

Pretreatment with *Lactobacillus*- and *Bifidobacterium*-containing yogurt can improve the efficacy of quadruple therapy in eradicating residual *Helicobacter pylori* infection after failed triple therapy^{1–3}

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ABSTRACT

Background: *Lactobacillus*- and *Bifidobacterium*-containing yogurt (AB-yogurt) can suppress *Helicobacter pylori*. Improvement of the eradication rate by quadruple therapy of residual *H. pylori* after failed triple therapy is needed.

Objective: We tested whether prior treatment with AB-yogurt improved the efficacy of quadruple therapy in eradicating residual *H. pylori* after failed triple therapy.

Design: One hundred thirty-eight patients in whom triple therapy failed were enrolled for a culture study of *H. pylori* to assess antimicrobial resistance. These patients were then randomly assigned in equal numbers to either a yogurt-plus-quadruple therapy group or a quadruple therapy-only group. The patients received 1 wk of quadruple therapy with or without a 4-wk pretreatment with AB-yogurt (400 mL/d). In the yogurt-plus-quadruple group, excessive $\delta^{13}\text{CO}_2/\text{mL}$ values of the ^{13}C -urea breath test were collected before and every 2 wk during the 4-wk ingestion of yogurt. For both groups, a ^{13}C -urea breath test was conducted ≥ 6 wk after the quadruple therapy to assess the outcome of residual *H. pylori* eradication.

Results: For the patients in the yogurt-plus-quadruple therapy group infected with either antibiotic-sensitive or -resistant *H. pylori*, the excessive $\delta^{13}\text{CO}_2/\text{mL}$ values of the ^{13}C -urea breath test were significantly decreased after the 4-wk ingestion of AB-yogurt ($P < 0.0001$). The yogurt-plus-quadruple therapy group had a higher *H. pylori* eradication rate than did the quadruple therapy-only group (intention-to-treat analysis: 85% compared with 71.1%, $P < 0.05$; per-protocol analysis: 90.8% compared with 76.6%, $P < 0.05$).

Conclusion: A 4-wk pretreatment with AB-yogurt can decrease *H. pylori* loads despite antimicrobial resistance, thus improving the efficacy of quadruple therapy in eradicating residual *H. pylori*. *Am J Clin Nutr* 2006;83:864–9.

KEY WORDS *Helicobacter pylori*, triple therapy, quadruple therapy, *Lactobacillus*, *Bifidobacterium*, yogurt

INTRODUCTION

Triple therapy, which combines a proton pump inhibitor with 2 antibiotics, is the current standard of therapy for eradicating *Helicobacter pylori* (1–5). Amoxicillin and clarithromycin plus a proton pump inhibitor is the first-line triple therapy choice recommended by the Maastricht-2 Consensus Group (1). However, this first-line regimen still has a 10–23% failure rate (2–8) and needs an effective rescue regimen, such as quadruple therapy (1, 9, 10). Many clinical studies have applied versatile regimens

of quadruple therapy to eradicate primary *H. pylori* infection; these regimens have eradication rates from 70% to 90% (9–12). Moreover, applying quadruple therapy as a second-line therapy to rescue the failure of amoxicillin-omeprazole-clarithromycin triple therapy may achieve only ≈ 75 –85% eradication rate (12, 13). Therefore, the application of new approaches to improve the efficacy of quadruple therapy as either the first line or, especially, the second line regimen is clinically important.

Increasing evidence has shown the direct suppression of *H. pylori* urease or growth in vitro by *Lactobacillus acidophilus*- and *Bifidobacterium*-containing yogurt (AB-yogurt) (14–16). Moreover, such yogurt can also exert therapeutic properties and improve the eradication rate of primary therapy against *H. pylori* in infected clinical patients (7, 15). In the present study, we investigated whether pretreatment with AB-yogurt improved the efficacy of quadruple therapy in the eradication of residual *H. pylori* after failed triple therapy.

Furthermore, the influence of antimicrobial-resistant *H. pylori* on the efficacy of quadruple therapy needs additional validation (9, 17), especially in areas of high endemic metronidazole-resistant *H. pylori*. Thus, the present study also tested whether the eradication efficacy of quadruple therapy against residual metronidazole-resistant *H. pylori* could be improved by pretreatment with AB-yogurt.

SUBJECTS AND METHODS

Patients and study design

One hundred thirty-eight dyspeptic patients with an initial diagnosis of duodenal ulcers or gastritis were consecutively enrolled after 1-wk of triple therapy (1 g amoxicillin, 500 mg clarithromycin, and 20 mg omeprazole twice daily) failed to eradicate *H. pylori* infection. The present study fulfilled the

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Consolidated Standards of Reporting Trials guidelines and was approved by the human ethics and research committee of our institute in Taiwan. The patients who were enrolled into the present study had good compliance (≥ 5 d) during the 1-wk triple therapy. Failure of triple therapy was defined as a positive ^{13}C -urea breath test (UBT), with an excessive $\delta^{13}\text{CO}_2/\text{mL}$ (ECR) value >2.5 (18). The same breath test was performed for each patient during the fifth week, after cessation of triple therapy. Medications, including proton pump inhibitors, bismuth salt, and antimicrobial agents, were withheld for ≥ 4 wk before each UBT, to reduce the possibility of interference with the results. Patients with evident milk intolerance were not included in the present study.

After obtaining informed consent, each of the 138 patients in whom triple-therapy failed underwent an endoscopy to obtain *H. pylori* cultures, as previously described (9, 13, 19). The successfully collected *H. pylori* isolates were then checked for the presence of antimicrobial resistance, which was defined by the minimal inhibitory concentration of an E-test (9, 13). Each patient underwent a gastric biopsy procedure to reconfirm *H. pylori* status by histology, regardless of a positive UBT. Patients with negative results for both histology and cultures obtained during the follow-up endoscopy, those known to be allergic to bismuth or metronidazole, or those having gastric malignancy were excluded. None of the 138 patients were excluded due to the above-mentioned conditions.

Helicobacter pylori

The infected patients were randomly assigned to 1 of 2 groups and received either 1-wk quadruple therapy with (yogurt-plus-quadruple therapy group) or without (quadruple therapy-only group) a 4-wk pretreatment supplement of *L. acidobacillus*– and *Bifidobacterium*-containing yogurt (AB-yogurt; President Enterprise Corporation, Tainan, Taiwan) for the eradication of *H. pylori*. The randomization was based on a prescheduled serial number. The AB-yogurt used in the present study was made with fermented milk with sugar, high-fructose corn syrup, pectin, galactooligosaccharide, and an approximately equal mixture of *L. acidophilus* La5, *Bifidobacterium lactis* Bb12, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus* at a concentration of $\geq 10^9$ bacteria/mL. The yogurt product containing the 2 specific isolates (*L. acidophilus* La5 and *Bifidobacterium lactis* Bb12) was previously validated to have a positive effect on *H. pylori* suppression (7, 15). In both groups, the regimen of 1-wk quadruple therapy, which included 1 g amoxicillin twice daily, 500 mg metronidazole twice daily, 20 mg omeprazole twice daily, and 120 mg bismuth subcitrate three times daily, was administered. In the yogurt-plus-quadruple therapy group, AB-yogurt was prescribed for each patient in dosages of 200 mL AB-yogurt twice daily for 4 wk (7). In contrast, the patients of the quadruple therapy-only group were prohibited to consume yogurt, although regular milk consumption was not prohibited during the study period. Moreover, all patients were instructed to maintain a regular dietary pattern and to avoid dairy products, honey, spicy foods, Chinese herbs, cranberries, and products with live lactic acid bacteria as much as possible during the study period (15).

In the yogurt-plus-quadruple therapy group, the ECR values of the UBT, which indirectly represented intragastric *H. pylori* loads, were serially collected before and every 2 wk during the 4-wk ingestion of yogurt. Drug compliance and side effects of the

rescue therapy were recorded at the clinics. The degree of drug compliance was categorized as “good” (7-d quadruple therapy completely ingested), “modest” (therapy ingested ≥ 5 d), and “poor” (therapy ingested <5 d), as previously described (9).

At least 6 wk after the rescue regimen, the UBT was repeated to check for *H. pylori* eradication. The staff that processed the UBTs was blinded to the patient’s grouping. For those with a negative result for the UBT after quadruple therapy, a repeat UBT was performed 3 mo after the rescue regimen ended to prevent a false negative result. Thus, both negative results on the UBT during the sixth week and third month were needed to define successful *H. pylori* eradication by the quadruple rescue therapy. Proton pump inhibitors and antibiotic medications were withheld from the subjects before the 6-wk test and for subjects who tested negative for *H. pylori* at 6 wk until the 3-mo follow-up test. To attain a statistical power of 0.8 and to achieve a 15% difference in the eradication rate between the 2 groups, the number of patients included had to be ≥ 100 and, thus, ≥ 50 patients per group.

Gastric biopsy samples for *Helicobacter pylori* culture and histology

For each patient, 2 pairs of gastric biopsy samples (each pair included one from the antrum and one from the lower body) were obtained during an endoscopy. Each pair of biopsy samples was sent for a culture and histologic staining (with haematoxylin and eosin) of *H. pylori* (13). Patients in whom gastric ulceration was found during the follow-up endoscopy were excluded. These 2 gastric biopsy samples were taken for *H. pylori* culture, as done in our previous studies (9, 13, 19). For each *H. pylori* isolate, the presence of clarithromycin, metronidazole, and amoxicillin resistance was defined by an E-test with a minimal inhibitory concentration of >1 , >1 , and >8 $\mu\text{g/mL}$, respectively (9, 13).

Statistics

Student’s *t* test, one-way analysis of variance (ANOVA) with Bonferroni correction, Bonferroni *t* test, chi-square test, and Fisher’s exact test were used, as appropriate, to determine parametric differences and nonparametric proportions. Pearson’s correlation coefficients were applied to test the correlation between the pretreatment ECR value and the difference between the 2 ECR values to check on 2 different time intervals. In addition, a 2-factor repeated-measures ANOVA was used for analysis of serial ECR measurements after AB-yogurt ingestion according to the clarithromycin resistance and metronidazole resistance status of the residual *H. pylori*. All tests of significance were two-tailed with a *P* value < 0.05 , and tests were conducted with SAS version 8.0 (SAS Institute Inc, Cary, NC) and SPSS version 8.0 (SPSS Inc, Chicago, IL) software programs. Data from all enrolled patients for rescue therapy were analyzed with an intention-to-treat analysis. The patients who stopped medication, had poor drug compliance, or who were lost to follow-up were excluded from the per-protocol (PP) analysis.

RESULTS

Demographic background and compliance with quadruple therapy of the study groups

All 138 enrolled patients had a positive histology of *H. pylori* infection and were randomly assigned in equal numbers to 1 of

TABLE 1The demographic characteristics, side effects, and drug compliance of the 2 study groups enrolled after failed triple therapy¹

Variables	Quadruple therapy group (n = 69)	Yogurt-plus-quadruple therapy group (n = 69)	P
Mean age (y)	46.4	48.9	NS
Women [n (%)]	31 (44.9)	30 (43.4)	NS
Endoscopic findings (n)			
DU:NUD	39:30	38:31	NS
Compliance [n (%)]			
Good (7 d)	38 (55.1)	42 (60.9)	NS
Modest (≥ 5 and < 7 d)	26 (37.7)	23 (33.3)	NS
Poor (< 5 d) ²	5 (7.2)	4 (5.8)	NS
Side effects (n)			< 0.05
Nausea or vomiting	14	6	
Constipation	15	6	
Diarrhea	18	9	
Metallic taste	18	6	
<i>Helicobacter pylori</i> isolates (n) ³			
MR:MS	21:28	22:29	NS
CR:CS	30:19	32:19	NS

¹ DU, duodenal ulcer; NUD, nonulcer gastritis; MR, metronidazole resistant; MS, metronidazole sensitive; CR, clarithromycin resistant; CS, clarithromycin sensitive.

² Includes the number of dropouts.

³ One hundred *H. pylori* isolates (49 from patients in the quadruple therapy group and 51 from the yogurt-plus-quadruple therapy group) were collected before rescue therapy.

the 2 study groups. No significant differences in demographic features, endoscopic diagnoses, and compliance with rescue therapy were observed between the 2 study groups ($P > 0.05$); side effects were more frequent in the quadruple therapy-only group than in the yogurt-plus-quadruple therapy group (Table 1).

Antimicrobial resistance of the residual *H. pylori* between the 2 study groups

One hundred *H. pylori* isolates were obtained from the 138 enrolled patients, including 49 isolates from the quadruple therapy-only group and 51 isolates from the yogurt-plus-quadruple therapy group. None of the 100 collected isolates were resistant to amoxicillin. No significant differences in the distributions of the clarithromycin- and metronidazole-resistant *H. pylori* isolates were observed between the 2 study groups (Table 1; $P > 0.05$).

Rescue efficacy of the quadruple therapy with and without AB-yogurt pretreatment

All 138 patients had histologies that were positive for residual *H. pylori* infection and received 1 wk of quadruple therapy. Excluded from the PP analysis were 4 patients in the yogurt-plus-quadruple therapy group (3 dropped out during follow-up and 1 showed poor drug compliance) and 5 patients in the quadruple therapy-only group (3 dropped out during follow-up and 2 showed poor drug compliance). Accordingly, 129 patients (65 patients in the yogurt-plus-quadruple therapy group and 64 patients in the quadruple therapy-only group) completed the rescue therapy protocol. The eradication rate for residual *H. pylori* was higher in the yogurt-plus-quadruple therapy group than in the quadruple therapy-only group (intention-to-treat analysis: 85.5% compared with 71.1%, $P < 0.05$; PP analysis: 90.8% compared with 76.6%, $P < 0.05$; Table 2).

Effect of metronidazole resistance on the eradication outcome

The present study additionally found that the patients infected with metronidazole-resistant *H. pylori* had a lower PP eradication rate with quadruple therapy than did the patients who were infected with metronidazole-sensitive *H. pylori* [57.8% (22 of 38 patients) compared with 90.5% (48 of 53 patients), $P < 0.01$ (2-tailed Fisher's exact test)].

AB-yogurt decreased the ECR of UBT indicating the suppression of *H. pylori* loads

No significant difference in the mean pretreatment ECR value of UBT was observed between the yogurt-plus-quadruple therapy group and the quadruple therapy-only group (16.9 ± 7.8 compared with $0.17.8 \pm 7.9$, $P > 0.05$). Of the 65 patients who completed the study design in the yogurt-plus-quadruple group, the ECR of wk 4, but not that of wk 2, was significantly lower

TABLE 2Eradication rates of rescue therapy for *Helicobacter pylori* infection¹

	Per-protocol analysis	Intention-to-treat analysis
Quadruple therapy only group		
[n (%)]	49 (76.6) ²	49 (71.1) ³
(95% CI)	(66.3, 86.9)	(60.4, 81.8)
Yogurt-plus-quadruple therapy group		
[n (%)]	59 (90.8) ⁴	59 (85.5) ³
(95% CI)	(83.8, 97.8)	(77.2, 93.8)

¹ Significantly different *H. pylori* eradication rates between the 2 study groups, $P < 0.05$ (chi-square test).

² Total n = 64.

³ Total n = 69.

⁴ Total n = 65.

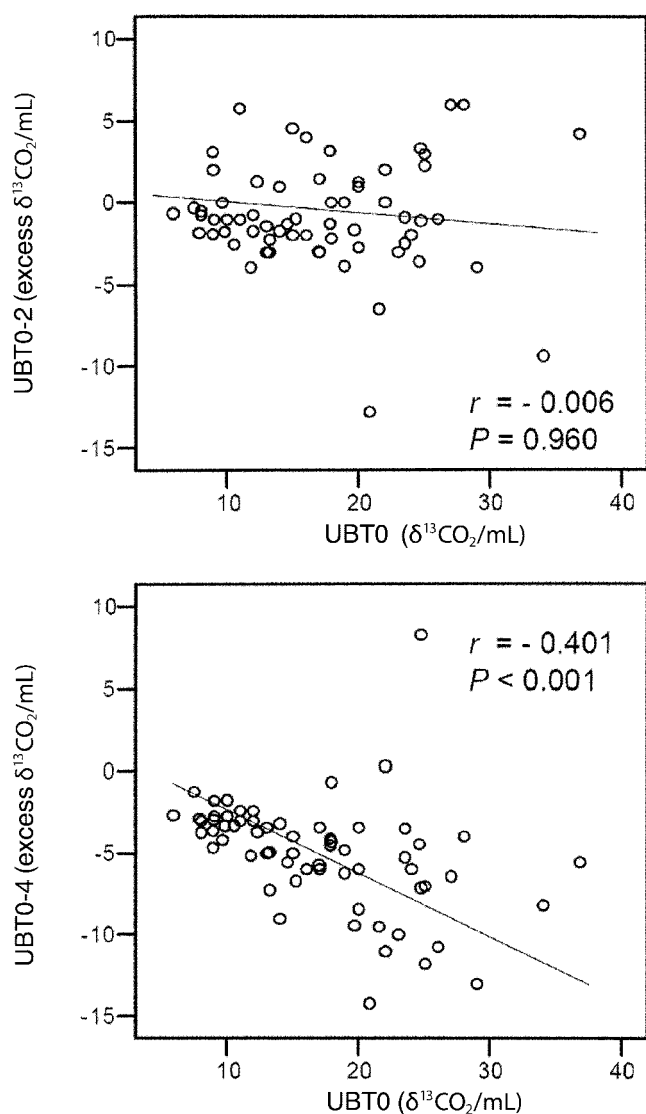


FIGURE 1. Correlation between urea breath test (UBT) values at week 0 (UBT0) and the difference between UBT0 values and values at week 2 (UBT0-2) or week 4 (UBT0-4) in the yogurt-plus-quadruple therapy group. $n = 65$ (○). The correlation between UBT0 and UBT02 was not significant (Pearson's correlation coefficient: $r = -0.006$; $P = 0.960$). The correlation between UBT0 and UBT04 was significant ($r = -0.401$, $P < 0.001$).

than that of wk 0 [11.8 ± 6.2 for week 4 compared with 16.9 ± 6.9 for week 0, $P < 0.001$; week 2 compared with week 0: 16.2 ± 7.6 compared with 16.9 ± 6.9 , $P > 0.5$ (Bonferroni t test)]. The ECR of week 4 was also lower than that of week 2 [11.8 ± 6.2 for week 4 compared with 16.2 ± 7.6 for week 2, $P < 0.001$ (Bonferroni t test)].

The pretreatment ECR value did not show a significant correlation with the difference in the ECR value between week 0 and week 2 ($P = 0.960$, $r = -0.006$; **Figure 1**). In contrast, after the 4-wk ingestion of AB-yogurt, a significant negative correlation was observed between the baseline ECR value and the difference in the ECR value from week 0 to week 4 ($P < 0.001$, $r = -0.401$; **Figure 1**).

The serial ECR values at the different time sessions for patients infected with different *H. pylori* resistant strains is shown

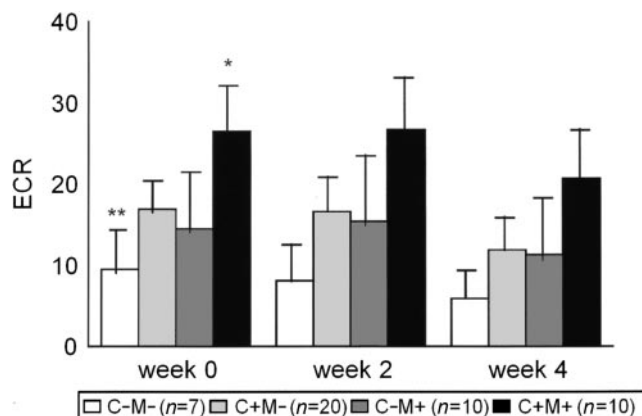


FIGURE 2. Serial mean ($\pm$ SD) excess $\delta^{13}\text{CO}_2/\text{mL}$ (ECR) values of the urea breath test performed at enrollment into the study (week 0), week 2 (2 wk after yogurt ingestion), and week 4 (4 wk after yogurt ingestion) are listed for the patients infected by *Helicobacter pylori* isolates with different antimicrobial resistant status, including clarithromycin- and metronidazole-sensitive *H. pylori* infection (C-M-; $n = 7$), clarithromycin-resistant and metronidazole-sensitive *H. pylori* infection (C+M-; $n = 20$), clarithromycin-sensitive and metronidazole-resistant *H. pylori* infection (C-M+; $n = 10$), and clarithromycin- and metronidazole-resistant *H. pylori* infection (C+M+; $n = 10$). *The ECR of the C+M+ subgroup was significantly higher than the ECRs of the other 3 subgroups at week 0, $P < 0.001$ (one-way ANOVA with Bonferroni correction). **The ECR of the C-M- subgroup was significantly lower than that of the C+M- subgroup at week 0, $P = 0.004$ (one-way ANOVA with Bonferroni correction). A 2-factor repeated-measures ANOVA uncovered a significant main effect of time ($P < 0.001$) but no significant main effect of resistance status on the ECR values after AB-yogurt ingestion; the status-by-time interaction was not significant for the ECR values after AB-yogurt ingestion.

in **Figure 2**. The ECR of the clarithromycin- and metronidazole-resistant subgroup was significantly higher than that of the other 3 subgroups at week 0 ($P < 0.001$, one-way ANOVA with Bonferroni correction). The ECR values after AB-yogurt ingestion according to the clarithromycin and metronidazole resistance status of residual *H. pylori* decreased significantly over time ($P < 0.001$, 2-factor repeated-measures ANOVA) and all were not related to the presence or absence of either metronidazole or clarithromycin resistance ($P > 0.05$).

DISCUSSION

In the present study, a 4-wk pretreatment with AB-yogurt before quadruple therapy improved the eradication rate of residual *H. pylori* after failed triple therapy (Table 2). Moreover, in the yogurt-plus-quadruple therapy group, the ECR values of UBT were significantly decreased in the clarithromycin- and metronidazole-resistant *H. pylori* residuals after a 4-wk ingestion of AB-yogurt, which indicated the suppression of residual *H. pylori* loads (Figures 1 and 2). These findings provide support for the ingestion of AB-yogurt for 4 wk before the start of quadruple therapy to significantly decrease both antibiotic-sensitive and -resistant residual *H. pylori* loads, thus obtaining improved rescue efficacy after failed triple therapy.

Several studies have confirmed that supernatant fluids and food products that contain certain *Lactobacillus* species can reduce *H. pylori* densities in humans (20, 21). Wang et al (15) showed that the UBT values of primary *H. pylori*-infected humans could be significantly decreased after ≥ 4 wks of AB-yogurt ingestion. However, in the present study, we found that

the suppression effect of AB-yogurt remained significant for residual *H. pylori* loads after failed triple therapy. These data suggest an important clinical application of AB-yogurt in improving the efficacy of rescue therapy against residual *H. pylori*, which is usually unmanageable during rescue treatment due to a high prevalence of antimicrobial resistance.

At least 6 possible mechanisms can explain how *H. pylori* loads are decreased by the AB-yogurt. First, on the basis of the findings by Wang et al (15), there may be a direct competition between *H. pylori* and the *Lactobacillus* and *Bifidobacteria* in AB-yogurt for nutrients, thus resulting in a reciprocal inhibition between the different bacterial species. Second, *Lactobacillus* may directly inhibit *H. pylori* attachment to the gastric epithelium (22). Third, attachment of *Lactobacillus* and *Bifidobacterium* in AB-yogurt to the gastric epithelium may produce a barrier effect and thereby decrease *H. pylori* attachment. Fourth, *Lactobacillus* and *Bifidobacterium* have been found to exert a positive immunomodulatory effect in the gut (23–25) and thus could suppress gastric *H. pylori* loads. Fifth, ingestion of *Bifidobacterium*-containing yogurt counteracts the hydrogen-producing action of coliform bacteria in the bowels, which mediate increased colonization of *H. pylori* loads in the stomach (26). Accordingly, a decrease of hydrogen production by coliform bacteria in the bowel may have decreased *H. pylori* loads. Finally, the direct inhibition of urease, which is an important colonization factor for *H. pylori*, by *Lactobacillus* and *Bifidobacterium* may have played some role.

In the present study, we excluded patients with milk intolerance before randomization. Only 4 patients in the yogurt-plus-quadruple therapy group did not complete the study design. However, only 1 of the 4 patients had poor tolerance of the 4-wk ingestion of AB-yogurt. This indicates that pretreatment with AB-yogurt can be well tolerated in milk-tolerant patients who have residual *H. pylori* after failed triple therapy. Moreover, the adverse effects of quadruple therapy were evidently lower in the yogurt-plus-quadruple therapy group than in the quadruple therapy-only group (Table 1). These data provide additional support for the finding that pretreatment with AB-yogurt may diminish the side effects of quadruple therapy while serving as a rescue regimen for failed triple therapy.

High prevalence rates of antimicrobial resistance were observed in the *H. pylori* isolates of patients with failed triple therapy (Table 1). In both study groups, the patients who were infected with metronidazole-resistant *H. pylori* had a lower PP eradication rate with quadruple therapy than those who were infected with metronidazole-sensitive *H. pylori* ($P < 0.05$). This finding indicates that metronidazole resistance is still a major factor in determining the outcome of quadruple therapy as a rescue regimen. Therefore, it would be interesting to investigate whether ingestion of AB-yogurt can decrease bacterial loads of metronidazole-resistant *H. pylori* isolates.

A 2-factor repeated-measures ANOVA showed a significant main effect of time ($P < 0.001$), but no significant main effect of resistance status or status-by-time interaction, on the ECR value after AB-yogurt ingestion. These data indicate that the *H. pylori* loads could be significantly decreased in patients infected by metronidazole resistant isolates as well as other isolates. After the 4-wk ingestion of AB-yogurt, a significant negative correlation was found between the baseline ECR value and the difference in ECRs between week 0 and week 4 ($P < 0.001$, $r = -0.401$; Figure 1). These data suggest that more reduction in the

ECR value after a 4-wk ingestion of AB-yogurt occurs in the patients with a higher initial ECR value at baseline than in those with a lower ECR value at baseline. Therefore, combining 4-wk AB-yogurt can decrease the bacterial loads of residual *H. pylori* despite their antimicrobial resistance. The clinical administration of such pretreatment is widely helpful for those with high residual bacterial loads or with any antimicrobial-resistant *H. pylori* isolates.

Because the present study included patients with refractory *H. pylori* after failure of a standard first line therapy, we measured the efficacy of a fortified yogurt (yogurt plus probiotic isolates together) instead of simply an unfortified yogurt. Nevertheless, it is of scientific interest to know whether the yogurt or the probiotic was more effective in increasing the success rate. Because yogurt is part of daily food consumption, it would be interesting to know whether yogurt types with or without different probiotic isolates exert different effects. Moreover, because different quadruple therapies may yield different rescue rates for failed triple therapy (9, 13, 17), it is prudent to determine whether supplementation of such yogurt to different quadruple therapy regimens results in the same positive rescue effect. In conclusion, ≥ 4 -wk, but not 2-wk, pretreatment with AB-yogurt can decrease bacterial loads of *H. pylori* despite their antimicrobial resistance and can thus improve the efficacy of quadruple therapy in the eradication of residual *H. pylori* after failed triple therapy. 

B-SS was responsible for obtaining grant funding and for conducting the entire study. H-CC and A-WK collected cases for clinical therapy. Y-JY was responsible for the urea breath test analyses. S-TW served as a statistical consultant for the analyses of the study results. J-JW and H-BY reviewed the histology results. J-JW was responsible for checking the status of *H. pylori* antimicrobial resistance. None of the researchers had any conflicts of interest.

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