmaceutical, Tokyo, Japan) dissolved in 100 mL of water was administered orally. The second breath sample was obtained 20 minutes later, and the cutoff value was 2.6‰. The collected samples were analyzed using an isotope ratio mass spectrometer (UBiT-IR300; Otsuka Pharmaceutical).

5. Statistical analysis

Eradication rates were evaluated using intention-to-treat (ITT) and per-protocol (PP) analyses. The ITT analysis included all the assigned patients; patients with an unknown infection status were considered having eradication failure. The PP analysis excluded patients with an unknown *H. pylori* status after therapy, those who took less than 90% of the treatment dose, and those lost to follow-up or with missing data.

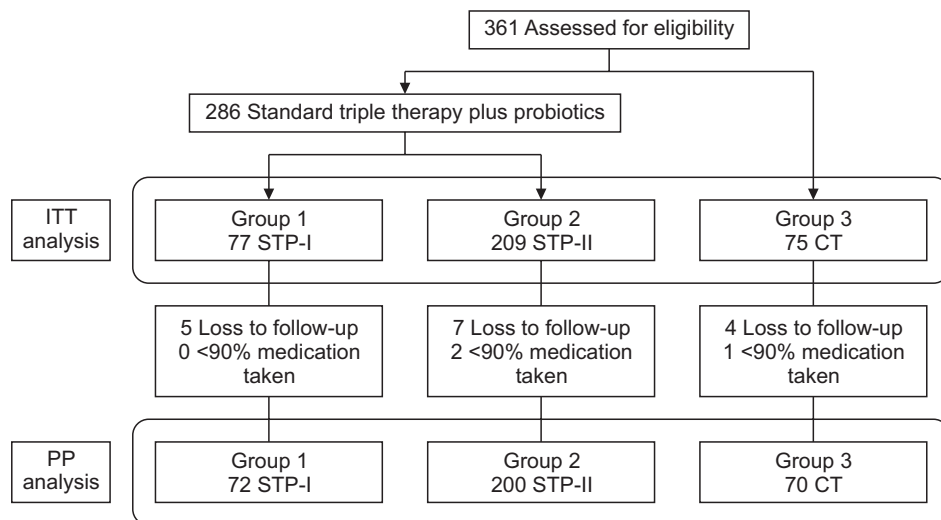


Fig. 1. Study protocol flow chart. ITT, intention-to-treat; PP, per-protocol; STP, standard triple therapy combined with probiotics; STP-I, *Bacillus subtilis* and *Streptococcus faecium* culture; STP-II, *Lactobacillus casei* var. *rhamnosus* culture; CT, concomitant therapy.

The outcomes were analyzed using the Student t-test, the chi-square test and, Fisher exact tests. Independent factors influencing treatment efficacy were evaluated by univariate analysis using the chi-square and Fisher exact tests; p-values <0.05 were considered statistically significant. Multivariate analysis was also performed to identify factors influencing the eradication rate. The analysis was conducted using PASW Statistics for Windows version 19.0 (IBM Corp., Armonk, NY, USA). Statistical power was calculated by using G power version 3.1 (Universität Düsseldorf, Düsseldorf, Germany), on the basis of a non-inferiority margin of 15% and an expected level for the primary outcome of 85% with a power of 0.80 and α -value of 0.05.

RESULTS

1. Study group characteristics

Fig. 1 shows the flow chart of patients who received each treatment regimen for *H. pylori* infection during the study period. A total of 361 patients were analyzed in the ITT population. Among them, 286 patients received STP: 77 were treated using STP-I and 209 using STP-II. Meanwhile, 75 patients received CT. Of all 361 patients, 272 from the STP group, and 70 from the CT group were analyzed using PP. Table 1 shows the baseline characteristics, which did not differ between groups.

2. Outcomes of CT and STP

H. pylori eradication rates, compliance, and side effects are listed in Tables 2 and 3. In the ITT analysis, the eradication rates

Table 1. Demographic Characteristics of the Study Population

Characteristic	STP		CT	p-value
	STP-I	STP-II		
No. of patients	77	209	75	
Age, mean \pm SD, yr	51.6 \pm 14.6	56.3 \pm 12.0	52.4 \pm 13.2	0.116
Sex (male/female)	42/35	114/95	38/37	0.549
Comorbidity, %				
Hypertension	13.0	17.2	25.3	0.064
Diabetes	7.8	6.7	8.0	0.764
Current smoking, %	29.9	23.0	24.7	0.883
Alcohol intake, %	36.4	34.4	26.7	0.175
Endoscopic diagnosis, %				
Presence of ulcer	83.1	62.7	76.0	0.189
Atrophic change*	35.1	60.3	52.0	0.817
Internal metaplasia, %	35.1	40.7	30.7	0.176

STP, standard triple therapy combined with probiotics; STP-I, *Bacillus subtilis* and *Streptococcus faecium* culture; STP-II, *Lactobacillus casei var. rhamnosus* culture; CT, concomitant therapy.

*Endoscopic finding of atrophic border consisting of visible transparent vessels or mucosal thinning.

Table 2. Eradication and Compliance rates in CT and STP Groups

	STP	CT	p-value	STP-I	STP-II	p-value
<i>H. pylori</i> eradication						
Intention-to-treat	239/286 (83.6)	65/75 (86.7)	0.512	58/77 (75.3)	181/209 (86.6)	0.022
Per-protocol	237/272 (87.1)	64/70 (91.4)	0.324	58/72 (80.6)	179/200 (89.5)	0.003
Compliance	272/286 (95.1)	70/75 (93.3)	0.541	72/77 (93.5)	200/209 (95.7)	0.447

Data are presented as number/number (%).

CT, concomitant therapy; STP, standard triple therapy combined with probiotics; STP-I, *Bacillus subtilis* and *Streptococcus faecium* culture; STP-II, *Lactobacillus casei var. rhamnosus* culture; *H. pylori*, *Helicobacter pylori*.

Table 3. Side Effects in CT and STP Groups

	STP (n=274)	CT (n=71)	p-value	STP-I (n=72)	STP-II (n=202)	p-value
Side effect	35 (12.8)	20 (28.2)	0.002	8 (11.1)	27 (13.4)	0.623
Dyspepsia	12 (4.4)	6 (8.5)		3 (4.2)	9 (4.5)	
Nausea/vomiting	8 (2.9)	5 (7.0)		1 (1.4)	7 (3.5)	
Dry mouth	7 (2.6)	4 (5.6)		1 (1.4)	6 (3.0)	
Diarrhea	4 (1.5)	3 (4.2)		1 (1.4)	3 (1.5)	
Abdominal pain	3 (1.1)	1 (1.4)		1 (1.4)	2 (1.0)	
Other	1 (0.4)	1 (1.4)		1 (1.4)	0	

Data are presented as number (%).

Since side effects were the cause of discontinuation of the medication, patients who did not take more than 90% of the medication were included in the analysis.

CT, concomitant therapy; STP, standard triple therapy combined with probiotics; STP-I, *Bacillus subtilis* and *Streptococcus faecium* culture; STP-II, *Lactobacillus casei var. rhamnosus* culture.

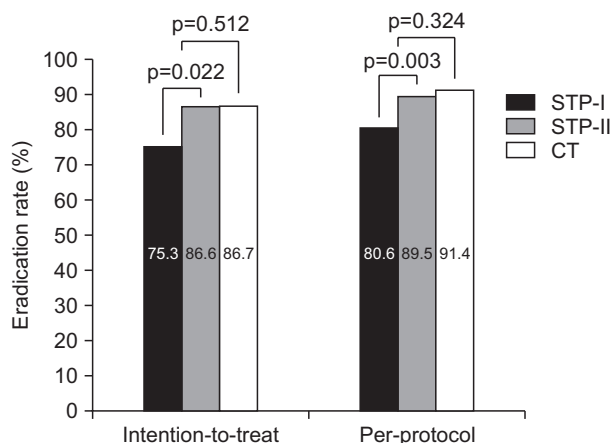


Fig. 2. Overall *Helicobacter pylori* eradication rates using standard triple therapy (STT) plus *Bacillus subtilis* and *Streptococcus faecium* culture (STP-I), STT plus freeze-dried *Lactobacillus casei* var. *rhamnosus* culture (STP-II), or concomitant therapy (CT).

were 83.6% (95% confidence interval [CI], 79.0 to 87.7) in the STP group and 86.7% (95% CI, 78.7 to 93.3) in the CT group. The eradication rates in the PP analysis were 87.1% (95% CI, 81.2 to 89.7) in the STP group and 91.4% (95% CI, 83.6 to 97.1) in the CT group. There was no significant difference in eradication rates between the STP and CT groups. However, in both the ITT and the PP analyses, there was a significant difference in the eradication rate between the STP-I and STP-II groups ($p=0.022$ and $p=0.003$, respectively). Fig. 2 shows the eradication rates in the STP and CT groups. Both the STP and CT groups showed good compliance (95.1% and 93.3%, respectively), and there was no significant difference in compliance between the two groups. There was also no significant difference in compliance between the STP-I and STP groups.

The CT group showed more serious adverse events than the STP groups. Common adverse events were dyspepsia and nau-

Table 4. Univariate Analysis of Clinical Factors Affecting the Eradication Rate in Each Group

Clinical factor	Standard triple therapy plus probiotics			Concomitant therapy		
	No. of patients	Eradication rate, %	p-value	No. of patients	Eradication rate, %	p-value
Sex			0.143			0.374
Male	125	89.9		36	94.4	
Female	149	84.0		35	88.6	
Presence of ulcer			0.796			0.016
(+)	193	87.6		56	96.4	
(-)	81	86.4		15	73.3	
Atrophic change			0.191			0.107
(+)	144	84.7		35	85.7	
(-)	130	90.0		36	97.2	
Intestinal metaplasia			0.726			0.658
(+)	110	86.4		22	95.5	
(-)	164	87.8		49	89.8	
HTN			0.212			0.625
(+)	43	81.4		17	88.2	
(-)	231	88.3		54	92.6	
Type 2 DM			1.000			0.006
(+)	17	88.2		6	50.0	
(-)	257	87.2		65	95.4	
Alcohol intake			0.366			0.166
(+)	97	89.7		18	83.3	
(-)	177	85.9		53	94.3	
Current smoking			0.545			0.611
(+)	66	89.4		16	87.5	
(-)	208	86.5		55	92.7	
Probiotics			0.048			
STP-I	72	80.6				
STP-II	202	89.6				

Patients who did not take more than 90% of the patients were included in the analysis because they were eradicated.

HTN, hypertension; DM, diabetes mellitus; STP, standard triple therapy plus probiotics; STP-I, *Bacillus subtilis* and *Streptococcus faecium* culture; STP-II, *Lactobacillus casei* var. *rhamnosus* culture.

Table 5. Multivariate Analysis of Clinical Factors Related to Eradication Failure in Each Group

Clinical factor	Coefficient	SE	OR (95% CI)	p-value
Standard triple therapy plus probiotics				
Age	0.04	0.02	1.04 (1.01–1.07)	0.011
Type of probiotic (STP-I vs STP-II)	0.92	0.39	2.50 (1.17–5.37)	0.019
Concomitant therapy				
Type 2 DM	5.02	1.62	152.12 (6.34–3,648.4)	0.002
Alcohol	3.56	1.40	35.08 (2.27–541.97)	0.011

SE, standard error; OR, odds ratio; CI, confidence interval; STP, standard triple therapy plus probiotics; STP-I, *Bacillus subtilis* and *Streptococcus faecium* culture; STP-II, *Lactobacillus casei* var. *rhamnosus* culture; DM, diabetes mellitus.

sea/vomiting. Other side effects reported were dry mouth, diarrhea, and abdominal pain, among others. There was no significant difference in side effects between STP-I and STP-II (Table 3).

3. Clinical factors affecting the efficacy of CT and STP

Univariate analysis was performed to identify clinical factors that affected the efficacy of STP and CT for *H. pylori* infection (Table 4). In the CT group, the eradication rate was significantly higher in patients with peptic ulcer than in those with only gastritis ($p=0.016$). Type 2 diabetes mellitus (DM) also affected the eradication rate in the CT group; specifically, patients with type 2 DM had a lower eradication rate than those without DM ($p=0.006$). In the STP group, the eradication rate differed depending on the kind of probiotics used. Specifically, the eradication rate in the STP-II group was higher than that in the STP-I group ($p=0.048$). No other factors in the STP group or CT groups affected the eradication response.

Multivariate analysis revealed that the eradication rate was inversely correlated with age in the STP group ($p=0.011$). The type of probiotic used also affected the eradication rate. In the CT group, type 2 DM and alcohol consumption lowered the eradication rate ($p=0.002$ and $p=0.011$, respectively). Table 5 shows the multivariate analysis of clinical factors related to the eradication failure in each group.

DISCUSSION

Previous studies have suggested that CT is more effective than STT for *H. pylori* eradication in areas where antibiotic resistance is high.^{9,15} In some countries, including South Korea, many clinicians prescribe CT for *H. pylori* eradication. However, CT has more side effects than STT, and some studies showed that probiotics were effective for the eradication of *H. pylori* in the Asian population including Korea. For this reason, some investigators have considered adding a probiotic regimen to STT instead.^{16–18}

In the present study, we investigated the effects of probiotics on *H. pylori* eradication. Probiotics have been shown to exert *in vitro* and *in vivo* bactericidal effects against *H. pylori*, suggesting that they interfere with *H. pylori* colonization.¹⁹ Even

though a meta-analysis showed that probiotics with STT plus a 14-day course of treatment did not improve the eradication of *H. pylori* infection, some meta-analyses showed that certain single-strain probiotics or multi-strain probiotics as adjunct therapy improve *H. pylori* eradication and decrease the adverse effect of antibiotics.^{7,20–22} Furthermore, a meta-analysis suggested that probiotic preparations during STT improved the eradication rate, particularly in Asian patients.²³ It is widely believed that probiotics can improve *H. pylori* eradication. In the ITT analysis, the overall eradication rates in the STP and CT groups were 83.6% and 86.7%, respectively, with no significant between-group difference ($p=0.512$). The eradication rates in both groups were higher than those reported in previous studies in Korea. This result may be due to the high compliance of the participants in this study, the different types of probiotics, and the relatively high presence of ulcers in this study.^{18,24–26} In our study, *Lactobacillus* strain was used predominantly, which seems to be more effective than other probiotics. In addition, the eradication rate was higher in the presence of ulcer; the relatively high proportion of ulcer in our study was due to the high eradication rate.

STP was not inferior to CT in terms of *H. pylori* eradication. Likewise, in our PP analysis, the overall eradication rate did not differ between the STP and CT groups. Because the resistance rates against metronidazole in Korea were relatively high compared with those in other countries, STP may be effective in populations with high resistance rates.

In the current study, STP showed a lower rate of side effects than CT. The most common side effect was dyspepsia; others were nausea, vomiting, and dry mouth, among others. Indeed, such side effects are one of the known limitations of CT. Conversely, probiotics exert a health benefit on the host beyond inherent basic nutrition.²⁷ Many studies have shown that probiotics are useful to prevent and treat not only gastrointestinal diseases such as necrotizing enterocolitis, antibiotic-associated diarrhea, and inflammatory bowel disease, but also upper respiratory tract infections, atopic eczema in cow's milk allergy, and infectious disease.^{28–32} In addition, probiotics are non-pathogenic microorganisms that rarely induce side effects.

We used two probiotics; *B. subtilis* combined with *S. faecium* (STP-I) and freeze-dried *Lactobacillus casei* var. *rhamnosus* cul-

ture (STP-II). *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* are representative strains of probiotics.³³ Among them, *Lactobacillus* and *Streptococcus* were the most commonly used probiotic types, and these two strains were selected for the study. STP-I showed somewhat lower eradication rates than STP-II in this study. A meta-analysis showed that multi-strain probiotics improved *H. pylori* eradication rates, prevented any adverse reactions, and reduced antibiotic-associated diarrhea, especially probiotics including *Lactobacillus* and *Bifidobacterium*.⁷ Another meta-analysis showed that *Lactobacillus*-containing probiotic supplementation increased the *H. pylori* eradication rate.³⁴ Although the study comparing the efficacy of *Lactobacillus* and other probiotics was not performed on a large population, *Lactobacillus* may be more effective for *H. pylori* eradication than other probiotics. A number of mechanisms have been proposed to explain the efficacy of probiotics in treating *H. pylori*. For example, probiotic bacteria may modulate *H. pylori* activity through both immunological and non-immunological mechanisms.³⁵ Furthermore, they may reduce the cytokine reaction, reinforce the gastric defense mechanism, interact with the host's innate immune system, and have direct bacteriostatic or bactericidal effects.³⁶ Therefore, the differences in the eradication rate seen in the present study may have arisen because different probiotics inhibit *H. pylori* colonization through different mechanisms.

In addition, various clinical factors may have affected the eradication rate in each group. Patients who did not have ulcerous changes showed a lower eradication rate in the CT group by univariate analysis. That is, the present study indicated that gastric ulcer is a predictor of successful eradication. In a similar regard, previous studies have shown that the eradication rates of STT (according to endoscopic stage) were significantly different in patients with gastric ulcer.³⁷ This may be because severe inflammatory reactions occur at an early stage after ulceration; this inflammation degrades the gastric mucus and epithelial layers, which may allow charged antibiotics in the gastric lumen to better penetrate the epithelium and alter vascular epithelial permeability, leading to better systemic delivery of drugs.³⁸

Type 2 DM was associated with poor *H. pylori* eradication in the CT group by both univariate and multivariate analysis. Various studies have reported a higher prevalence of *H. pylori* infection and a lower eradication rate in patients with DM.^{39,40} Although the association of *H. pylori* infection with DM is still controversial, this study showed that STP may be a better treatment for *H. pylori* infection than CT in patients who have an ulcer or type 2 DM.⁴¹ Alcohol consumption was also associated with resistance to eradication in the CT group. Alcohol has been shown to affect the mucosal barrier and histology of the stomach, and the inflammatory changes occur that influence *H. pylori*.⁴²

This study has several limitations. First, this was a retrospective study conducted at a single center. Second, the interview

regarding side effects after treatment was not well organized, and was therefore insufficient. Third, the study population was too small. However, when calculating statistical power, the number of patients was considered sufficient. The numbers of patients and controls required to demonstrate non-inferiority were calculated. The calculated sample size was 69 for each intervention group to show the non-inferiority of STP, compared with CT. Nonetheless, this study provides valuable insight into the treatment of *H. pylori* infection because it is the first study to compare CT with STT plus probiotics. Finally, we did not test antibiotic susceptibility which may affect the clinical outcome of *H. pylori* eradication therapy.

In conclusion, STP and CT showed encouraging efficacies as first-line treatments for *H. pylori* infection. To avoid side effects, it may be feasible to add probiotics to STT. Specifically, freeze-dried *Lactobacillus casei var. rhamnosus* culture showed better efficacy than *B. subtilis* and *S. faecium* culture in the STP group. Ulcerous changes and type 2 DM were found to be important determinants of eradication in the CT group. Multivariate analysis revealed that, in the STP group, age and type of probiotic were independently predictive of eradication failure. In the CT group, the independent predictive factors were type 2 DM and alcohol intake.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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