

## Probiotics: A New Strategies for Prevention and Therapy of Diarrhea Disease

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**Abstract:** In this review the evidence from human clinical scenarios and the impact of probiotics to modulate the human gut microecology to prevention and management of diarrhea disease. Probiotics not only help digestive tract function, they also reduce the presence of less healthful organisms by competing with them for the limited available space. For this reason, use of probiotics can help prevent infectious diarrhea. Antibiotics can breakdown the balance of microbial ecology of the gut by killing and eradicate beneficial bacteria. When this happens, opportunistic bacteria and harmful yeasts can move in and flourish. The development of probiotic, aims to “coin with two faces or Two Sides of a Coin”, which is accomplished by providing a microbial stimulus to the host immune system by means of beneficial live microorganism cultures that are characteristic of the healthy, human gut microbiota, ie, probiotics and reinforce the different lines of gut defense, which are immune exclusion, immune elimination and immune regulation. They were also shown to stimulate nonspecific host resistance to microbial pathogens, thereby aiding in pathogen eradication. Consequently, the best documented clinical trials of probiotics is in the treatment of diarrhea. Other health effects of probiotic bacteria have not been well established. Well-designed placebo-controlled studies with validated outcome variables are needed to determine the health effects of probiotics.

**Key words:**

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### INTRODUCTION

Diarrhea is defined to most individuals, diarrhea means an increased frequency or decreased consistency of bowel movements; however, the medical definition is more exact than this. In many developed countries, the average number of bowel movements is three per day. However, researchers have found that diarrhea best correlates with an increase in stool weight; stool weights above 10 oz (300 g) per day generally indicates diarrhea<sup>[1]</sup>. This is mainly due to excess water, which normally makes up 60–85% of fecal matter. In this way, true diarrhea is distinguished from diseases that cause only an increase in the number of bowel movements (hyperdefecation), or incontinence (involuntary loss of bowel contents). Diarrhea is also classified by physicians into acute, which lasts one to two weeks and chronic, which continues for longer than 23 weeks. Viral and bacterial infections are the most common causes of acute diarrhea. The description of diarrhea in many cases, acute infectious diarrhea is a mild, limited annoyance. However, worldwide acute infectious diarrhea has a huge impact, causing over five million deaths per year. While most deaths are among children under five years of age in developing nations, the impact, even in developed countries, is

considerable. For example, over 250,000 individuals are admitted to hospitals in the United States each year because of one of these episodes. Rapid diagnosis and proper treatment can prevent much of the suffering associated with these devastating illnesses. Chronic diarrhea also has a considerable effect on health, as well as on social and economic well being. Patients with celiac disease, inflammatory bowel disease and other prolonged diarrheal illnesses develop nutritional deficiencies that diminish growth and immunity. They affect social interaction and result in the loss of many working hours. Diarrhea occurs because more fluid passes through the large intestine (colon) than that organ can absorb. As a rule, the colon can absorb several times more fluid than is required on a daily basis. However, when this reserve capacity is overwhelmed, diarrhea occurs. Diarrhea is caused by infections or illnesses that either lead to excess production of fluids or prevent absorption of fluids<sup>[2]</sup>. Also, certain substances in the colon, such as fats and bile acids, can interfere with water absorption and cause diarrhea. In addition, rapid passage of material through the colon can also do the same. Symptoms related to any diarrheal illness are often those associated with any injury to the gastrointestinal tract, such as fever, nausea, vomiting and abdominal pain.

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All or none of these may be present depending on the disease causing the diarrhea. The number of bowel movements can vary-up to 20 or more per day. In some patients, blood or pus is present in the stool. Bowel movements may be difficult to flush (float) or contain undigested food material. The most common causes of acute diarrhea are infections (the cause of traveler's diarrhea), food poisoning and medications<sup>[3]</sup>. Medications are a frequent and often over-looked cause, especially antibiotics and antacids. Less often, various sugar free foods, which sometimes contain poorly absorbable materials, cause diarrhea. Chronic diarrhea is frequently due to many of the same things that cause the shorter episodes (infections, medications, etc.); symptoms just last longer. Some infections can become chronic. This occurs mainly with parasitic infections (such as *Giardia*) or when patients have altered immunity (AIDS)<sup>[3]</sup>.

#### **Principal Criteria of a Potentially Useful Probiotics:**

The word probiotic is derived from two Greek words meaning 'for life'. Early attempts to use the term to mean a microbial substance which stimulates the growth of another microorganism<sup>[4]</sup> or tissue extracts which improved microbial growth<sup>[5]</sup> did not gain general acceptance. Parker<sup>[6]</sup> first used the word probiotic in the context of animal feed supplementation and defined it as: Organisms and substances which contribute to intestinal microbial balance. Fuller<sup>[7]</sup> redefined probiotics by removing the reference to '&substances' which could include antibiotics and microbial stimulants. His revised definition is: A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance. This modified version stresses the need for the supplement to be composed of viable microorganisms and is the most widely accepted probiotic definition. A probiotic effect is, therefore, mediated through the gut microflora by ingestion of viable microorganisms. Such a definition entails preparations specifically designed for probiotic use as well as traditional yoghurts and other fermented foods. In 1998, the European probiotic yoghurt market alone was estimated to be worth a value in the region of C520 million<sup>[8]</sup>, with the UK market reported as being the fastest growing. Probiotic products currently on the market are presented in the form of powders, tablets or capsules, liquid suspensions and sprays. Most preparations destined for human consumption are in fermented milks or given as powders or tablets. They can contain one or several species of bacteria or fungi. Although the word probiotic by definition was not established until 1965, the concept was worked upon by Metchnikof at the beginning of the century. Metchnikof had for a long time believed that the complex microbial population in

the colon was having an adverse effect on the host through so-called & autointoxication. "In The Prolongation of Life" Metchnikof reported that Bulgarian peasants, who consumed large quantities of fermented milk had longevity. As such, Metchnikof began to modify the colonic microflora through ingestion of soured milks. He used a Gram-positive rod which he called the Bulgarian bacillus and later *Bacillus bulgaricus*<sup>[9]</sup>. It is probable that this organism later became known as *Lactobacillus bulgaricus* and is now called *L. delbrueckii* subsp. *Bulgaricus* which together with *Streptococcus thermophilus* is responsible for the traditional fermentation of milk into yoghurt. Over the past decade, much attention has been given to microbial functions that affect host health and nutrition. The relationship between the intestinal microflora and the host is so specific that alteration in the balance of organisms might result in illness<sup>[10]</sup>. Gastrointestinal disorders of infective aetiology are endemic and constitute a significant health problem, especially in developing countries. The major manifestation of enteric infection is diarrhoea which carries a high morbidity. The spread of antibiotic resistance has renewed interest in both physicians and scientists in probiotic use and has led to the discovery that some micro-organisms are capable of protecting the gastrointestinal tract from invasion by pathogenic or opportunistic bacteria<sup>[11]</sup>

**Mechanisms of Probiotic Activity:** The probiotic mechanism which prevents gastrointestinal disturbances, is still not definitively or completely understood despite many studies having been carried out over the last 20 years. However knowledge of gut ecology suggests several mechanisms including the suppression of harmful bacteria and viruses, stimulation of local and systemic immunity and the modification of gut microbial metabolic activity<sup>[12]</sup>.

The exact manner in which probiotics may achieve their effect(s) is still uncertain. However, a number of mechanisms may be speculated upon<sup>[13]</sup> The characteristics essential for a probiotic are: (1) adherence to human cells; (2) gastric acid and bile stability; (3) production of antimicrobial substances; and (4) activity against pathogenic bacteria. Adherence to human intestinal cells is the first step in the mechanism of probiotic action. In fact, the microorganisms of probiotics are tested for their ability to colonize intestinal epithelia and although the molecular mechanism of adhesion is not understood, hydrophobic bacterial cells are efficient in adhering to the tissue surfaces. The capability to colonise is very important because bacteria ingested as probiotics must multiply in and colonise the gut<sup>[14, 15]</sup> Moreover, to reach and colonise the intestine, the bacteria have to be

resistant to acid pH and to biliary acids. Activity against pathogenic bacteria can be by several different mechanisms: directly by producing bacteriocins or antibiotics, by a competitive mechanism of adhesion, by competitive nutrition or indirectly by modulating the local immune system <sup>[16]</sup>. Probiotic preparations currently on the market occur in various forms: processed in yoghurt, suspended in milk, freeze-dried or air-dried. They are generally composed of large numbers of one or more bacterial species which are common constituents of normal intestinal flora. The most commonly used bacterial strains are: *Bacillus subtilis*, *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium cereus*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium thermophilus*, *Enterococcus faecium*, *Lactobacillus acidophilus*, *Lactobacillus GG*, *Lactobacillus casei*, *Saccharomyces boulardii* and *Saccharomyces cerevisiae*. There is evidence that the oral ingestion of micro-organisms produces a protective effect on the gut flora. A significant number of studies refer to evidence of beneficial effects of probiotics in several gut disorders, but it is very difficult to assess the clinical efficacy of these products. There are rivers of literature, over the past 10 years, there have been numerous publications on probiotics (2,632 papers) primarily addressing the digestive tract (1,440 papers), particularly *Lactobacillus* than *Bifidobacterium* but a limited number of controlled trials involving specific clinical conditions for which various probiotic preparations have been shown to have a beneficial therapeutic or prophylactic effects.

#### Probiotics:

**The Evidence in Prevention of Diarrhea:** A number of benefits in the ingestion of probiotics have been reported. These include the following.

**1- Lactose Malabsorption:** Lactose malabsorption results from insufficient activity of lactase in the human gut and causes abdominal distension, excessive flatulence and/or diarrhea. Over half the world's population is unable to utilize lactose effectively. It has been established that lactose administered in yoghurt can be utilized more efficiently than the same amount given in untreated milk <sup>[17]</sup>. Moreover, probiotic strains can produce  $\beta$ -galactosidase which improves tolerance to lactose.

**2- Traveller's Diarrhea:** Traveller's diarrhea is a common syndrome affecting healthy travelers not only in developing countries but also in Europe. The incidence of Traveller's diarrhea ranges from 20 to 50% depending on the origin and the destination of the traveller as well as the mode of travel. The diarrhoea

is self-limiting but even minor attacks can interrupt a holiday, causing inconvenience and discomfort. Various infectious agents have been described as the cause of Traveller's diarrhea. Toxin-producing *Escherichia coli* are the most commonly isolated organism. Probiotics have been shown to have beneficial effect in preventing some forms of Traveller's diarrhea (Table 1). If live acid bacteria are administered during the risk period <sup>[18,19]</sup>. Oksanen *et al.* <sup>[20]</sup> have evaluated the efficacy of *Lactobacillus GG* in preventing diarrhoea in 820 persons traveling from Finland to Turkey. The incidences of diarrhoea in the placebo group (46.5%) and in the patients receiving *Lactobacillus GG* (41%) were very similar. However in another study *Lactobacillus GG* reduced the occurrence of Traveller's diarrhea in one of the two destination cities (29.3%) compared with the placebo group (39.5%). A placebo controlled double-blind study <sup>[21]</sup> was conducted to study the ability of freeze-dried *Lactobacillus GG* in preventing Traveller's diarrhea. In this study *Lactobacillus GG* reduced the occurrence of Traveller's diarrhea by 39.5%. In a similar double-blind study <sup>[22]</sup> 56 Danish tourists on a 2-week trip to Egypt, were given live lyophilised bacteria (*L. acidophilus*, *B. bifidum*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus*). The incidence of diarrhoea in the group receiving the lactic acid bacteria was 43%, but was 71% in the placebo group. Moreover, enterotoxigenic *E. coli* (ETEC) was recovered in 31 and 50% of stool samples (collected from patients with diarrhoea only) of the treatment and placebo groups, respectively.

In two different studies <sup>[23,24]</sup> capsules containing  $2 \times 10^8$  -  $2 \times 10^9$  lyophilised whole *L. acidophilus* were administered to travellers to study the ability of *L. acidophilus* to prevent Traveller's diarrhea. Of the treated group in the first trial 25.7% and 53.2% in the second one remained diarrhoea free whereas the rate of prevention using the placebo was 23.8 and 47.0%, respectively. In these trials the differences between treated and placebo group were not significant. In a second study the prevention of Traveller's diarrhea by the administration of *S. cerevisiae* to 1231 people traveling all over the world was studied. The people were divided into three groups: a placebo group, a group taking 250 mg and a group taking 500 mg of *S. cerevisiae*:day. One hundred and seventy-three of 406 subjects (42.6%) in the placebo group developed Traveller's diarrhea, but only 33.6 and 31.8% of the groups treated with 250 or 500 mg of *S. cerevisiae*, respectively. The infection rates in the groups receiving *S. cerevisiae* were significantly lower ( $P < 0.002$ ) <sup>[25]</sup>. In another study <sup>[26]</sup> using Austrian tourists given *S. boulardii*, results suggested that the yeast significantly reduced the frequency of diarrhoea in a

**Table 1:** Biotherapeutic agents in treatment of TD and AD

Study	Disease	Biotherapeutic agent	Study size	Frequency in disease		
				Treated	Placebo	Significant
Oksanen <i>et al.</i> [14]	T.D	<i>Lactobacillus</i> GG	820	38.9% a 29.3% b	42.30% 39.50%	P= n.s. P < 0.005
Salminen and Daughton [15]	T.D.	<i>Lactobacillus</i>	156	23.90 %	40%	P < 0.005
Black <i>et al.</i> [16]	T.D.	<i>L. acidophilus</i> , <i>S. thermophilus</i> , <i>B. bifidum</i> , <i>L. bulgaricus</i>	81	43 %	71.00%	P= n.s.
Katellaris and Farthing [17]	T.D.	<i>L. acidophilus</i>				
Kollaritsch <i>et al.</i> [18]	T.D.	<i>S. cerevisiae</i>	1231	31.80%	42.60%	P < 0.005
Kollaritsch and Wiedermann [19]	T.D.	<i>S. boulardii</i>	1016	28.7%	39.10%	P < 0.005
Cetina-Sauri and Sierra Basto [33]	A.D.	<i>S. boulardii</i>	130	15%	60.00%	P < 0.001
Hotcher <i>et al.</i> [34]	A.D.	<i>S. boulardii</i>	92	3%	12.00%	P < 0.005
Mitra and Golam. [35]	A.D	<i>E. faecium</i>	153	3.3days <sup>c</sup> 3.3days <sup>c</sup>	2 days <sup>d</sup> 2.2days <sup>d</sup>	P = n.s

<sup>a</sup> First destination. <sup>b</sup> Second destination. <sup>c</sup> Diarrhoea caused by *V. cholerae*. <sup>d</sup> Diarrhoea caused by enterotoxigenic *E. coli*.

dose dependent manner. The rates of diarrhoea were 39.1% in the placebo group, 31.4% in the group receiving *S. boulardii* 250 mg /day and 28.7% for those receiving *S. boulardii* 1000 mg / day.

**3. Antibiotic Associated Diarrhea:** One of the most popular areas is that of antibiotic associated diarrhoea. Mild or severe episodes of diarrhoea are most common side effects of antibiotic therapy. It is well established that the normal microflora may be suppressed during microbial therapy and the consequent 'microbial vacuum' may be filled by opportunistic or pathogenic strains<sup>[27]</sup>. Changes in the microflora may also encourage the emergence of resistant strains and at least a third of antibiotic associated diarrhoea is due to *Clostridium difficile*. It has been suggested that probiotics which are able to restore and replace the normal flora should be used. In particular, probiotics should be used in high risk patients such as the elderly, hospitalised or immunocompromised. Several clinical trials have used *S. boulardii*, *Lactobacillus* spp. and *Bifidobacterium* spp. In antibiotic associated diarrhoea (Table 2). Studies carried out on *S. boulardii* confirm the persistence of the micro-organism in the gut during antibiotic therapy and data obtained in animal models have shown the decrease of *C. difficile* in the presence of *S. boulardii*. The effect of administration of *S. boulardii* in hospitalized patients, receiving antibiotic therapy showed that 9.5% of patients treated with *S. boulardii* developed antibiotic associated diarrhoea, while in the control group the percentage was 22%<sup>[28]</sup>. In a large double-blind study nine of 199 patients treated with either

tetracycline or b-lactam antibiotics whilst receiving *S. boulardii* developed diarrhoea compared with 33 of 189 receiving only placebo<sup>[29]</sup>. In another study of 193 patients receiving a broad spectrum b-lactam antibiotic, 14.6% in the placebo group developed diarrhoea but only 7.2% of those patients receiving *S. boulardii*<sup>[30]</sup>. *Lactobacillus* GG produces antimicrobial substances which have a broad spectrum of activity against bacteria, including *C. difficile*. *Lactobacillus* GG was therefore given to 11 patients as treatment for relapsing *C. difficile* colitis developing after antibiotic treatment. In eight of the patients diarrhoea stopped immediately and the other three patients responded after a further treatment with *Lactobacillus* GG. None of the patients suffered any relapses<sup>[31]</sup>. The efficacy of *Lactobacillus* GG in preventing antibiotic associated diarrhoea was investigated in healthy human volunteers receiving erythromycin<sup>[32]</sup>. The results indicated that subjects who took *Lactobacillus* GG yoghurt had less diarrhoea compared with a control group receiving pasteurised yoghurt. Moreover, the *Lactobacillus* GG colonised the bowel in spite of erythromycin treatment. Colonisation of patients has also been observed during penicillin and ampicillin therapy. In another study by Bennet *et al.*<sup>[33]</sup>, *Lactobacillus* GG was administered to nine symptomatic patients with recurrent *C. difficile* diarrhoea. After 7–10 days of administration (10<sup>9</sup> cfu twice daily), there was an improvement in all the patients treated. One of the characteristics of *Lactobacillus* GG is its ability to colonise the gastrointestinal tract. In particular, colonisation of the human gut was observed in healthy volunteers given oral antibiotics (penicillin-

**Table 2:** Biotherapeutic agents and treatment of AAD

Study	Biotherapeutic agent	Patient	Study size	Frequency in disease		Significant
				Treated	Placebo	
Surawicz <i>et al.</i> [21]	<i>S. boulardii</i>	Hospital patients on any antibiotic	388	4.50%	17.50%	$P < 0.001$
Adam <i>et al.</i> [22]	<i>S. boulardii</i>	Hospitalized on any antibiotic	180	9.50%	21.80%	$P < 0.05$
McFarland <i>et al.</i> [23]	<i>S. boulardii</i>	Patients on b-lactam	193	7.20%	14.60%	$P < 0.05$
Siitonen <i>et al.</i> [25]	<i>Lactobacillus GG</i>	Healthy volunteers on erythromycin	16	2 days	8 days	$P < 0.05$
Gotz <i>et al.</i> [28]	<i>L. acidophilus</i>	Hospitalized patients on ampicillin	72	8.30%	21%	$P < 0.21$
Wunderlich <i>et al.</i> [31]	<i>E. faecium</i>	Treatment with ampicillin sulphamethoxazole, trimethoprim, clindamycin, erythromycin, penicillin	45	8.70%	27.20%	$P = \text{n.s.}$
Bellomo <i>et al.</i> [32]	<i>E. faecium</i>	Paediatric patients	104	3.2 days	3.1 days	$P = \text{n.s.}$

V, erythromycin acistrate and ampicillin) when treated twice a day with 150 ml of *Lactobacillus GG* fermented yoghurt. Significant colonisation was obtained, in particular, during erythromycin and ampicillin administration<sup>[34]</sup>. Other evidence of the beneficial effects of the administration of probiotics was observed when a mixture of *L. acidophilus* and *Lactobacillus bulgaricus* or a placebo was administered to 79 hospitalized patients on treatment with ampicillin. No patients treated with lactobacilli developed diarrhoea<sup>[35]</sup>, compared with six of 43 (14%) patients in the control group. In another study<sup>[36]</sup>, a preparation containing a mixture of *L. acidophilus* and *B. bifidum* (1.8 x10<sup>9</sup> cfu / day) was given to 19 infants treated with ampicillin. It was shown that the number of lactobacilli was increased significantly following the normalisation of the microflora<sup>[36]</sup>. The same results were observed during the administration of *L. acidophilus*, after 7 days of clindamycin treatment. During clindamycin treatment *C. albicans* was recovered from 8:10 volunteers; but in three of four patients given *L. acidophilus* supplementation, *Candida albicans* had disappeared<sup>[37]</sup>. In a double blind trial<sup>[38]</sup>, *E. faecium* SF 68 or placebo was given to 45 patients who were receiving a 7-day course of prophylactic antibiotics. Of the *E. faecium* SF 68 group 8.7% developed diarrhoea compared with 27.2% in the placebo group. Although *E. faecium* SF 68 was shown to be effective in reducing the incidence of antibiotic associated diarrhoea in this study, the number of patients was too small for statistical analysis. In a paediatric study<sup>[39]</sup>, one group of patients with diarrhoea was given *E. faecium* (3 x10<sup>7</sup> cfu) and the other group a mixture of *L. acidophilus* (5x10<sup>8</sup> cfu), *L. bulgaricus* (4x10<sup>9</sup> cfu) and *Streptococcus lactis* (4x10<sup>9</sup> cfu). The treatment was continued for a few

days after clinical recovery (3–10 days); the results showed that the duration of diarrhoea was less in the group treated with *E. faecium*. Some authors have criticised the use of this particular probiotic from the point of view of safety as it is well known that this species can indirectly cause very dangerous infections as many strains contain plasmids which code for resistance to multiple antibiotics, including vancomycin.

**4. Acute Diarrhoea:** The major manifestation of enteric infection is diarrhoea. Although rehydration therapy is efficacious in many circumstances, its acceptance is low since it neither reduces stool frequency or shortens the duration of diarrhoea and furthermore, is difficult to implement in small children. The use of probiotics may therefore be a suitable alternative (Table 1). In a double-blind placebo-controlled study<sup>[40]</sup>, 130 pediatric patients (aged 3 months – 3 years) were divided into two groups: group I of 65 patients treated with 200 mg of *S. boulardii* and group II of 65 patients treated with placebo. After 24 h a reduction of stool frequency was observed in group I and after 96 h, the percentage of clinically recovered patients was significantly higher ( $P < 0.001$ ) in the group treated with *S. boulardii* (85%) compared with 40% in the placebo group. A similar study used 92 patients (mean age 38 years) with Acute diarrhoea. After 1 week of treatment with 3, 4 capsules of 50 mg *S. boulardii* or placebo, only 3916% of given *S. boulardii* still had a liquid stool, whereas in the placebo group the percentage was 12933% ( $P < 0.05$ )<sup>[41]</sup>. The therapeutic efficacy of *Streptococcus faecium* SF68 in acute watery diarrhoea caused by *Vibrio cholerae* and enterotoxic *E. coli* was evaluated in 183 adults. No differences were found between the administration of either *S. faecium* or placebo<sup>[42]</sup>.

**Other Forms of Diarrhea:** Radiation therapy to abdominal, pelvic, lumbar, or para-aortic fields can result in changes to normal bowel function. Factors contributing to the occurrence and severity of intestinal complications depend on total dose, fractionation, volume of bowel irradiated and concomitant chemotherapy. Common side effects of intestinal enteritis include diarrhea. A common complication in cancer patients treated with radiotherapy is acute diarrhoea <sup>[43]</sup>. A probiotic preparation, VSL#3 (VSL Pharmaceuticals, Fort Lauderdale, MD, USA), has been evaluated for the preventive effect in 190 patients who had postoperative radiotherapy after surgery for sigmoid, rectal or cervical cancer <sup>[44]</sup>. The probiotic product VSL#3 contained strains of *L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbruekii ssp. bulgaricus*, *B. longum*, *B. breve*, *B. infantis* and *S. salivarius ssp. thermophilus*. In the placebo group, 52% of the patients developed diarrhoea compared with 38% of patients receiving VSL#3. Furthermore, patients treated with placebo developed more severe diarrhoea. A double-blind and placebo-controlled study has been performed to determine the efficacy of *L. rhamnosus* (Antibiophilus, Germana Pharmazeutika GmbH, Vienna, Austria) compared with a placebo product in the treatment of patients suffering from mild to moderate radiation-induced diarrhoea <sup>[45]</sup>. Two hundred and five patients with radiation-induced diarrhoea lasting for about 2 weeks before recruitment were included. The group receiving the active probiotic required less and later rescue medication (opioid treatment for pain management expected to induce constipation) compared with the placebo group. The difference between the groups was not statistically significant. The probiotic product showed superior efficacy with respect to the number of bowel movements and faeces consistency.

**Artificial Nutrition & Tube-fed Patient and Diarrhoea:** Patients receiving nasogastric tube feeding frequently develop diarrhea, occurring in 2–63% of patients <sup>[46]</sup>. The diarrhoea has a range of aetiologies, hypoalbuminaemia and concomitant drug therapy have been implicated. The preventive effect of *Sac. boulardii* on diarrhoea in critically ill tube-fed patients has been assessed in a multicentre study <sup>[47]</sup>. The study was randomized, double-blind and placebo controlled. Adult patients who were expected to require enteral nutrition for at least 6 days were included in the study. Diarrhoea occurred in 14% of feeding days in the active group and in 20% of feeding days in the placebo group. These findings are in contrast to the results of a study where *L.*

*acidophilus* and *L. bulgaricus* (Lactinex) were used for the prevention of diarrhoea in patients that were tube-fed <5 days <sup>[48]</sup>. The administration of lactobacilli did not alter the risk of diarrhoea. However, in this study only the incidence of diarrhoea was measured and the influence by the length of the monitoring period was not adjusted for <sup>[47]</sup>.

**Conclusions:** Probiotics are attractive biological products with extremely interesting characteristics. Beneficial effects on human health have been widely demonstrated, but their mechanism of action is not completely understood. There is still much discussion on their role in pharmacokinetics, dose-effects, posology, antimicrobial resistance and plasmid-mediated resistance to antibiotics. Very few controlled studies are available but encouraging results have been obtained with *S. boulardii* for all the gastrointestinal disorders that we have considered. Favourable results have also been obtained with *Lactobacillus* GG, particularly when it is administered as living bacteria. The studies using *E. faecium* showed this probiotic to be ineffective in the treatment of AD caused by *V. cholerae* or enterotoxigenic *E. coli*. Current efforts to improve the efficacy of probiotics are presently being directed at modifying the different bacterial strains or yeasts in order to increase their ability to colonise the gut wall. It may become possible to genetically manipulate micro-organisms to combine improved colonisation of the gut with the ability to produce other beneficial effects. Results reported in literature are interesting, whenever probiotics are used in comparison with placebo, but the statistical significance does not always support the clinical results. Larger trials might give better statistical information. It is also necessary that the mechanisms of action of probiotics should be better understood so that their role in the balance of an ecosystem can be appreciated. In particular the colonisation of vagina by selected probiotics such as *L. acidophilus*, might help to re-equilibrate this habitat in cases of a dysfunctional microflora as might occur with vaginitis, vaginosis or hormonal disturbances. One could hypothesise that a-haemolytic streptococci might be used to normalise the oral flora after microbial disorders such as pharyngitis and otitis. To understand when to use probiotics, more evidence of beneficial effects, are needed not only in infectious diseases, but also for other clinical disorders (lactose intolerance, malabsorption syndromes, constipation, halitosis or effects of hormonal disturbance). In particular is necessary to have a better understanding of the ways in which bacterial metabolic products act

on the local ecosystem. Another direction of research is the administration of a combination of probiotics and prebiotics. Prebiotics are defined as non-digestible food ingredients that beneficially act on the host by stimulating the growth and/or the activity of one or more members of the colonic flora. Prebiotics may be non-digestible carbohydrates (oligo or polysaccharides), protein, peptides or some types of lipid<sup>[49]</sup>. Good results have been obtained with fructooligosaccharides which are selectively fermented by most strains of bifidobacteria. In particular, Wang and Gibson<sup>[50]</sup> demonstrated that, in the presence of fructooligosaccharides, bifidobacteria grew better than bacteroides, clostridia or coliforms; the latter were possibly repressed or only present at low levels. Probiotic oral administration is both useful and safe, but more controlled studies explaining the mechanisms of action and their clinically significant application are needed. There can be no doubt that the more we found about probiotics, the more interesting it becomes and that we still have a lot to learn.

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