

Effect of Different Probiotic Preparations on Anti-*Helicobacter pylori* Therapy-Related Side Effects: A Parallel Group, Triple Blind, Placebo-Controlled Study

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OBJECTIVES: Several studies show that probiotics may prevent side effects during therapy against *Helicobacter pylori* (*H. pylori*). Other reports indicate competitive interaction between some probiotics and *H. pylori*. We compared efficacy of two different probiotics and one probiotic combination with placebo for preventing anti-*H. pylori* therapy-related side effects and for improving the eradication rate.

METHODS: A total of 85 *H. pylori* positive, asymptomatic patients were randomized in four groups to receive probiotic or placebo both during and for 7 days after a 1-wk triple therapy scheme (rabeprazole 20 mg *b.i.d.*, clarithromycin 500 mg *b.i.d.*, and tinidazole 500 mg *b.i.d.*). Group I (n = 21) received *Lactobacillus GG*; group II (n = 22), *Saccharomyces boulardii*; group III (n = 21), a combination of *Lactobacillus spp.* and biphidobacteria; and group IV (n = 21), placebo. Subjects filled in weekly symptom questionnaires for 4 wk. Blinded investigators collected and analyzed data. *H. pylori* status was rechecked after 5–7 wk.

RESULTS: Side effects occurred mainly during the eradication week. None of them caused therapy discontinuation. In all probiotic-supplemented groups, there was a significantly lower incidence of diarrhea and taste disturbance during the eradication week with respect to the placebo group. Overall assessment of tolerability was significantly better in the actively treated patients than in the placebo group. No differences in the incidence of side effects between the probiotic groups were observed. The *H. pylori* eradication rate was almost identical between the probiotic and placebo groups.

CONCLUSIONS: All the probiotics used were superior to placebo for side effect prevention, but were not associated with better compliance with antibiotic therapy. The effect of probiotic supplementation on side effects during anti-*H. pylori* regimens seemed to be independent of the probiotic species used. (Am J Gastroenterol 2002;97:2744–2749. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

Multiple antibiotic schemes against *Helicobacter pylori* (*H. pylori*) infection carry the potential burden of GI side effects. In fact, despite the fact that 2-wk-long triple antibiotic regimens have progressively been abandoned as a first line approach to the infection, poor treatment tolerability—most often related to antimicrobials—is a cause of concern and may lead to treatment interruption. Today, bacterial resistance and side effect occurrence represent the second most frequent cause for anti-*H. pylori* treatment failure in clinical practice (1). A strategy targeted to improve treatment tolerability might increase compliance and eventually raise eradication rate.

A probiotic is defined as a living microbial species that, upon administration, may positively affect bowel microecology and improve health conditions (2). Previous data have shown, in a placebo-controlled fashion, efficacy of *Lactobacillus GG* in preventing several side effects associated to anti-*H. pylori* therapy. A separate open label study with a different strain, *L. acidophilus* La1, has documented higher eradication rates in patients whose treatment is supplemented with this probiotic than in control subjects who were given antibiotic therapy alone (3, 4). The report from the Maastricht 2000 consensus conference on *H. pylori* include probiotics as “possible” tools for management of the infection (5).

On the other hand, use of probiotics in antibiotic-associated diarrhea dates to decades ago, and its impact has been proved in several placebo-controlled trials. Studies have been conducted in pediatric and adult populations showing preventive effects both for *Lactobacillus spp.* strains and for *Saccharomyces boulardii* (*S. boulardii*) on the occurrence of diarrhea during and after antibiotic administration (6–10).

Many commercially available preparations containing probiotics are available both in the European community and in the United States. Most preparations contain single probiotic strains. Others are based on cocktails of several

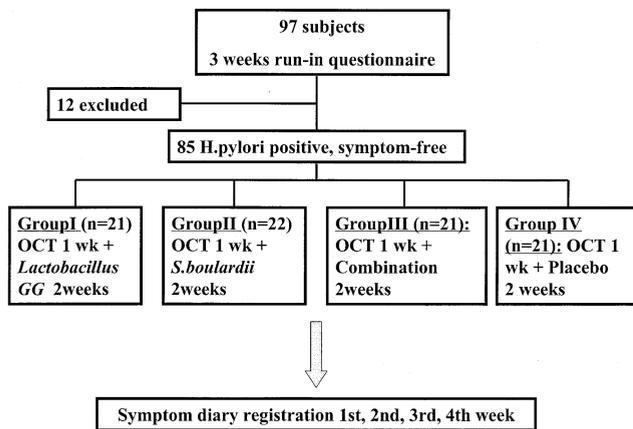


Figure 1. Outline of study profile.

different strains, and the amount of bacterial colonies they contain is profoundly variable.

The aim of the present study was to test the efficacy of two different widely available, single strain probiotic preparations, along with the efficacy of a multistrain combination *versus* placebo, for preventing side effects during a standard anti-*H. pylori* therapy, and, as a secondary endpoint, for improving the eradication rate.

MATERIALS AND METHODS

Study Subjects and Protocol

The study profile is outlined in Figure 1. A total of 97 subjects (age range 18–61 yr, 54 women and 43 men) were enrolled in the study. Subjects had voluntarily undergone *H. pylori* testing with the ^{13}C urea breath test and had tested positive. Subjects underwent *H. pylori* testing in the framework of a survey conducted in an urban area of the city of Rome, Italy. All subjects declared themselves as free of GI symptoms at enrollment. They wished to be treated for *H. pylori* after asking and receiving information by the inpatient physician on the impact of *H. pylori* infection on the community, and its association with chronic gastritis, peptic ulcer, and gastric cancer. Subjects, who gave written informed consent, initially answered a questionnaire on GI and extraintestinal symptoms, drug history, and reactions. This questionnaire was filled out at the end of each week in a 3-wk run-in period. Subjects who recorded occurrence of any symptoms or who even incidentally used any drug associated with GI side effects were excluded from the study.

After the run-in period, 12 subjects were excluded because of the occurrence of fever or flu-like syndrome (four patients), use of a calcium channel blocker (three patients), L-thyroxine (one patient), occasional use of laxatives (three patients), or anticholinergic drugs (one patient). These subjects were offered a PPI and dual antibiotic scheme against *H. pylori*.

The remaining 85 *H. pylori* positive patients were randomized by computer to four groups. The computer list was generated and kept by the pharmacy, so that none of the investigators knew the treatment allocation. For each patient, a marked, numbered box containing the sachets was designated. Treatment groups were as follows: group I (n = 21) received rabeprazole 20 mg *b.i.d.*, clarithromycin 500 mg *b.i.d.*, and tinidazole 500 mg *b.i.d.* (collectively designated as RCT) for 7 days, plus a *Lactobacillus GG* preparation (Giflorex, Errekappa Euroterapici, Milan, Italy) administered *b.i.d.* during the antibiotic week and for 1 wk thereafter. Group II (n = 22) received RCT for 7 days plus a *S. boulardii* preparation (Codex, SmithKline Beecham, Milan, Italy) given twice during the antibiotic week and 1 wk thereafter. Group III (n = 21) received RCT for 7 days plus a probiotic multistrain combination (Ferzym, Specchia-sol, Milan, Italy) administered *b.i.d.* during the antibiotic week and 1 wk thereafter. Group IV (n = 21) received RCT for 7 days plus placebo administered with the same regimen of probiotic preparations. The probiotic strains, prescription regimen, and amount of colony forming units per single dose are shown in Table 1.

Placebo was administered in the same amount of sachets of probiotic schemes (2 sachets/day). Boxes containing active study treatments and placebo were identical in shape and color, and contained the same number of sachets. No trademark identifications were present, either on the probiotic or the placebo sachets.

H. pylori status was rechecked in all patients 5 to 7 wk after the end of the RCT week by means of ^{13}C urea breath test. Adherence to the study protocol was evaluated by counting the empty boxes returned at the control visit (day of control ^{13}C Urea breath test).

Side Effects Evaluation

The questionnaire proposed and validated by De Boer *et al.*, which is specifically designed for anti-*H. pylori* therapy side effects, was filled in by study participants at the end of the antibiotic week and last day of the each of the next 3 wk

Table 1. Prospectus of Probiotic Preparations Used

Active Treatment Group	Species Contained	Total CFU Administered*	Other Active Contents
Group 1	<i>Lactobacillus casei subsp. rhamnosus (GG)</i>	$6 \cdot 10^9$ /sachet	None
Group 2	<i>Saccharomyces boulardii</i>	$5 \cdot 10^9$ /sachet	None
Group 3	<i>Lactobacillus acidophilus</i> <i>Bifidobacterium lactis</i>	$5 \cdot 10^9$ /capsule (in sachet)	Vitamin B ₁ Vitamin B ₆ Vitamin B ₁₂ Vitamin PP Pantotenic acid

* Amount of colony forming units (CFU) for the combination is approximate and includes all probiotic species.

(11). Each questionnaire included the following side effects record boxes: taste disturbance, nausea, loss of appetite, vomiting, diarrhea, bloating, constipation, skin rash, and epigastric pain. A grading scale was provided for each symptom, scoring intensity from 1 to 5 (1 = no side effects; 2 = slight discomfort, not interfering with daily activities; 3 = moderate discomfort, sometimes interfering with daily activities; 4 = severe discomfort, inability to perform daily working activities; and 5 = severe discomfort, subject forced to discontinue treatment). An identical grading scale (1–5) was used to record overall assessment of treatment tolerability, which was assessed in a separate form by each patient at the end of the eradication week. Two outpatient physicians (M.G., L.S.) trained patients on how to fill out the questionnaires. Data from the questionnaires were collected by two separate blinded investigators (S.D.C. and A.A.), who performed the control visit, and the data were analyzed by a blinded statistician (M.C.).

Statistical Analysis

A total sample size of 73 subjects was calculated as appropriate to detect a difference of 20% in symptom occurrence between active treatment and placebo groups. We assumed an expected incidence of any side effect in 25% of subjects treated with antibiotics, with an 80% power to detect differences and a two-sided α of 0.05.

The χ^2 test was used to analyze symptoms score reported, the Kruskal-Wallis test to analyze differences in overall assessment of tolerability score, and the Tukey-Kramer test to assess pairwise differences among groups. Calculations were performed using JMP software (SAS Institute, Cary, NC).

RESULTS

No major side effects leading to treatment discontinuation were observed. Compliance was optimal in all groups. All subjects (21 of 21) completed therapy in the *Lactobacillus GG* group. In the combination group, 21 of 22 subjects (95%) completed therapy in the *S. boulardii* group and 20 of 21 (95%) in the placebo group. The subject in *S. boulardii* group who did not complete therapy was excluded because of incomplete adherence to the antibiotic treatment because of self-reported lack of motivation; the subject in the placebo group was excluded because of inadequate filling of symptom reports in week 1 and 3 of the study. All the remaining subjects completed the regimen assigned and returned properly filled out questionnaires, as separately assessed by the two investigators.

Differences among treatment groups in side effect occurrence were observed only during week 1 of observation (Fig. 2). The incidence was three of 21 subjects (15%) for both groups I and II; five of 21 subjects (24%) in group III; and 12 of 20 subjects (60%) in the placebo group, with an overall value of $p = 0.0025$. Detailed information on type of side effects is provided in Table 2. The incidence of diarrhea

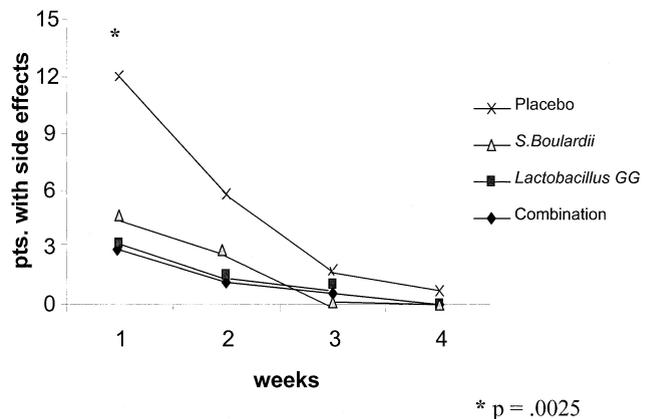


Figure 2. Incidence of side effects reported during the 4 wk of follow-up.

was significantly lower in all three probiotic treatment groups compared to the placebo group. The relative risk for diarrhea during week 1 for individuals actively treated versus placebo was 0.16 (95% CI = 0.04–0.56). There was also a lower incidence of taste disturbance in all active treatment groups. The relative risk for taste disturbance during week 1 was 0.15 (95% CI = 0.05–0.46). No substantial difference in occurrence of other side effects was registered. A lower incidence of diarrhea incidence persisted during week 2 among all of the probiotic groups, with borderline significance. All of the differences were observed between subjects treated with any of the probiotic preparation versus placebo. None of the probiotic species or combinations used showed substantial superiority over the others.

The overall judgment of tolerability, based on a five-point scale, was significantly superior in all treatment groups compared to the placebo group ($p = 0.0016$). All of the probiotic preparations were associated with better tolerability compared to placebo, but there were no significant differences among the probiotic treatment groups (Table 3).

H. pylori eradication rates, assessed using the ^{13}C urea breath test, were not significantly different between probiotic and placebo groups. In the *Lactobacillus GG* group, *H. pylori* was eradicated in 16 of 21 patients (76%); in the *S. boulardii* group, it was eradicated in 17 of 20 patients (81%); in the combination group, in 18 of 21 patients (86%); and in the placebo group, in 16 of 20 patients (80%).

Cost Data

The additional cost to the antibiotics and to the proton pump inhibitor of each dose of any of the probiotic preparations used was Euro 0.84 for the single strain preparation, and Euro 0.38 for the combination, with a final cost of 11.8 Euros and 5.3 Euros respectively, for the full 2 wk, to be added to the price of a triple anti-*H. pylori* regimen.

Table 2. Side Effect Frequencies During Eradication Week

Symptom	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 4 (%)	p Value
Nausea	9.5	5	9.5	15	0.75
Vomiting	0	0	0	5	0.36
Diarrhea	5	5	5	30	0.018*
Constipation	19	14.2	9.5	20	0.77
Loss of appetite	0	9.5	5	15	0.28
Taste disturbance	9.5	5	5	40	0.0027*
Epigastric pain	14.2	14.2	5	14.2	0.7
Bloating	19	19	9.5	19	0.77
Belching	5	0	9.5	0	0.29
Skin rash	0	0	5	0	0.39

p Values based on χ^2 test.

* Significant.

DISCUSSION

In this randomized, placebo-controlled study, all three groups of patients on a standard anti-*H. pylori* regimen supplemented with probiotics reported a lower incidence of side effects compared to those in subjects whose regimens were supplemented with placebo. The effect was significant during week 1 of follow-up, which corresponded to the course of antibiotic treatment. Overall treatment tolerability was better in all active treatment groups compared to placebo. None of the probiotic preparations used was associated with a lower incidence of any side effects or with better overall tolerability compared to another preparation. No major side effects were recorded, and compliance was optimal in all groups. Study dropouts were not because of side effects. The incidence of diarrhea and taste disturbance (the main side effects) was reduced in the active treatment groups compared with the placebo group. There were no significant differences among groups in the study secondary endpoint, *i.e.*, the rate of *H. pylori* eradication.

Probiotics have shown efficacy against antibiotic-associated diarrhea in several randomized controlled studies (12). The rationale for their efficacy is mostly based on restoration of normal flora colonization. Also, for *Lactobacillus GG*, the inhibition of macrolides prokinetic action has been proposed (13). Many animal experiments indicate some degree of immune stimulation by probiotic species, and oral bacteriotherapy is a hot topic in the current experimental therapeutics of inflammatory bowel disease. To date, there is no definitive evidence on the mechanisms by which these biological agents influence the course of human disease (14–16).

Occurrence of side effects in anti-*H. pylori* therapy is

mostly attributed to the use of antibiotics in moderate to high doses and in combination. Although some specific side effects such as diarrhea and bloating could be related to the disruption of gut microflora from antimicrobials, the link with bowel microecology for other common side effects such as taste disturbance is difficult to prove. In fact, although the probiotic combination used in this study contained vitamins that could protect against the development of glossitis, taste disturbance was lower even in patients treated with probiotics alone.

In a previous study, we showed the efficacy of supplementation with *Lactobacillus GG* versus placebo during anti-*H. pylori* therapy for preventing such side effects as diarrhea, bloating, and taste disturbance (3). The aim of the present study was, besides validation of results previously obtained with *Lactobacillus GG*, to compare different probiotic preparations that are commercially available for prevention of antibiotic-associated side effects. Choosing symptom free subjects and including a run-in period was mandatory for discriminating previous GI symptoms from newly occurring complaints. The use of an anti-*H. pylori* multiple antibiotic regimen provided a convenient sample of subjects, maintaining homogeneity among study groups with regard to both the type of antibiotics administered and the length of therapy. Using a nitroimidazole agent such as tinidazole also reasonably lowered the probability of a major event such as *C. difficile*-related diarrhea. If we had chosen amoxicillin, a mainstay drug for first line anti-*H. pylori* therapy that is more frequently associated with GI side effects than are other antibiotics, we might have increased the incidence of diarrhea. This could have helped to detect differences among active treatments and placebo, but

Table 3. Assessment of Treatment Tolerability*

Side Effect Burden	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 4 (%)
None	85.7	81	85.7	40
Mild	4.8	9.5	4.7	25
Moderate	9.5	9.5	4.7	25
Severe	0	0	4.7	10
Forced discontinuation	0	0	0	0

* All active treatments vs placebo, $p = 0.0016$.

with risk of decreasing compliance without significant improvement in the eradication rate as shown by previous trials (17), and also with greater risk of harming subjects with regard to *C. difficile* colitis. Moreover, we chose to be consistent with our study on the effect of *Lactobacillus GG* by using the same antibiotic regimen (3).

A recent study has also shown a temporary alteration of intestinal microflora immediately after the end of triple therapy using omeprazole, metronidazole, and clarithromycin in *H. pylori*-infected subjects. Such a regimen is almost identical to that used in the present study. The alteration of microflora included reduction in concentration of *Enterococcus spp.*, *Bifidobacterium spp.*, and an increase in concentration of aerobes in general and specifically of *C. albicans* (18). The effect of *Lactobacillus GG* on restoring intestinal microflora has been shown by several studies, as well as that of *S. boulardii*, which in turn may potentially inhibit *C. albicans* overgrowth, as shown by studies in mice (19). The probiotic combination used in the present study contained *Bifidobacteria*, which could act by replacing the losses observed by Buhling *et al.* in their study.

Compared to previous data from our group, no benefit was observed from probiotics on the occurrence of bloating in the present study, but the beneficial effect on diarrhea and on taste disturbance was confirmed. Taste disturbance is a side effect most commonly reported with the use of both nitroimidazoles and clarithromycin. There is no evidence to explain to what extent it could be related to intestinal microflora. There is also no satisfactory explanation for a positive effect of a probiotic on this symptom, although this effect was observed in both of the placebo-controlled trials that we conducted.

The use of any one of the studied probiotic preparations corresponded to an absolute risk reduction of 0.25 for diarrhea, so that the number of patients needed to be treated to prevent occurrence of one case of diarrhea was four.

To determine whether adding a probiotic to a first line anti-*H. pylori* regimen might be a cost-effective option was outside the aim of this study. However, the present data support the Maastricht 2000 consensus conference statement, which included probiotics as possibly useful "side tools" for the management of *H. pylori* infection. In this study, probiotics were not useful to increase treatment compliance, as already suggested by previous data, but, rather, to significantly improve treatment tolerability.

It should be noted that we did not observe any difference among groups in the *H. pylori* eradication rate. The positive result on eradication obtained in a different study with *L. acidophilus* is not in contrast with our data, as the *L. acidophilus* in that study was administered as a single probiotic with its own culture supernatant, whereas in the current study it was present only as a partial component of the combination used (4).

It is intriguing that a beneficial effect was observed for all probiotic preparations, regardless of the species contained and regardless of whether a single strain or a strain combi-

nation was used. It could be speculated that a symptomatic effect could be reached on the basis of microflora steady-state restoration, irrespective of the strain intervening to "repair" disruption. The answer to this question is unlikely to be obtained from a clinical study.

The sample size in the present study was powered to analyze differences from the three active treatment arms and placebo, with an effect size detectable of 20% in symptom occurrence, which we considered to be the minimal clinically relevant effect. On the other hand, this study was not explicitly designed and powered to show whether one probiotic species worked slightly better than another or *vice versa*.

This study has some limitations. Until the pathophysiological mechanisms of probiotics action are understood at the molecular level, symptomatic benefits should be considered with caution, and appropriate patient selection for clinical trials will be difficult. In our study, we did not perform stool assessment for bacterial recovery. However, for the species used, and for two of the three commercial preparations used, fecal recovery studies have been carried out with positive results (20, 21). Also, the resistance to the two antibiotics used in the triple regimen has been documented for *Lactobacillus GG*, whereas *S. boulardii* is a yeast, and yeast concentration was shown to be unaltered after antibiotic administration in the study by Buhling *et al.* (19, 22). A complete stool assessment for all actively treated subjects would have been extremely demanding in terms of resources and expertise, and eventually unjustified, considering that the probiotic species used have already been tested in human studies and in different clinical settings. A further limitation to our results is generalizability: in fact, we were obliged to use symptom-free subjects who wished to have *H. pylori* eradicated so as to detect a net response in terms of symptoms reported. Thus, we are not able to predict from these data whether similar results could be achieved in individuals who are symptomatic or who have lesions such as peptic ulcer. For these patients, evaluation of side effects occurrence would be much more complex. Other limitations include the facts that rigorous, reliable dose-seeking studies on probiotics have not been conducted and that, despite the confirmatory nature of our data compared with previous studies, little is known still on the optimal number of probiotic colony forming units that should be administered.

In conclusion, our data show that all three probiotic preparations supplementing a standard anti-*H. pylori* regimen were associated with lower incidence of self-reported side effects and with better treatment tolerability compared to placebo, although there was no indication of any difference in effectiveness among the various agents used.

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REFERENCES

1. Deltenre M, Ntounda R, Jonas C, et al. Eradication of *Helicobacter pylori*: Why does it fail? Ital J Gastroenterol Hepatol 1998;30(suppl 3):S326–8.
2. Fuller R. Probiotics in human medicine. Ann Med 1990;22:37–41.
3. Armuzzi A, Cremonini F, Bartolozzi F, et al. The effect of oral administration of *Lactobacillus GG* on antibiotic-associated gastrointestinal side effects during *Helicobacter pylori* eradication therapy. Aliment Pharmacol Ther 2001;15:163–9.
4. Canducci F, Armuzzi A, Cremonini F, et al. A lyophilized and inactivated culture of *Lactobacillus acidophilus* increases *Helicobacter pylori* eradication rates. Aliment Pharmacol Ther 2000;14:1625–9.
5. Malfertheiner P, Mégraud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection—the Maastricht 2–2000 Consensus Report. Aliment Pharmacol Ther 2002;16:167–80.
6. Vanderhoof JA, Whitney DB, Antonson DL, et al. *Lactobacillus GG* in the prevention of antibiotic-associated diarrhea in children. J Pediatr 1999;135:564–8.
7. Szajewska H, Kotowska M, Mrukowicz JZ, et al. Efficacy of *Lactobacillus GG* in prevention of nosocomial diarrhea in infants. J Pediatr 2001;138:361–5.
8. Gotz V, Romankiewicz JA, Moss J, et al. Prophylaxis against ampicillin-associated diarrhea with *Lactobacillus* preparation. Am J Hosp Pharm 1979;36:754–7.
9. Surawicz MC, Elmer GW, Speelman P, et al. Prevention of antibiotic-associated diarrhea by *Saccharomyces boulardii*: A prospective study. Gastroenterol 1989;96:981–8.
10. Mc Farland LV, Surawicz CM, Greenberg RN, et al. Prevention of beta-lactam-associated diarrhea by *Saccharomyces boulardii* compared with placebo. Am J Gastroenterol 1995;90:439–48.
11. De Boer WA, Thys JC, Borody TJ, et al. Proposal for use of a standard side effect scoring system studies exploring *Helicobacter pylori* treatment regimens. Eur J Gastroenterol Hepatol 1996;8:641–3.
12. Cremonini F, Di Caro S, Bartolozzi F, et al. The impact of probiotics in antibiotic-associated diarrhea: A meta-analysis of placebo-controlled trials. Gastroenterology 2001;120:A215.
13. Lewis SJ, Freedman AR. Review article: The use of biotherapeutic agents in the prevention and treatment of gastrointestinal disease. Aliment Pharmacol Ther 1998;12:807–22.
14. Isolauri E, Sutas Y, Kankaanpää P, et al. Probiotics. effects on immunity. Am J Clin Nutr 2001;73(suppl 2):S444–50.
15. Erickson KL, Hubbard NE. Probiotic immunomodulation in health and disease. J Nutr 2000;130(suppl 2):S403–9.
16. Shanahan F. Probiotics in inflammatory bowel disease. Gut 2001;48:609.
17. Madsen K, Cornish A, Soper P, et al. Probiotic bacteria enhance murine and human intestinal epithelial barrier function. Gastroenterology 2001;121:580–91.
18. Gasbarrini A, Ojetti V, Armuzzi A, et al. Efficacy of a multistep strategy for *Helicobacter pylori* eradication. Aliment Pharmacol Ther 2000;14:79–83.
19. Buhling A, Radun D, Muller WA, et al. Influence of anti-*Helicobacter pylori* triple-therapy with metronidazole, omeprazole, clarithromycin on intestinal microflora. Aliment Pharmacol Ther 2001;15:1445–52.
20. Berg R, Bernasconi P, Fowler D, et al. Inhibition of *Candida albicans* translocation from the gastrointestinal tract of mice by oral administration of *Saccharomyces boulardii*. J Infect Dis 1993 Nov;168:1314–8.
21. Saxelin M, Pessi T, Salminen S. Fecal recovery following oral administration of *Lactobacillus* strain GG (ATCC 53103) in gelatine capsules to healthy volunteers. Int J Food Microbiol 1995;25:199–203.
22. Elmer GW, McFarland LV, Surawicz CM, et al. Behaviour of *Saccharomyces boulardii* in recurrent *Clostridium difficile* disease patients. Aliment Pharmacol Ther 1999;13:1663–8.