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Probiotics and intestinal health effects: a clinical perspective

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Probiotics are viable non-pathogenic micro-organisms which, when ingested, exert a positive influence on host health or physiology. We have critically analysed the evidence for the efficacy of specific probiotic strains in human gastrointestinal diseases. The best evidence can be obtained with randomised controlled trials which avoid bias. Good evidence has been obtained with several strains in the prevention or treatment of antibiotic-associated disorders, in the treatment (and to a lesser extent prevention) of gastroenteritis and acute diarrhoea and in the alleviation of lactose intolerance. We also analysed the recent randomised controlled trials performed in patients with *Clostridium difficile* or *Helicobacter pylori*, inflammatory bowel disease, irritable bowel syndrome, non-ulcer dyspepsia and colon cancer.

Probiotics: Intestine: Gastroenteritis: Inflammatory bowel disease: Antibiotic-associated diarrhoea

Introduction

Probiotics have been defined as viable non-pathogenic micro-organisms which, when ingested, exert a positive influence on host health or physiology (Schrezenmeir & de Vrese, 2001). They consist either of bacteria, especially lactobacilli and bifidobacteria but also *Escherichia coli*, enterococci or yeast (*Saccharomyces*). Some products contain a single strain while others consist of mixtures of several strains. The evidence supporting their efficacy in the treatment or prevention of intestinal disorders is increasing owing to a more systematic approach (Marteau *et al.* 1993). This paper summarises the evidence for positive effects of some probiotics in intestinal health, focusing on recent data and discussing the perspectives. The levels of evidence are based on study design and the methodological quality of individual studies, the best evidence coming from randomised controlled trials (RCT) with minimal bias.

The strength of evidence for positive effects of probiotics in intestinal disorders is good for antibiotic-associated diarrhoea, gastroenteritis and lactose intolerance. It is rapidly increasing, although more slowly, for inflammatory bowel disease and intestinal infections.

Antibiotic-associated intestinal disorders

Intestinal disorders, especially diarrhoea, occur frequently in patients who receive antibiotics, and result from a decrease in the colonisation resistance and fermentation capacity of the endogenous intestinal flora. RCT have shown that several probiotics (but not all) can prevent or shorten antibiotic-associated intestinal disorders (mainly diarrhoea); (Bergogne-Berezin, 2000; Marteau *et al.* 2001). Good evidence for clinical efficacy has been obtained for *Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG and *Enterococcus faecium* SF68 (Table 1). However, some trials using the same products were negative and the reason for the discrepancy between studies is unclear (Table 1). Dose–response studies are lacking but most positive trials have used large doses. The mechanism involved is also unclear as multiple biological effects of the probiotics may contribute to the clinical efficacy. For example, *S. boulardii* can favourably influence population levels of *Clostridium difficile* in the colon, toxin production, the signalling pathway induced by bacterial infection, and intestinal secretion (Elmer *et al.* 1996; Czeruka *et al.* 2000). The cost-effectiveness of the use of probiotics together with antibiotics has not been assessed. Experts often recommend probiotic prevention with an active strain in high-risk subjects such as elderly subjects or patients receiving several antibiotics or those who had previous episodes of antibiotic-associated intestinal disorders (Bergogne-Berezin, 2000).

Gastroenteritis

Gastroenteritis is the main cause of acute diarrhoea, a frequent disorder that heals, usually spontaneously, within a

Abbreviations: IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; RCT, randomised controlled trial.

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Table 1. Randomised controlled trials performed with *Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG, and *Enterococcus faecium* SF68 to prevent antibiotic-associated diarrhoea

Probiotic/antibiotic	Number of subjects	Diarrhoea probiotic *v.* placebo	Reference
S. boulardii			
β-Lactamins or tetracyclins	388	4·5 % *v.* 17·5 %*	Adam *et al.* (1977)
Miscellaneous	180	9·5 % *v.* 21·8 %*	Surawicz *et al.* (1989)
β-Lactamins	193	7·2 % *v.* 14·6 %*	McFarland *et al.* (1995)
Miscellaneous	69	14 % *v.* 20 % (NS)	Lewis *et al.* (1998)
L. rhamnosus GG			
Miscellaneous	188	7 % *v.* 25 %*	Vanderhoof *et al.* (1999)
Miscellaneous	119	5 % *v.* 16 %*	Arvola *et al.* (1999)
Clarithromycin + tinidazole	60	+*	Armuzzi *et al.* (2001)
Miscellaneous	302	29·3 % *v.* 29·9 % (NS)	Thomas *et al.* (2001)
E. faecium SF68			
Antituberculous	200	5 % *v.* 18 %*	Borgia *et al.* (1982)
Miscellaneous	45	8·7 % *v.* 27·2 %*	Wunderlich *et al.* (1989)

* $P < 0{\cdot}05$, (NS); No statistically significant difference.

few days. The use of oral rehydration solutions is the main treatment, especially in infants and elderly people, but it does not shorten the duration of diarrhoea.

Curative treatment

More than fifteen RCT demonstrated a beneficial effect of some but not all probiotic products in infantile or adult gastroenteritis (see references in Marteau *et al.* 2001). *L. rhamnosus* GG repeatedly shortened diarrhoea to about half in infants with rotavirus diarrhoea (Shornikova *et al.* 1997*a*). It also proved effective in the treatment of acute diarrhoea in children in Asia, Peru, Pakistan, Karelia (Raza *et al.* 1995; Pant *et al.* 1996; Shornikova *et al.* 1997*a*; Oberhelman *et al.* 1999). In a recent European RCT (Guandalini *et al.* 2000), 287 children aged 1–36 months with acute diarrhoea received an oral rehydration solution which was supplemented either with *L. rhamnosus* GG (at least 10^9 cfu per 250 ml) or with a placebo. The duration of diarrhoea was significantly shortened by the probiotic in the children with rotavirus infection: 56 ± 17 h versus 77 ± 42 h, but not in those who were rotavirus negative ($n = 186$). *L. rhamnosus* GG administration also shortened the duration of hospital stay (Guandalini *et al.* 2000). Heat-inactivated *L. rhamnosus* GG was clinically as effective as the viable lactobacillus in the prevention of diarrhoea in one study (Kaila *et al.* 1995). *E. faecium* strain SF68 significantly shortened diarrhoea in four RCT (Wunderlich *et al.* 1989). Other probiotics such as *Lactobacillus casei* strain Shirota (Sugita and Togawa, 1994) and *Lactobacillus reuteri* (Shornikova *et al.* 1997*b*) are probably also effective but there is less evidence as fewer studies have been performed.

Prevention

Saavedra *et al.* (1994) demonstrated for the first time that giving some probiotics to infants admitted to hospital could significantly reduce the risk of diarrhoea and shedding of rotavirus. In a double-blind placebo-controlled trial, fifty-five children admitted to a chronic medical care unit were randomised to receive a standard milk formula or the same plus *Bifidobacterium bifidum* and *Streptococcus thermophilus*. During follow-up, diarrhoea occurred in 7 % of the children receiving the probiotics versus 31 % of the controls, and the shedding of rotavirus was reduced (10 % versus 39 %). Four trials have used the *L. rhamnosus* strain GG and provided conflicting results. In a double-blind RCT (Szajewska *et al.* 2001), eighty-one children aged 1–36 months who were hospitalised for reasons other than diarrhoea received either *L. rhamnosus* GG 6×10^9 cfu or a placebo orally twice daily for the duration of their hospital stay. The probiotic reduced the risk of nosocomial diarrhoea (6·7 % versus 33·3 %). In this study, the prevalence of rotavirus infection was similar in the *L. rhamnosus* GG and placebo groups (20 % versus 27·8 %) but the risk of rotavirus gastroenteritis was reduced (27·2 % versus 16·7 %). Another double-blind RCT performed in Italy included 269 children and failed to confirm the protective effect of *L. rhamnosus* GG against nosocomial infection with rotavirus (Mastretta *et al.* 2002). In another RCT which included 204 undernourished Peruvian children, *L. rhamnosus* GG had no preventive effect against diarrhoea in breast-fed infants but it reduced the risk of diarrhoea in non-breast-fed infants (4·7 episodes of diarrhoea per infant per year in the probiotic group versus 5·9 in the placebo group; Oberhelman *et al.* 1999). A Finnish study included 571 healthy children aged 1–6 years attending day care centres and who were followed for seven months during the winter. Half of the children received *L. rhamnosus* GG and the other half a placebo. The authors reported a trend for a decrease in respiratory infections but no effect on the risk of diarrhoea (Hatakka *et al.* 2001).

Lactose intolerance

Lactose maldigestion is a frequent situation in adults and in subjects with acute or chronic enteritis or bowel resection. Alleviation of lactose intolerance has been one of the first effects of probiotics to be demonstrated (Marteau *et al.* 1997). The best evidence has been obtained with yoghurt bacteria that contain high levels of lactase that is rapidly released when the bacteria are lysed by bile salts in the

gastrointestinal tract (Marteau *et al.* 1990). Other probiotics containing lactase such as *Lactobacillus acidophilus* may also be active but their higher resistance to bile probably explains why they are less efficient than yoghurt bacteria (Marteau *et al.* 1997). In clinical practice, replacement of milk by yoghurt or fermented dairy products allows better digestion and/or decreases diarrhoea and other intolerance symptoms in subjects with lactose intolerance, in children with diarrhoea, and in subjects with short bowel syndrome (Arrigoni *et al.* 1994; Marteau *et al.* 1997).

Probiotic strains which are rapidly destroyed in the duodenum such as yoghurt bacteria, or lactococci could be used as vectors for enzymes or oral immunisation (Mercenier *et al.* 2000). We recently showed that an oral treatment with genetically modified *Lactococcus lactis* expressing *Staphylococcus hyicus* lipase enhanced lipid digestion in pigs with experimental pancreatic insufficiency (Drouault *et al.* 2001). The clinical interest of this new way of delivery needs to be studied in more detail.

Intestinal infections and colonisation by pathogenic bacteria

The protective effects of probiotics against intestinal infections have been demonstrated in animal models (Reid *et al.* 2001). Several mechanisms have been suggested which are not exclusive, such as production of various acids, hydrogen peroxide or bacteriocins, competition for nutrients or adhesion receptors, anti-toxin actions and stimulation of the immune system. Open studies have suggested a beneficial role of *L. rhamnosus* GG, *S. boulardii* and *Lactobacillus plantarum* LP299v during *C. difficile*-related infections. However, such observational studies do not provide strong evidence. Two placebo-controlled RCT demonstrated some efficacy of *S. boulardii* to decrease the risk of recurrence of *C. difficile* infection (McFarland *et al.* 1994; Surawicz *et al.* 2000). The first trial compared the efficacy of the standard antibiotic treatment combined either with *S. boulardii* (1 g/d for 28 d) or with a placebo. The risk of recurrence was significantly reduced by the probiotic for the subjects who had had several episodes of *C. difficile* infection (34·6 % versus 64·7 %) but not in the subjects treated for a first episode of *C. difficile* infection (McFarland *et al.* 1994). In the second study, a significant decrease in the risk of recurrence was observed in patients treated with a high dose of vancomycin plus *S. boulardii* versus those who received a high dose of vancomycin plus placebo (Surawicz *et al.* 2000).

Colonisation of the gastric mucosa by *Helicobacter pylori* is common and strongly associated with gastritis, duodenal and gastric ulcers, gastric carcinoma and lymph oma. Several probiotic strains, especially lactobacilli, exhibit antagonistic properties against *H. pylori in vitro* (Michetti, 2001). An open study showed a reduction of the urease activity of *H. pylori* in patients treated with a supernatant of *Lactobacillus johnsonii* LA1 (Michetti *et al.* 1999). In a recent trial by Felley *et al.* (2001), fifty-five volunteers with *H. pylori* infection received clarithromycin and were randomised to receive in addition either a fermented milk containing *L. johnsonii* LA1 or a placebo. The probiotic proved to significantly reduce the density of *H. pylori* and the intensity of gastric inflammation. Canducci *et al.* (2000) treated 120 *H. pylori* positive patients with the standard therapy (rabeprazole, clarithromycin and amoxicillin) together with either an inactivated culture of *L. acidophilus* or a placebo. The eradication rate of *H. pylori* was 87 % in the probiotic group versus 70 % in the control group ($P=0{\cdot}02$). Armuzzi *et al.* (2001) performed an RCT in sixty subjects with *H. pylori* infection who were treated with rabeprazole, clarithromycin and tinidazole. Half received *L. rhamnosus* GG for 14 days and the others received a placebo. The efficacy of the treatment did not differ between the two groups (83 % versus 80 %) but tolerance to the treatment was better in the probiotic group.

Traveller's diarrhoea

Acute diarrhoea occurs frequently in travellers to high-risk areas. Three double-blind RCT have suggested some preventive efficacy of *L. rhamnosus* GG and S. *boulardii* (Oksanen *et al.* 1990; von Kollaritsch *et al.* 1993; Hilton *et al.* 1997). Unfortunately, these studies had some methodological problems and the evidence for the effect remains low. The first trial reported a reduction of diarrhoea by *L. rhamnosus* GG administration to subjects travelling to one destination in Turkey (Oksanen *et al.* 1990); however, the effect was not observed in subjects travelling to another destination. Overall, the reduction of the risk was not significant. In the second RCT, 400 American travellers received *L. rhamnosus* GG or a placebo (Hilton *et al.* 1997). More than one third were excluded from the analysis because they did not take the medication. When considering only the subjects who took the capsules, the risk of diarrhoea was 3·9 % with the probiotic versus 7·4 % with the placebo ($P=0{\cdot}05$). Although these results are interesting and strengthen the interest in the field, the statistical analysis based only on subgroups in the two studies (and not on an intention to treat basis) is questionable. The same limitation applies for the RCT with *S. boulardii* (von Kollaritsch *et al.* 1993), as only 1016 out of the 3000 Austrian travellers were compliant. Although it is not possible to medically recommend any probiotic at the present time to prevent traveller's diarrhoea, the likelihood for some agents to be effective is high and more thorough studies need to be performed.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is characterised by chronic intestinal inflammation of unknown origin and seems to be influenced by some members of the endogenous flora (Sartor, 1997). Several RCT have recently been performed with probiotics in various IBD-related conditions. The evidence for a relevant effect is now sufficiently strong to prescribe three probiotics to patients: VSL#3, *E. coli* Nissle 1917 and *S. boulardii*. VSL#3 (CSL, Milan, Italy) contains a mixture of four strains of lactobacilli (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. bulgaricus*), three strains of bifidobacteria (*B. longum*, *B. breve*, *B. infantis*) and one strain of *S. thermophilus*.

E. coli Nissle 1917 is a well defined non-pathogenic *E. coli*, and *S. boulardii* is a non-pathogenic yeast.

Ulcerative colitis

Three double-blind RCT compared the efficacy of *E. coli* Nissle 1917 to mesalazine, i.e. the standard treatment, for the maintenance of remission in ulcerative colitis (Kruis *et al.* 1997; Rembacken *et al.* 1999; Kruis *et al.* 2001). The effects did not differ between the probiotic and the anti-inflammatory treatment and the authors concluded that the probiotic was effective. However, it must be stressed that the demonstration of the superiority of the probiotic over placebo has not been made and that the anti-inflammatory treatment used as control in these studies was not optimally effective. In the first trial (Kruis *et al.* 1997), 120 patients with inactive ulcerative colitis received either 1·5 g/d of mesalazine or 5×10^{10} viable *E. coli* Nissle 1917. After 12 weeks, both treatments seemed equally effective, as 11·3 % of the subjects receiving mesalazine and 16 % of those receiving the probiotic had relapsed (no significant difference). However, the study was judiciously criticised, as its statistical power was low (because of the short duration of the treatment). In the second trial, *E. coli* strain Nissle 1917 was compared to mesalazine in 116 patients with ulcerative colitis followed for one year (Rembacken *et al.* 1999). All patients were also initially given a 1-week course of oral gentamycin and steroids. Remission was obtained in 75 % of the patients in the mesalazine group versus 68 % in the *E. coli* group (no significant difference). When remission was reached, the steroids were stopped, and the dose of mesalazine was reduced to 1·2 g/d. After 1 year, relapse occurred in 73 % of the patients in the mesalazine group versus 67 % in the *E. coli* group (no significant difference). This second trial was criticised, as the relapse rate in the mesalazine group was far higher than expected from the literature (i.e. 30 %). In a third trial (Kruis *et al.* 2001), 327 patients with quiescent ulcerative colitis received either the probiotic or mesalazine 1·5 g/d for 1 year. The relapse rate was 45 % in the probiotic group versus 36·4 % in the mesalazine group (no significant difference).

Pouchitis

Gionchetti *et al.* (2000*a*) performed a double-blind RCT comparing the effect of VSL#3 and placebo to prevent recurrence of chronic relapsing pouchitis. Forty patients with chronic relapsing pouchitis were studied. Remission was induced by one month of ciprofloxacin and rifabutin, and the probiotic mixture (6 g/d) or the placebo were then prescribed for nine months. A relapse occurred in 15 % of the subjects in the VSL#3 group versus 100 % in the placebo group ($P < 0{\cdot}001$). The same authors studied the effect of VSL#3 to prevent pouchitis in forty patients who had ileo-pouch anal anastomosis for ulcerative colitis (Gionchetti *et al.* 2000*b*). Patients received either VSL#3 (3 g/d) or placebo for one year after surgery. The risk of pouchitis was significantly lower in the probiotic group: 10 % versus 40 %.

Crohn's disease

In a double-blind RCT, thirty-two patients with Crohn's disease received either 1 g/d of *S. boulardii* plus mesalazine 2 g/d or mesalazine 3 g/d for 1 year to prevent relapse (Guslandi *et al.* 2000). Fewer patients relapsed in the probiotic group (1/16 versus 6/16). Campieri *et al.* (2000) compared the efficacy of a combination of rifaximin 1·8 g/d for three months followed by either VSL#3 or mesalazine 4 g/d to prevent postoperative recurrence of Crohn's disease in forty patients. After one year, the risk of severe endoscopic relapse was 20 % in the probiotic group versus 40 % in the control group. Malchow (1997) in a double-blind RCT treated twenty-eight subjects suffering from Crohn's disease of the colon with *E. coli* Nissle 1917 or placebo. The rate of relapse was significantly lower in the probiotic group (33 % versus 63 %). These promising trials need to be confirmed with a higher number of patients and more rigorous design.

Irritable bowel syndrome and non-ulcer dyspepsia

Some probiotics, especially acidophilus or bifidus milks, have been reported to relieve constipation in short uncontrolled series (Marteau *et al.* 1993). However, these studies were not controlled. Two RCT showed that a milk fermented by *Bifidobacterium animalis* strain DN-173 010 shortened colonic transit time in healthy women (Bouvier *et al.* 2001; Marteau *et al.* 2002). This was also observed in elderly subjects (Méance *et al.* 2002). Halpern *et al.* (1996) showed in a randomised, double-blind, cross-over trial that administration of heat-killed lactobacilli (Lacteol fort®) for six weeks was more efficient than placebo to relieve symptoms of irritable bowel syndrome (IBS). However, the low number of patients included and the poor compliance to treatment do not allow any definitive conclusion. Hentschel *et al.* (1997) assessed the efficacy of two probiotic preparations containing lactobacilli and *E. coli* (Hylac® and Hylac N forte®, Germany) in 126 subjects suffering from non-ulcer dyspepsia, and did not observe any amelioration. In a recent RCT, there was no difference between *L. rhamnosus* GG 10^{10} cfu/d and the placebo to alleviate symptoms of IBS in twenty-four patients (O'Sullivan & O'Morain, 2000). At the present time, the level of evidence that probiotics may help subjects with IBS or non-ulcer dyspepsia is low and no recommendation can be made.

Colon cancer

The endogenous flora and the immune system play a role in the modulation of carcinogenesis, and some probiotics seem effective to prevent or help treat tumours in animal models. Several trials have shown that some probiotics may reproducibly decrease the faecal levels of enzymes, mutagens, and secondary bile salts that may be involved in colon carcinogenesis (Wollowski *et al.* 2001). In addition, some epidemiological studies suggested that consumption of fermented dairy products might have protective effects against large colon adenomas (Boutron *et al.*

1996). The prospect of using probiotics to decrease colon cancer risk is thus open and intervention trials are needed.

Conclusions

Probiotics allow modulation of the endogenous intestinal flora and the immune system and can be used to modulate activities of the gastrointestinal tract. The evidence for positive effects of some probiotics in specific clinical situations is now strong, owing to a more systematic approach. Further research is needed particularly RCT. All the clinical trials described in this paper contribute to our view of the potential application of probiotics in the future. Important developments in this field can be expected, and the use of genetically modified probiotics could provide even further opportunities.

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