

Effect of *Lactobacillus GG* Supplementation on Antibiotic-Associated Gastrointestinal Side Effects during *Helicobacter pylori* Eradication Therapy: A Pilot Study

A. Armuzzi^{a,d} F. Cremonini^a V. Ojetti^a F. Bartolozzi^b F. Canducci^a
M. Candelli^a L. Santarelli^a G. Cammarota^a A. De Lorenzo^d P. Pola^c
G. Gasbarrini^a A. Gasbarrini^c

Departments of ^aInternal Medicine, ^bHygiene and ^cMedical Pathology, Catholic University, Rome, and Department of ^dHuman Nutrition, Tor Vergata University, Rome, Italy

Key Words

Helicobacter pylori · Probiotics · *Lactobacillus GG* · Antibiotic therapy

Abstract

Background: One-week triple therapy is currently regarded as the reference of anti-*Helicobacter pylori* treatment. However, antibiotic-associated gastrointestinal side effects are among the major pitfalls of such regimens. Probiotic supplementation may be regarded as a therapeutic tool to prevent or reduce these troublesome drug-related manifestations. **Aim:** To determine whether the addition of the probiotic *Lactobacillus GG* to an anti-*H. pylori* standard triple therapy could help to prevent or minimize the occurrence of gastrointestinal side effects. **Methods:** One hundred and twenty healthy asymptomatic subjects screened positive for *H. pylori* infection and deciding to receive eradication therapy were randomized either to 1-week pantoprazole (40 mg b.i.d.), clarithromycin (500 mg b.i.d.), tinidazole (500 mg b.i.d.) or to the same regimen supplemented with *Lactobacillus GG* for 14 days. Patients filled in validated questionnaires during follow-up to determine the type and severity of side

effects and to judge overall tolerability. **Results:** Bloating, diarrhea and taste disturbances were the most frequent side effects during the eradication week and were significantly reduced in the *Lactobacillus GG*-supplemented group (RR = 0.4, CI 0.2–0.8; RR = 0.3, CI 0.1–0.8; RR = 0.3, CI 0.1–0.7, respectively). The same pattern was observed throughout the follow-up period. Overall assessment of treatment tolerability showed a significant trend in favor of the *Lactobacillus GG*-supplemented group ($p = 0.03$). **Conclusions:** *Lactobacillus GG* supplementation beneficially affects *H. pylori* therapy-related side effects and overall treatment tolerance.

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Introduction

The 'rediscovery' of *Helicobacter pylori* and the recognized association between infection and a wide range of gastrointestinal illnesses has profoundly modified management and the therapeutic approach towards most of these conditions [1]. To date, there are numerous treatment options for curing *H. pylori* infection and still many are under investigation [2]. One-week triple therapy, com-

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Antonio Gasbarrini, MD
Patologia Medica, Università Cattolica
Policlinico Gemelli, Largo Gemelli 8
I-00168 Rome (Italy)
Tel. +39 06 30154294, Fax +39 06 35502775, E-Mail angiologia@rm.unicatt.it

binning acid suppression with two antibiotics, is currently considered as the gold standard of anti-*H. pylori* treatment [1]. In fact, it represents the best choice if criteria such as efficacy, tolerability, simplicity of administration, compliance and cost are considered [3–5]. Nevertheless, inappropriate regimen prescription, primary and secondary bacterial resistance, poor patient compliance (closely dependent on the frequency and duration of drug administration and on side effects) are among factors which may render *H. pylori* eradication a hard task [6]. In particular, antibiotic-associated gastrointestinal side effects are considered one of the major drawbacks of triple therapies, although they are generally mild [7]. The high prevalence of side effects might induce motivated and/or dyspeptic patients to break off therapy, with the risk of treatment failure or possible development of antibiotic-resistant strains.

Antibiotic treatments are often associated with gastrointestinal side effects, such as diarrhea, nausea, vomiting, bloating, abdominal pain [8]. These manifestations have been related to quantitative and qualitative changes in the intestinal microflora due to unabsorbed or secreted antibiotics in the intestinal content, with the resulting reduction in normal saprophytic flora and overgrowth and persistence of potentially pathogenic antibiotic-resistant indigenous strains [9, 10].

Current evidence supports the concept that probiotics are effective tools for controlling overgrowth of potentially pathogenic microorganisms and that oral administration of probiotics may be useful for preventing or lowering the occurrence of antibiotic-associated side effects [11]. In particular, it has been documented that *Lactobacillus casei* *sps.rhamnosus* (*Lactobacillus GG*), a probiotic of human origin, exerts a beneficial effect in the prevention and treatment of many types of intestinal disturbances [12].

Since no formal prospective study has been performed to observe the benefits of probiotic supplementation in reducing the pitfalls of eradication regimens, we examined the effect of adding a *Lactobacillus GG* preparation on antibiotic-associated side effects and treatment tolerability, during and after a standard triple *H. pylori* eradication therapy.

Patients and Methods

The study was a single-center, open, prospective, randomized trial carried out on 120 *H. pylori*-positive healthy asymptomatic volunteers (male/female 54/66; mean age 37 ± 11 years), working at the Gemelli Hospital (Catholic University Teaching Hospital) in Rome

as physicians, biologists, nurses or administrative personnel, from May 1 to July 31, 1999. The study population consisted of subjects attending a screening program for the assessment of the prevalence and risk factors for *H. pylori* infection among healthcare workers [13]. Both ^{13}C -urea breath test and enzyme-linked immunosorbent assay for *H. pylori* IgG antibody measurements were performed. Those *H. pylori*-positive asymptomatic subjects who wished to be cured were included in the study, which was approved by the Ethics Committee of the Catholic University. Subjects were defined as asymptomatic in the absence of dyspeptic symptoms and active organic disease, and were not taking any medication at time of enrollment. Only asymptomatic subjects were considered in order to avoid any possible interference between pretreatment symptoms and newly occurring gastrointestinal drugs side effects.

Six weeks after completion of triple therapy the ^{13}C -urea breath test was repeated to check whether eradication had been achieved.

Treatment

Subjects were randomly assigned to a 7-day triple therapy consisting of pantoprazole 40 mg b.i.d. (before breakfast and dinner), clarithromycin 500 mg b.i.d. (0.5 h after breakfast and dinner), tinidazole 500 mg b.i.d. (0.5 h after breakfast and dinner; group 1, male/female 28/32, mean age 36.8 ± 10 years), or to the same regimen supplemented with a probiotic preparation (freeze-dried powder) containing *Lactobacillus GG* (6×10^9 of viable bacteria, Giflorex®, Errekappa Euroterapici S.p.A., Milan, Italy) b.i.d. (2 h after breakfast and dinner, mixed with water) for 14 days, during and the week after eradication therapy (group 2, male/female 26/34, mean age 37 ± 11.3 years). The method of ‘closed envelopes’ was used for drug administration.

Side Effects and Treatment Tolerability Evaluation

For each subject, the side effect profile and treatment tolerability were assessed using the questionnaire proposed by de Boer et al. [14], slightly modified. To obtain the highest compliance in registering any possible treatment-related side effects, we endeavored to educate and train the subjects (both by verbal explanations and printed instructions) to fill out the questionnaire. In particular, each subject had to report the presence of symptoms (taste disturbances, loss of appetite, nausea, vomiting, stomach pain, bloating, diarrhea, constipation, headache) and was asked to judge each side effect according to severity: mild (effect observed, but could be disregarded), moderate (effect sometimes interfered with daily activities) or severe (effect continuously interfered with daily activities). The side effect questionnaire was filled in four times (once a week: during eradication regimen and at the end of the 1st, 2nd and 3rd week thereafter). Moreover, in order to evaluate the impact of side effects on treatment compliance, subjects had to provide an overall judgement of tolerability based on a 5-point scale (a = no side effects; b = slight discomfort, not interfering with daily activities; c = moderate discomfort, sometimes interfering with daily activities; d = severe discomfort, subject could finish the treatment but work was not possible; e = severe discomfort, subject forced to discontinue treatment) [14]. Finally, protocol adherence was verified through tablet/sachet count in medication containers brought back by the subjects shortly after finishing therapy. Subjects returning empty medication boxes were considered compliant.

Statistical Analysis

For each symptom, the relative risk (RR) and 95% confidence interval (CI) in the *Lactobacillus GG*-supplemented group (group 2)

with respect to control group (group 1, not supplemented) were calculated. When RR and CI values were <1, *Lactobacillus GG* supplementation was considered a significant protective factor for that individual side effect. Symptom severity and overall judgement of tolerability scores were analyzed by means of Fisher's exact test. Mann-Whitney U test was used to compare differences in *H. pylori* eradication between groups. A p value of < 0.05 was considered statistically significant. Calculations were made using the STATA 6.0 program (STATA Corporation, College Station, Tex., USA).

Results

Side Effect Profile

Thirty-seven of 60 subjects (61.6%) in group 1 and 26 of 60 (43.3%) subjects in group 2 experienced at least one side effect during the eradication regimen (RR = 0.7, 95% CI 0.5–0.9, p = 0.04). Table 1 shows the incidence of side effects (bloating, nausea, taste disturbances, loss of appetite and diarrhea) most frequently reported by the groups during both the eradication week and follow-up. In particular, bloating, diarrhea and taste disturbances were significantly lower in the *Lactobacillus GG*-supplemented group (table 1; fig. 1). In both groups, side effects progressively decreased during follow-up (table 1). However, a significant difference between groups remained both for

Fig. 1. Side effect frequencies that were significantly different between study groups during both the triple-therapy week and follow-up. **a** Bloating. Triple-therapy week: RR = 0.4, 95% CI 0.2–0.8; 1st week: RR = 0.5, 95% CI 0.3–0.8; 2nd week: RR = 0.3, 95% CI 0.1–0.6; 3rd week: RR = 0.4, 95% CI 0.1–1.2. **b** Diarrhea. Triple-therapy week: RR = 0.3, 95% CI 0.1–0.8; 1st week: RR = 0.2, 95% CI 0.04–0.8; 2nd week: RR = 0.5, 95% CI 0.1–2.6; 3rd week: nought. **c** Taste disturbances. Triple-therapy week: RR = 0.3, 95% CI 0.1–0.7; 1st week: RR = 0.3, 95% CI 0.1–0.9; 2nd and 3rd weeks: nought. □ = Group 1; ■ = group 2. *Significant; NS = not significant.

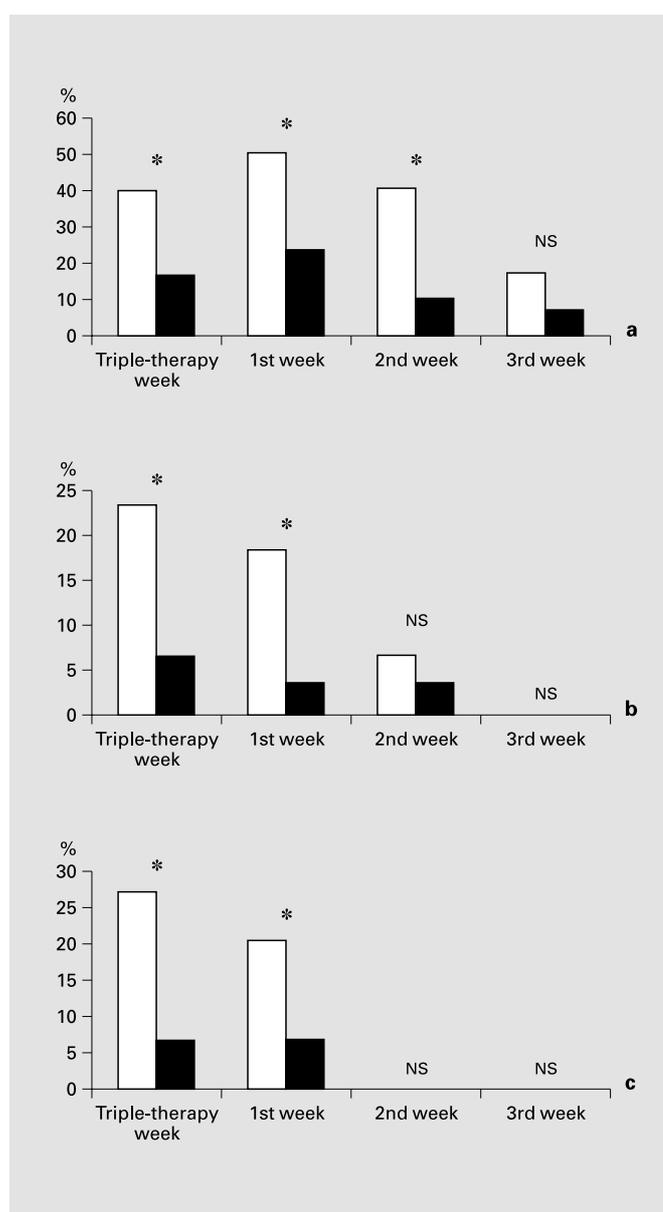


Table 1. Frequencies of side effects most often reported by the 2 groups during the eradication week and follow-up

Symptoms	Triple therapy week				1st week				2nd week				3rd week			
	Group 1 %	Group 2 %	RR	95% CI	Group 1 %	Group 2 %	RR	95% CI	Group 1 %	Group 2 %	RR	95% CI	Group 1 %	Group 2 %	RR	95% CI
Taste disturbances	26.6	6.6	0.3	0.1–0.7*	20	6.6	0.3	0.1–0.9*	–	–	–	–	–	–	–	–
Loss of appetite	18.3	11.6	0.6	0.3–1.5	15	8.3	0.6	0.2–1.6	3.3	–	–	–	–	–	–	–
Nausea	23.3	26.6	1.1	0.6–2.1	20	13.3	0.7	0.3–1.5	10	6.6	0.7	0.2–2.2	6.6	6.6	1	0.3–3.8
Bloating	40	16.6	0.4	0.2–0.8*	50	23.3	0.5	0.3–0.8*	40	10	0.3	0.1–0.6*	16.6	6.6	0.4	0.1–1.2
Diarrhea	23.3	6.6	0.3	0.1–0.8*	18.3	3.3	0.2	0.04–0.8*	6.6	3.3	0.5	0.1–2.6	–	–	–	–

* Significant.

Table 2. Comparison of taste disturbances, bloating and diarrhea severity between study groups during the eradication week

Symptoms	Group 1				Group 2				p value
	none	mild	moderate	severe	none	mild	moderate	severe	
Taste disturbances, %	73.3	23.3	3.3	–	93.3	6.7	–	–	0.007
Bloating, %	60	31.7	8.3	–	83.3	15	1.7	–	0.014
Diarrhea, %	76.7	18.3	5	–	93.3	6.7	–	–	0.023

Table 3. Overall judgement of treatment tolerability reported by the study groups

Subjects		Five-point scale					Total
		0	1	2	3	4	
Group 1	n	23	22	12	–	3	60
	%	38.3	36.7	20	–	5	100
Group 2	n	34	18	7	1	–	60
	%	56.7	30	11.7	1.6	–	100

p = 0.07 (Fisher's exact test); after test for trend: p = 0.03.

diarrhea and taste disturbances until the 1st week, while a significant difference in bloating lasted until the 2nd follow-up week (table 1; fig. 1). At the end of the study, symptoms, when present, did not significantly differ between study groups (table 1). The incidence of other reported side effects such as stomach pain (group 1 vs. group 2; triple-therapy week: 10 vs. 6.6%, RR = 0.7, 95% CI 1.2–2.2; 1st week: 6.6 vs. 6.6%, RR = 1, 95% CI 0.3–3.8; 2nd week: 3.3 vs. 0%; 3rd week: nought), vomiting (group 1 vs. group 2; triple-therapy week: 6.6 vs. 3.3%, RR = 0.5, 95% CI 0.1–2.6; 1st week: 3.3 vs. 0%; 2nd and 3rd week: nought), constipation (group 1 vs. group 2; triple-therapy week: 6.6 vs. 10%, RR = 1.5, 95% CI 0.4–5.0; 1st week: 10 vs. 6.6%, RR = 0.7, 95% CI 0.2–2.2; 2nd week: 3.3 vs. 3.3%, RR = 1, 95% CI 0.1–6.9; 3rd week: 3.3 vs. 3.3%, RR = 1, 95% CI 0.1–6.9) and headache (group 1 vs. group 2; triple-therapy week: 3.3 vs. 6.6%, RR = 2, 95% CI 0.4–10.5; 1st week: 6.6 vs. 3.3%, RR = 0.5, 95% CI 0.1–2.6; 2nd week: 3.3 vs. 3.3%, RR = 1, 95% CI 0.1–6.9; 3rd week: 3.3 vs. 0%) was lower and no significant differences appeared between groups.

With respect to side effect severity, mild (especially) to moderate symptoms were reported during the eradication

week, whilst only mild side effects were reported the following weeks by both groups. Significant differences were observed for taste disturbances (p = 0.007), bloating (p = 0.01) and diarrhea (p = 0.02; table 2), while with regard to other experienced symptoms such as loss of appetite (group 1 vs. group 2; none: 81.7 vs. 88.3%; mild: 13.3 vs. 8.3%; moderate: 5 vs. 3.3%; severe: nought), nausea (group 1 vs. group 2; none: 76.7 vs. 73.3%; mild: 18.3 vs. 21.7%; moderate: 5 vs. 5%; severe: nought), vomiting (group 1 vs. group 2; none: 93.3 vs. 96.7%; mild: 6.7 vs. 3.3%; moderate and severe: nought), stomach pain (group 1 vs. group 2; none: 90 vs. 93.3%; mild: 10 vs. 6.7%; moderate and severe: nought), constipation (group 1 vs. group 2; none: 93.3 vs. 90%; mild: 6.7 vs. 10%; moderate and severe: nought) and headache (group 1 vs. group 2; none: 96.7 vs. 93.3%; mild: 3.3 vs. 6.7%; moderate and severe: nought) side effect severity score between groups was not significant.

Treatment Tolerability

Based on the 5-point scale overall judgement of tolerability adopted, in group 1, 23 of 60 subjects reported no side effects, 22 of 60 subjects reported slight discomfort, 12 of 60 subjects reported moderate discomfort, while 3 of 60 subjects (5%) reported severe discomfort forcing them to discontinue treatment. In particular, 1 subject quit therapy because of arising diarrhea, nausea, vomiting during the 2nd day of therapy, another because of the occurrence of stomach pain, bloating and taste disturbances after 4 days of therapy, and another because of the occurrence of nausea, loss of appetite, taste disturbances, bloating and diarrhea after 3 days of therapy. In the *Lactobacillus GG*-supplemented group (group 2) 34 of 60 subjects reported no side effects, 18 of 60 subjects reported slight discomfort, 7 of 60 subjects reported moderate discomfort, 1 of 60 subjects reported severe discomfort, but none of them had to discontinue treatment (table 3). Fisher's exact test between groups did not show significant dif-

ferences ($p = 0.07$), but further statistical analysis by means of the test for trend gave significant differences ($p = 0.03$).

Based on the tablet/sachet count after bringing back the medication containers, all subjects who finished therapy were '100% adherent' with respective protocols.

H. pylori Eradication

No significant differences were observed between groups with respect to success in *H. pylori* eradication, both when evaluated for intention to treat (ITT) or per protocol (PP) analyses (group 1 vs. group 2; ITT: 76.6 vs. 80%, $p = 0.6$; PP: 80.7 vs. 80 %, $p = 0.9$).

Discussion

This pilot study describes the effects of the oral administration of probiotics (*Lactobacillus GG*) on antibiotic-associated gastrointestinal morbidity during and after anti-*H. pylori* standard triple therapy. Probiotic supplementation tended to improve treatment tolerability.

This observation could be useful based upon some considerations. In fact, in the treatment of *H. pylori*-associated gastrointestinal diseases various antibiotic regimens are currently used in clinical practice. Efficacy has been considered the most important criterion for drug choice. Because of the synergistic activity of antimicrobial combinations, 7-day triple regimens, combining an acid suppressor agent with two antibiotics, are currently preferred to dual therapies [1]. The frequency and duration of drug administration and the occurrence of side effects that may influence patient compliance should be considered before selection [15]. The use of different scoring systems, the difficulty to define a symptom as a 'side effect', or the investigators' carelessness in registering such complaints, make it very difficult to compare the side effect profile among the different eradication regimens [7]. It should also be emphasized, however, that with an easy-to-manage population particularly skilled in the use of health care tools (in our case, questionnaires and protocol compliance), as with physicians, nurses or hospital personnel, data can assume more reliability, but also an overestimation could lead to drawing premature conclusions, as can often happen. Even because of these discordances, frequencies of side effect occurrence reported by several triple-therapy studies range from low to very high [2, 7], but, generally, symptom severity is mild or at most moderate. Overall treatment tolerability, meaning how side effects may influence patient compliance [7], is an essential end

point. In triple therapy studies there are conflicting results concerning side effect-influenced compliance, but there is little evidence that side effects may strongly affect final eradication rates [3]. Such a tendency, however, may not be identical in the whole community setting.

At present, no ideal therapy for *H. pylori* infection exists which is effective, simple, safe, side effect-free and cheap at the same time. Reduction of any further discomfort in patients already complaining of dyspeptic symptoms must be considered. Patients may also be reluctant to start or to comply with antibiotic therapy because of the troublesome associated gastrointestinal complaints. A safe and simple approach to this issue could be to administer probiotics.

Probiotics are defined as live microbial organisms which, when ingested, beneficially affect human health, including the amelioration or prevention of a specific disease state [16]. The efficacy of taking prophylactic probiotics together with antibiotics, in preventing or decreasing gastrointestinal antibiotic-associated side effects, has been investigated in several studies [11]. *Lactobacillus GG*, a probiotic strain of human origin, has most of the general characteristics (survival in gastric and bile secretions, adherence, colonization, antimicrobial production, immune stimulation, antigenotoxic activity, prevention of pathogens) proposed for a good probiotic strain [12]. In particular, *Lactobacillus GG* has been documented to be effective in various clinical situations such as shortening the duration and severity of Rotavirus diarrhea [17], decreasing the incidence of traveler's diarrhea [18], preventing and treating relapses of *Clostridium difficile* colitis [19], and preventing or ameliorating antibiotic-associated diarrhea [20–22]. *Lactobacillus GG* resistance to a wide range of clinically important antibiotics [23] and the good colonization observed during some antibiotic treatment [20, 24] could make the development of antibiotic-probiotic combination therapies possible for several conditions.

Our study showed a high incidence of gastrointestinal side effects during anti-*H. pylori* triple therapy. The standard side effect scoring system [14] we used is one of the most accurate proposed to date since it summarizes previously adopted questionnaires [24–27]. In the *Lactobacillus GG*-supplemented group a significant reduction in the percentage of subjects who experienced at least one side effect has been observed. Bloating, taste disturbances and diarrhea during the eradication week were significantly lower in both incidence and severity.

Quantitative and qualitative alterations of normal gastrointestinal flora have recently been demonstrated after

7 days of anti-*H. pylori* therapies, based on omeprazole, clarithromycin or amoxicillin and metronidazole, with the disturbance most pronounced in the clarithromycin-treated group [10]. Most of the antibiotic-associated gastrointestinal side effects reported in our study probably reflect such a microbiological disruption, given that *Lactobacillus GG* supplementation may partially restore the normal intestinal microecology and, therefore, be beneficial in preventing or significantly decreasing some of these unpleasant manifestations. An additive mechanism by which *Lactobacillus GG* is able to prevent diarrhea could be the postulated inhibition of macrolides prokinetic action [11, 28, 29]. Taste disturbances are a commonly occurring phenomenon with antibiotic administration, especially when using nitroimidazole-derived drugs [30]. A plausible explanation for a positive effect of probiotics on reducing taste disturbances is difficult to find and a possible placebo effect can first be invoked to explain the observed benefit.

Finally, with regard to treatment tolerability, a significant result at test for trend analysis of improved treatment tolerance has been documented in the *Lactobacillus GG*-supplemented group, with a progressive decrease at follow-up in both groups. Still, the study performed has the

potential bias of not having a placebo-controlled design, and the outcomes, which were all based on subjective parameters, could in part be influenced by such an issue.

Lowering the incidence and obtaining a more rapid relief of some symptoms in *Lactobacillus GG*-supplemented subjects during the post-treatment period could be considered helpful for patients (adults and, notably, children) in whom eradication fails. In fact, they could be less reluctant to start or more compliant to follow a further eradication attempt. The clinical impact of these data, if confirmed, might therefore be relevant for improving treatment tolerability and probiotic supplementation could be proposed for routine practice in this setting. However, adding *Lactobacillus GG* to traditional anti-*H. pylori* schemes did not seem to affect the eradication rate, even if different conclusions might be drawn when using other probiotic species [31].

In conclusion, this open study demonstrates that probiotic supplementation, during and after a standard triple *H. pylori* eradication therapy, may beneficially affect therapy-related symptomatology and, perhaps, overall treatment tolerance. Double-blind placebo-randomized trials, however, remain essential to confirm or modify these preliminary results.

References

- 1 The European *Helicobacter pylori* Study Group: Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. *Gut* 1997;41:8–13.
- 2 Harris A: Current regimens for treatment of *Helicobacter pylori* infection. *Br Med Bull* 1998;54:195–205.
- 3 Penston JG, McColl KEL: Eradication of *Helicobacter pylori*: An objective assessment of current therapies. *Br J Clin Pharmacol* 1997;43:223–243.
- 4 Gasbarrini A, Ojetti V, Armuzzi A, Branca G, Canducci F, Sanz Torre E, Candelli M, Pastorelli A, Anti M, Fedeli G, Fadda G, Pola P, Gasbarrini G: Efficacy of a multistep strategy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2000;14:79–83.
- 5 Cammarota G, Cannizzaro O, Ojetti V, Cianci R, Pastorelli A, Armuzzi A, Gentiloni N, Gasbarrini A, Pirozzi G, Gasbarrini G: Five-day regimens containing ranitidine bismuth citrate plus high-dose clarithromycin and either amoxicillin or tinidazole for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2000;14:73–77.
- 6 Deltenre M, Ntounda R, Jonas C, De Koster E: Eradication of *Helicobacter pylori*: Why does it fail? *Ital J Gastroenterol Hepatol* 1998;30 (suppl 3):S326–S328.
- 7 de Boer WA, Tytgat GNJ: The best therapy for *Helicobacter pylori* infection: Should efficacy or side-effect profile determine our choice? *Scand J Gastroenterol* 1995;30:401–407.
- 8 Marteau P, Rambaud JC: Potential of using lactic acid bacteria for therapy and immunomodulation in man. *FEMS Microbiol Rev* 1993;12:207–220.
- 9 Nord CE, Heimdal A, Kager L: Antimicrobial induced alterations of the human oropharyngeal and intestinal microflora. *Scand J Infect Dis* 1986;49:64–72.
- 10 Adamsson I, Nord CE, Lundquist P, Sjostedt S, Edlund C: Comparative effects of omeprazole, amoxicillin, plus metronidazole versus omeprazole, clarithromycin plus metronidazole on the oral, gastric and intestinal microflora in *Helicobacter pylori*-infected patients. *J Antimicrob Chemother* 1999;44:629–640.
- 11 Lewis SJ, Freedman AR: The use of biotherapeutic agents in the prevention and treatment of gastrointestinal disease. *Aliment Pharmacol Ther* 1998;12:807–822.
- 12 Saxelin M: *Lactobacillus GG* – A human probiotic strain with thorough clinical documentation. *Food Rev Int* 1997;13:293–313.
- 13 Gasbarrini G, Gasbarrini A, Anti M, Armuzzi A, Franceschi F, Lippi ME, Candelli M, Paolucci M, Cicconi V, Cammarota G, Pretolani S, Strofollini T: The CUE (Catholic University Epidemiological) study: Prevalence of *H. pylori* infection in a population working at a university hospital. *Gut* 1998;43(suppl 2):A43.
- 14 de Boer WA, Thys JC, Borody TJ, Graham DY, O'Morain CO, Tytgat GNJ: Proposal for use of a standard side effect scoring system in studies exploring *Helicobacter pylori* treatment regimens. *Eur J Gastroenterol Hepatol* 1996;8:641–643.
- 15 Peura D: *Helicobacter pylori*: Rational management options. *Am J Med* 1998;105:424–430.
- 16 Fuller R: Probiotics in human medicine. *Ann Med* 1990;22:37–41.
- 17 Isolauri E, Kaila M, Mikkanen H, Ling WH, Salminen S: Oral bacteriotherapy for viral gastroenteritis. *Dig Dis Sci* 1994;12:2595–2600.
- 18 Hilton E, Kolakowski P, Singer C, Smith M: Efficacy of *Lactobacillus GG* as a diarrheal preventive in travelers. *J Trav Med* 1997;4:41–43.

- 19 Biller JA, Katz AJ, Flores AF, Buie TM, Gorbach SL: Treatment of recurrent *Clostridium difficile* colitis with *Lactobacillus GG*. *J Pediatr Gastroenterol Nutr* 1995;21:224–226.
- 20 Siitonen S, Vapaatalo H, Salminen S, Gordin A, Saxelin M, Wikberg R, Kirkkola AL: Effect of *Lactobacillus GG* yoghurt in prevention of antibiotic associated diarrhoea. *Ann Med* 1990;22:57–59.
- 21 Arvola T, Laiho K, Torkkeli S, Mykkanen H, Salminen S, Maunula L, Isolauri E: Prophylactic *Lactobacillus GG* reduces antibiotic-associated diarrhea in children with respiratory infections: A randomized study. *Pediatrics* 1999; 104:64.
- 22 Vandehoof JA, Whitney DB, Antonson DL, Hanner TL, Lupo JV, Young RJ: *Lactobacillus GG* in the prevention of antibiotic-associated diarrhea in children. *J Pediatr* 1999;135:564–568.
- 23 Charteris WP, Kelly PM, Morelli L, Collins JK: Antibiotic susceptibility of potentially probiotic *Lactobacillus* species. *J Food Prot* 1998;61: 1636–1643.
- 24 Goldin BR, Gorbach SL, Saxelin M, Barakat S, Gualtieri L, Salminen S: Survival of *Lactobacillus* species (strain GG) in human gastrointestinal tract. *Dig Dis Sci* 1992;37:121–128.
- 25 de Boer WA, Driessen WMM, Jansz AR, Tytgat GNJ: Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. *Lancet* 1995;345:817–820.
- 26 Borody TJ, Andrews P, Fracchia G, Brandl S, Shortis NP, Bae H: Omeprazole enhances efficacy of triple therapy in eradicating *Helicobacter pylori*. *Gut* 1995;37:477–481.
- 27 Thys JC, van Zwet AA, Oey HB: Efficacy and side effects of a triple drug regimen for the eradication of *Helicobacter pylori*. *Scand J Gastroenterol* 1993;28:934–938.
- 28 Tomomasa T, Kuroume T, Arai H, Wakasashi K, Itoh Z: Erythromycin induces migrating motor complexes in human gastrointestinal tract. *Dig Dis Sci* 1986;31:157–161.
- 29 Bortolotti M, Brunelli F, Sarti P, Mari C, Miglioli M: Effects of oral clarithromycin and amoxicillin on interdigestive gastrointestinal motility of patients with functional dyspepsia and *Helicobacter pylori* gastritis. *Aliment Pharmacol Ther* 1998;12:1021–1025.
- 30 de Boer WA, Driessen WMM, Potters HVPJ, Tytgat GNG: Randomized study comparing one with two weeks of quadruple therapy for eradicating *Helicobacter pylori*. *Am J Gastroenterol* 1994;89:1993–1997.
- 31 Michetti P, Dorta G, Wiesel PH, Brassart D, Verdu E, Herranz M, Felley C, Porta N, Rouvet M, Blum AL, Cortesy-Theulaz I: Effect of whey-based culture supernatant of *Lactobacillus acidophilus (johnsonii)* La1 on *Helicobacter pylori* infection in humans. *Digestion* 1999;60: 203–209.