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Impact of supplement with Lactobacillus- *and* Bifidobacterium-*containing yogurt on triple therapy for* Helicobacter pylori *eradication*

B. -S. SHEU*, J. -J. WU†, C. -Y. LO†, H. -W. WU*, J. -H. CHEN*, Y. -S. LIN‡ & M. -D. LIN§
*Departments of *Internal Medicine, †Medical Technology, Institutes of ‡Microbiology and Immunology, and §Biochemistry, Medical College, National Cheng Kung University, Tainan, Taiwan*

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SUMMARY

Aim: To test whether supplements of *Lactobacillus*- and *Bifidobacterium*-containing yogurt (AB-Yogurt) affect the success of *Helicobacter pylori* eradication.

Methods: One hundred and sixty *H. pylori*-infected patients were randomized into a triple-plus-yogurt group or a triple-only group, receiving 1 week of triple therapy with and without supplements of AB-Yogurt, respectively. In the triple-plus-yogurt group, AB-Yogurt was continued for 4 weeks after triple therapy. Eight weeks later, patients were assessed for the success of *H. pylori* eradication. The stool samples of 22 randomly selected patients, 11 from each group, were provided on enrolment, at the first week and at the fifth week for evaluation of the percentage of *Bifidobacterium* in anaerobes.

Results: By intention-to-treat analysis, the triple-plus-yogurt group had a higher *H. pylori* eradication rate than the triple-only group (91% vs. 78%, $P < 0.05$). The per protocol *H. pylori* eradication rates were similar for both groups (93.5% vs. 89%, $P =$ N.S.). Only patients supplemented with AB-Yogurt showed restoration of the percentage of *Bifidobacterium* in the anaerobes of stools at the fifth week to the level in the stools on enrolment.

Conclusions: Supplement with AB-Yogurt can improve the intention-to-treat eradication rates of *H. pylori, and* can restore the depletion of *Bifidobacterium* in stools after triple therapy.

INTRODUCTION

One-week triple therapy, combining proton pump inhibitor plus two antibiotics, is currently regarded as the standard therapy for *Helicobacter pylori* eradication,[1, 2] and is well tolerated and simple to administer.[3–5] However, the eradication rates vary in the range 65–90%.[3–9] Poor patient compliance and bacterial resistance are the main factors contributing to treatment failure.[5, 10] Therefore, improvements in the eradication rate and drug compliance are needed in currently used, 1-week, proton pump inhibitor-based triple therapy. Moreover, the large dosages of 1-week antibiotic treatments may induce a change in the bowel flora and lead to gastrointestinal side-effects after triple therapy.[11, 12] Therefore, the restoration of the normal flora in the intestine, especially beneficial *Bifidobacterium* species, is also important in patients receiving triple therapy for *H. pylori* eradication.

Recently, *Lactobacillus* species have been demonstrated to have an inhibitory effect on the *in vitro* attachment of *H. pylori* to gastric cell lines.[13–15] Exogenous administration of *Lactobacillus* may thus help to prevent or treat *H. pylori* infection. Canducci *et al*. reported that

Correspondence to: Professor J. -J. Wu, Department of Medical Technology, Medical College, National Cheng Kung University, No. 1, University Road, Tainan, Taiwan 701.
E-mail: jjwu@mail.ncku.edu.tw

supplementation of triple therapy with a drug containing inactivated *Lactobacillus acidophilus* can increase the eradication rates of *H. pylori*.[16] Abundant live *Lactobacillus* and *Bifidobacterium* species exist in popular daily foods, such as yogurt.[17] As there are no data available, we tested whether supplements of yogurt containing abundant live *Lactobacillus* and *Bifidobacterium* species could improve the drug compliance and *H. pylori* eradication rate of triple therapy. Moreover, again because there are no data available, we tested whether supplementation with yogurt can restore the change in bowel flora caused by triple therapy.

MATERIALS AND METHODS

Patients

Between January and December 2001, a total of 160 patients, undergoing diagnostic upper endoscopy due to dyspeptic symptoms and proven to have *H. pylori* infection, were enrolled in this study. Gastric biopsies were taken from all patients during endoscopy for histology and rapid urease test (CLO test, Pharmacia) to evaluate the initial status of *H. pylori* infection. The presence of *H. pylori* infection was shown by positive results for both the rapid urease test and histology. To avoid problems in the evaluation of *H. pylori* status, the following patients were not included: those who had ingested bismuth salts, proton pump inhibitors, or antibiotics in the previous 8 weeks; those with a known allergy to penicillin; and those who had undergone previous gastrointestinal surgery. Patients with a past history of anti-*H. pylori* therapy or gastric malignancy were also excluded.

Study design

After obtaining informed consent, each patient was randomly allocated into one of two groups: those receiving 1-week triple therapy for the eradication of *H. pylori* with a supplement of *Lactobacillus*- and *Bifidobacterium*-containing yogurt (AB-Yogurt, President Corp., Tainan, Taiwan) (triple-plus-yogurt group) and those receiving 1-week triple therapy without the supplement (triple-only group). In the triple-plus-yogurt group, the regimen of 1-week triple therapy consisted of lansoprazole (30 mg) (before breakfast and dinner), amoxicillin (1 g) (half an hour after breakfast and dinner) and clarithromycin (500 mg) (half an hour after breakfast and dinner) twice daily. Half an hour after the antibiotics, 200 mL AB-Yogurt (containing at least 5×10^9 live organisms per bottle) was taken twice daily. The supplement of 200 mL AB-Yogurt was continued for 4 weeks after triple therapy in the triple-plus-yogurt group. In contrast, the triple-only group received the same regimen of triple therapy for 1 week, but were prohibited from consuming yogurt during the study period. At least 4 weeks after the cessation of AB-Yogurt intake in the triple-plus-yogurt group and 8 weeks after triple therapy in the triple-only group, all patients diagnosed with duodenal ulcer or non-ulcer dyspepsia were tested for the eradication of *H. pylori* by the ^{13}C-urea breath test.[18] If the ^{13}C-urea breath test was positive or gastric ulcer was present, a second endoscopy was performed to obtain gastric biopsies for histology and CLO test. The successful eradication of *H. pylori* was defined by one of the following two conditions: (i) negative results of histology and CLO test in the second endoscopy; (ii) a negative ^{13}C-urea breath test indicated by the cut-off point of less than 2.5.[19] Drug compliance and the side-effects of triple therapy in both groups were recorded at the visit in the first week. The degree of drug compliance was categorized as full (all 7 days of triple therapy were completely ingested), good (ingested at least 5 days of triple therapy) or poor (ingested less than 5 days of triple therapy). All enrolled patients who were tested for *H. pylori* eradication were included in the intention-to-treat analysis. Patients who dropped out due to severe adverse effects, those with poor drug compliance and those lost to follow-up for ^{13}C-urea breath test or endoscopy were excluded from the per protocol analysis of the *H. pylori* eradication rate. Based on the demand to attain a statistical power of 0.7 and to achieve a 15% improvement in the 75% predicted background eradication rate of the control group, the case number should be at least 154.

Serial stool samples on enrolment, at the first week visit (just after triple therapy) and at the fifth week visit were provided by 22 randomly selected patients (11 in the triple-plus-yogurt group and 11 in the triple-only group). Immediately after defecation, patients collected their stools in an airtight sterile plastic bag with an auto-sealed inlet. Patients were asked to seal the inlet after expelling the gas from the bag to maintain an anaerobic environment. These stool samples were transported to the hospital within 1 h after defecation and were immediately processed for stool culture to analyse the percentages of *Escherichia coli* and *Bifidobacterium* in aerobes and anaerobes, respectively.

Endoscopy and gastric biopsy

The same types of video endoscope (Olympus XQ 240, Olympus Corp., Tokyo, Japan) and biopsy forceps (Olympus FB-25N, Olympus Corp., Tokyo, Japan) were uniformly applied to obtain strips of gastric biopsy, including two from the antrum and two from the corpus. Two biopsy strips, one from the antrum and one from the corpus, were used for rapid urease test and histology (stained with haematoxylin and eosin), respectively.[20]

Stool culture

Stool culture for *E. coli and Bifidobacterium* was performed as described previously.[17] Briefly, approximately 0.2–0.4 g of stool was diluted with normal saline several times until the supernatant was clear. A serial 10-fold dilution was taken and 0.1 mL of the diluted sample was dispersed on appropriate agar plates. CDC plates (Becton Dickinson, Cockeysville, MD, USA) were used for the culture of total anaerobes and BFM agar plates, containing lactulose, methylene blue (methylthioninium chloride), propionic acid and lithium chloride,[18] were used for the selection of *Bifidobacterium*. Blood agar plates (Becton Dickinson) were used for the culture of total aerobes and MacConkey agar plates (Becton Dickinson) were used for the selection of *E. coli*. All anaerobic plates were incubated in an anaerobic chamber at 35 °C for 72 h, whereas aerobic plates were incubated at 35 °C for 16 h. *Bifidobacterium* and *E. coli* were identified by conventional techniques[21, 22] and/or with a Rapid ID 32A system (BioMerieus Vitek Inc, Hazelwood, MO, USA). The colony count was used to calculate the number of bacteria per gram of dry stool weight.

Statistics

Student's *t*-test and Pearson's chi-squared test were used to determine the parametric difference and non-parametric proportions between the two study groups. The difference between serial percentages of stool bacteria within the same group was tested by paired *t*-test. All tests of significance were two-tailed with a *P* value of less than 0.05.

RESULTS

Demographic background and outcome of the treatment groups

There was no difference in demographic background or endoscopic diagnosis between the two study groups (Table 1). Side-effects were more commonly found in the triple-only group than in the triple-plus-yogurt group

Table 1. Demographic characteristics and side-effects of triple therapy in both groups

Variable	Triple-plus-yogurt group ($n = 80$)	Triple-only group ($n = 80$)	*P*
Mean age (years)	47.8	45.9	N.S.
Females, % (*n*)	50 (40)	52.5 (42)	N.S.
Endoscopic findings, % (*n*)			
Gastric ulcer	15 (12)	20 (16)	N.S.
Duodenal ulcer	35 (28)	35 (28)	N.S.
Non-ulcer gastroduodenitis	50 (40)	40 (36)	N.S.
Compliance with triple therapy, % (*n*)			
Full (7 days)	67.5 (54)	43.8 (35)	< 0.05
Good (> 5 and < 7 days)	28.8 (23)	46.2 (37)	N.S.
Poor (< 5 days)	2.5 (2)	3.8 (3)	N.S.
Drop-out	1.3 (1)	6.2 (5)	N.S.
Side-effects (*n*)			
Nausea	5	8	N.S.
Vomiting	1	7	< 0.05
Constipation	1	8	< 0.05
Diarrhoea	2	10	< 0.05
Metallic taste	3	13	< 0.05
Bitterness of mouth	2	3	N.S.
Mild headache	1	4	N.S.
Subtotal	15	53	< 0.05

(Table 1). Also in Table 1, a significantly higher proportion of patients in the triple-plus-yogurt group completed the 7-day regimen than in the triple-only group (67.5% vs. 43.8%, $P < 0.05$). Only one patient lost to follow-up and two patients with poor drug compliance were excluded from the per protocol analysis in the triple-plus-yogurt group. In contrast, eight patients in the triple-only group (five lost to follow-up and three with poor drug compliance) were not enrolled for per protocol analysis. In Table 2, the *H. pylori* eradication rates by intention-to-treat analysis were significantly higher in the triple-plus-yogurt group than in the triple-only group (91.3% vs. 78%, $P = 0.045$). However, in the per protocol analysis, similar eradication rates were found in these two groups (93.5% vs. 88.9%, $P = 0.149$).

Change of bowel flora by triple therapy and restoration by AB-Yogurt

In each group, 11 randomly selected patients provided stool samples following the protocol. As shown in Table 3, the percentage of *E. coli* in stool specimens was not changed by triple therapy in either group. In contrast, the percentage of *Bifidobacterium* in stool specimens was decreased by triple therapy in both groups (paired *t*-test, $P < 0.05$). The percentage of *Bifidobacterium* in anaerobes in the fifth week stool sample was higher in the triple-plus-yogurt group than in the triple-only group (6.8% vs. 1.22%, $P < 0.05$). Patients receiving yogurt showed restoration of *Bifidobacterium* in the fifth week stool specimen to the level before triple therapy (6.8% vs. 5%, $P =$ N.S.). In patients without supplementation with yogurt, the percentage of *Bifidobacterium* in anaerobes in the fifth week stool sample was lower than the level before triple therapy (1.22% vs. 7.4%, $P < 0.05$).

Table 2. Eradication rates of *Helicobacter pylori* infection by triple therapy in the two study groups

	Eradication rate, % (*n*) (95% confidence interval)	
	Per protocol analysis	Intention-to-treat analysis
Triple-plus-yogurt group	93.5 (73/77) (89.5–97.3)	91.3 (73/80)* (88.8–94.2)
Triple-only group	88.9 (63/72) (84.8–92.8)	78.3 (63/80) (73.9–82.7)

*Significant difference in *H. pylori* eradication rate between the two groups by intention-to-treat analysis ($P = 0.045$).

DISCUSSION

The supplementation of the standard 1-week triple therapy with AB-Yogurt significantly increased the full drug compliance of patients with respect to those given the non-supplemented regimen (Table 1). Moreover, common side-effects, such as vomiting, constipation, diarrhoea and metallic taste, were significantly decreased in the triple-plus-yogurt group (Table 1). Because of the fewer side-effects and better drug compliance, drop-out events were lower in the triple-plus-yogurt group (Table 1). Accordingly, supplementation of standard triple therapy with AB-Yogurt significantly increased the *H. pylori* eradication rate with respect to that of the non-supplemented regimen by intention-to-treat analysis (Table 2). However, the *H. pylori* eradication rate by per protocol analysis was only slightly higher in the triple-plus-yogurt group than in the triple-only group and was not statistically significant (93.5% vs. 88.9%, $P = 0.149$). The study suggests that supplementation with AB-Yogurt containing live *Lactobacillus* and *Bifidobacterium* may exert a positive effect on *H. pylori* eradication rates by improving drug compliance with fewer side-effects.

The positive effect of AB-Yogurt on the *H. pylori* eradication rate by triple therapy is partially compatible with the report by Canducci *et al.*, which showed that inactivated *Lactobacillus acidophilus* can improve the *H. pylori* eradication rate by triple therapy by both intention-to-treat and per protocol analyses.[16] As the dosages of antibiotics (both clarithromycin and amoxicillin) used in this study were higher than those employed by Canducci *et al.*, the *H. pylori* eradication rate by per protocol analysis was higher in patients without supplementation with probiotics in this study than in that by Canducci *et al.* (88.9% vs. 72%). Because of the higher background eradication rate in our control patients, the increase in the eradication rate by per protocol analysis was not statistically significant, unlike that shown by Canducci *et al.*, who reported a significant improvement from 72% to 87%.[16] Nevertheless, our study confirmed that live bacteria in daily food, such as AB-Yogurt, may be as effective as inactivated *Lactobacillus* in improving the rate of *H. pylori* eradication by 1-week triple therapy.

It would be interesting to explain why supplementation with probiotics, such as inactivated or live bacteria in yogurt, can improve the *H. pylori* eradication rate by triple therapy. *In vitro* and animal reports have

Table 3. *Escherichia coli*/total aerobes ratio and *Bifidobacterium*/total anaerobes ratio of faeces before and after triple therapy (mean ± s.d.)

	Stool sampling time		
	Pre-treatment	1st week	5th week
E. coli/total aerobes ratio (%)			
Triple-plus-yogurt group	45.1 ± 23.4	42.2 ± 26.8	26.3 ± 25.9
Triple-only group	37.2 ± 25.9	55.1 ± 28.2	26.3 ± 31.8
P value	N.S.	N.S.	N.S.
Bifidobacterium/total anaerobes ratio (%)			
Triple-plus-yogurt group†§	5 ± 3.2	0.35 ± 0.07	6.81 ± 4.23
Triple-only group†‡	7.4 ± 4.5	0.86 ± 0.11	1.22 ± 0.89
P value	N.S.	N.S.	< 0.05*

s.d., standard deviation.
*P value less than 0.05 between triple-plus-yogurt group and triple-only group (Student's t-test).
†Significant difference ($P < 0.05$, by paired t-test) between the pre-treatment and the 1st week samples.
‡Significant difference ($P < 0.05$, by paired t-test) between the pre-treatment and the 5th week samples.
§Significant difference ($P < 0.05$, by paired t-test) between the 1st week and the 5th week samples.

demonstrated possible mechanisms responsible for the efficacy of these probiotics, including a direct, non-specific, bacteriostatic activity, stimulation of the growth of defensive acidogenic flora, increase in immunoglobulin A production, intense adherent capacity to human intestinal mucosecreting cells, and increase in the metabolic products of lactic acid fermentation.[23–29] Several *in vitro and* animal studies have also shown a reduction in the viability of *H. pylori* and of its adhesion to human gastric mucosecreting cells by *Lactobacillus* strains, independent of pH value and lactic acid levels.[13–15, 30, 31] Michetti *et al.* further confirmed a persistent reduction of ^{13}C-urea breath test values by *Lactobacillus* strains in humans,[13] implying that probiotics may possibly suppress the urease activity of *H. pylori.* As urease activity is vital for the colonization and persistence of *H. pylori*, pre-treatment with these probiotics may improve the current treatment outcome of triple therapy.

Few data are available on the changes that occur in the normal bowel flora after the large doses of antibiotics used in triple therapy for *H. pylori* eradication. In Table 3, the numbers of *Bifidobacterium* in stools were significantly changed by triple therapy. The restoration of *Bifidobacterium* in stools was delayed until at least 4 weeks after triple therapy. These findings indicate that triple therapy has an adverse effect on the healthy bowel flora, which may possibly account for the adverse events in the gastrointestinal tract.[12, 17, 25] As *Bifidobacterium* species have been shown to survive in the intestine and to provide health benefits,[17, 31–33] the restoration of *Bifidobacterium* after triple therapy should be an important issue and deserves further clinical exploration. In this study, despite supplementation with AB-Yogurt during triple therapy, depletion of *Bifidobacterium* was found at the end of treatment. Nevertheless, by continuing supplementation with AB-Yogurt for an additional 4 weeks after triple therapy, restoration of *Bifidobacterium* to the level before therapy was achieved (Table 3). This study thus confirms that the administration of AB-Yogurt during triple therapy aids drug compliance, leading to an improvement in the *H. pylori* eradication rate by intention-to-treat analysis, but cannot prevent the depletion of *Bifidobacterium* in stools at the end of triple therapy. Continued supplementation with AB-Yogurt is of clinical benefit and restores the normal bowel flora as early as within 1 month after therapy.

In summary, supplementation with AB-Yogurt can improve drug compliance and thus enhance the intention-to-treat eradication rate of *H. pylori* after triple therapy. Furthermore, continued supplementation with AB-Yogurt after triple therapy can restore *Bifidobacterium* in stools after 4 weeks.

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