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REVIEW

Probiotics in infectious diarrhoea in children: are they indicated?

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Abstract Infectious gastroenteritis continues to be a leading cause of mortality and morbidity worldwide. The cornerstone of treatment remains replacement of water and electrolyte losses with oral rehydration solution. Until a few years ago, probiotics were discussed primarily in the context of alternative medicine, but they are now entering mainstream medical practice since a decrease of the severity and duration of infectious gastroenteritis in approximately 24 hours has been shown for some strains. Therefore, probiotics are a potential add-on therapy in acute gastro-enteritis. The shortening of the duration of diarrhoea and the reduction in hospital stay result in a social and economic benefit. Evidence found in viral gastroenteritis is more convincing than in bacterial or parasitic infection. Mechanisms of action are strain specific and only those commercial products for which there is evidence of clinical efficacy should be recommended. Timing of administration is also of importance. In acute gastroenteritis, there is evidence for efficacy of some strains of lactobacilli (e.g. *Lactobacillus caseii* GG and *Lactobacillus reuteri*) and for *Saccharomyces boulardii*. Probiotics are "generally regarded as safe", but side effects such as septicaemia and fungaemia have very rarely been reported in high-risk situations. Although most studies conclude in a statistically significant shortening of the duration of diarrhea, the clinical relevance of this finding is limited. In conclusion, selected strains of probiotics result in a statistically significant but clinically moderate benefit in shortening the duration of diarrhoea caused by acute infectious gastroenteritis.

Keywords Diarrhoea · Gastroenteritis · Oral rehydration (solution) · Probiotic · Biotherapeutic agent

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Introduction

Acute infectious gastroenteritis remains the most common cause of diarrhoea worldwide and is a leading cause of death in childhood. Despite improvements in public health and economic wealth, the incidence of intestinal infections remains high in the developed world and continues to be an important clinical problem with relevant morbidity [10]. The risk of diarrhoeal disease is increased in selected groups including young infants, immune deficient individuals (HIV, cancer, chemotherapy, malnutrition), and people with a high exposure to pathogens (informal settlements, travellers, contaminated food, and medications buffering gastric acid), etc.

More than 2000 years ago, the Roman author Plinius The Old recommended fermented milk in the treatment of acute gastroenteritis. The term "probiotics" (meaning "for life") was not used until the 1960s. However, the healthy effects of certain bacteria have been noted for more than a century [38]. As early as in 1906, Tissier noted that a significant stool colonization with bifidobacteria was protective against the likelihood of the development of

diarrhoea in children [68]. Probiotics are non-pathogenic live micro-organisms that resist normal digestion to reach the colon alive, which, when consumed in adequate amounts, have a positive effect on the health of the host. Probiotics are marketed in several countries and widely used by paediatric health care providers [44]. The number of publications on probiotics in different diseases and conditions has literally exploded during recent years, especially in the area of acute infectious gastroenteritis. However, it is well known by opinion leaders that many negative reports remain unpublished.

The commercialised products

One of the major problems in this issue regards the (lack of) quality control of commercialised products. There are a multitude of foods and food-supplements that contain micro-organisms. Fermented alimentation features in most traditional cuisines. The food industry includes selected micro-organisms in food, primarily in milk-drinks or yogurts. Most probiotics in capsules are commercialised as food-supplements. After identification of the isolates using whole-cell protein profiling, wrong labelling was noted in 47% of the food supplements and 40% of the dairy products [66]. Mislabelling of food supplements is a worldwide problem [20]. As a consequence, it is impossible for the consumer and very difficult for the prescriber to separate food supplements among those with "good" from those with "poor" quality. In contrast, a biotherapeutic agent is a probiotic with proven therapeutic efficacy, and thus considered as medication. The legislation of food-supplements differs from that of medication. As a consequence, biotherapeutics are subject to a more stringent regulation and quality control than food supplements and dairy products. Fundamental research on the mechanisms of action of specific strains and clinical trials with commercialised products are mandatory. In vitro effects of a strain may display opposite behaviour in vivo [28]. Effects demonstrated for one strain cannot be extrapolated to other strains, even if they belong to the same species. Only these strains and their commercialized "controlled" product for which convincing data are available can be recommended. Since some commercialized products are combinations of different strains, repeated laboratory and clinical testing of every combination of strains is mandatory. *Lactobacillus acidophilus* LB has been shown to have antibacterial activity against *E. coli* [4, 15]. However, if the *E. coli* is present in the gastro-intestinal tract of the host prior to the *L. acidophilus* LB, as occurs in acute gastroenteritis, its antibacterial activity is strongly reduced by non-specific steric hindrance of the receptor sites [41]. Adherence of Bifidobacteria Bb12 improves in the presence of *Lactobacillus casei* GG, both in healthy infants and during episodes of diarrhoea, suggesting that synergism may as well occur [31].

Mechanisms of action

Per definition, a probiotic needs to be detectable alive throughout the entire digestive system. Most micro-organisms present in naturally fermented dairy products do not survive contact with gastric acid and bile. Only 1.5% of *L. acidophilus* and 37.5% of bifidobacteria present in food reach the ileum alive [41]. Probiotics do not colonize the gastro-intestinal tract as they become undetectable a few days after stopping the administration. This results in the absence of any risk for long-term side-effects. More studies are needed on pharmacodynamic and pharmacokinetic aspects, as the number of dose-related efficacy studies are minimal.

Every strain is different. Because the vast majority of probiotic products are commercialized as food supplements or dairy products, scientifically validated information regarding the strains is often limited. However, one lactobacillus does not equal another, as one *Saccharomyces* does not equal another.

There are many hypothesized mechanisms by which probiotics produce a healthy effect, including competitive inhibition with pathogenic bacteria, effects on barrier function, and effects on immune function [9, 37]. In general, probiotics help to improve the balance of the intestinal microflora. However, yeast probiotic organisms such as *Saccharomyces boulardii* do not change gastro-intestinal flora [17]. Dietary addition of prebiotic oligosaccharides such as oligofructose enriched inulin, or *L. casei* Shirota and *B. breve* result in a favourable effect on the colonic nitrogen metabolism, which in the case of the prebiotic, was accompanied by an increase in total faecal bifidobacteria [18]. Probiotics have an antimicrobial effect through modifying the microflora, secreting antibacterial substances, competing with pathogens to prevent their adhesion, and also competing with nutrients necessary for pathogen survival, producing an antitoxin effect, and reversing some of the consequences of infection on the gut epithelium such as secretory changes and neutrophil migration [43]. It is suggested that probiotic microorganisms compete for receptor sites in the intestinal lumen or compete with pathogens for nutrients [22]. While adherence of a probiotic strain to the gastrointestinal mucosa is reported as one of the major mechanisms of action, most beneficial effects are likely to be immune mediated. *S.boulardii* is known to influence inflammatory pathways (NF-κB, MAPK) mediated through soluble factors [58]. Other proposed mechanisms include enhancing host immune defenses via strengthening tight junctions between enterocytes, increasing immunoglobin A production, stimulating

cytokines and producing substances thought to secondarily act as protective nutrients (arginine, glutamine, short-chain fatty acids) for the gut [19, 22]. The polyamine increase induced by *S.boulardii* in humans results in a maturation of brush border disaccharidases and enzymes (lactase, sucrase, maltase and aminopeptidase, and an increase in the number of glucose carriers in the enterocyte-membrane) [8].

Since exact denomination of strains is complex, most clinicians are not familiar with this aspect, offering industry the possibility to provide misleading information. Demonstrated mechanisms of action in controlled laboratory conditions may not be reproducible in clinical trials.

Prevention of acute infectious gastroenteritis

Viral pathogens are the major causal organisms for infectious diarrhoea, accounting for up to 70–80% of all episodes. Rotavirus is the most prevalent pathogen and, as a consequence, rotavirus vaccination may to some extent alter the epidemiology of infectious gastroenteritis.

The longer an infant is breastfed and the longer breastfeeding is exclusive, the better the protection from infectious diseases such as gastroenteritis. Promotion of (exclusive) breastfeeding should be maximally endorsed. During recent years, attempts have been made to adapt the composition of second choice infant feeding, cow's milk based formula, to better mimic the immune development of breastfed infants. To recreate these benefits, probiotics and prebiotic oligosaccharides have been added to infant formula. Saran et al. [51] showed that feeding fermented milk to Indian infants over a period of 6 months resulted in a significantly better weight gain and a 50% reduction of infectious diarrhoea. The preventive beneficial action of probiotic-enriched formula is less obvious in the developed world. While most trials show a positive trend, the latter is not consistent [1]. However, no studies have suggested side-effects of probiotic formula in healthy infants. Data on the prevention of infectious gastroenteritis with prebiotic oligosaccharides are limited to one open-label trial in infants fed for 9 months with a prebiotic enriched formula [7].

More than ten years ago, Saavedra et al. [48] showed that *Streptococcus thermophilus* and *Bifidobacterium bifidum* (later renamed *B.lactis*) prevented nosocomial acquired diarrhoea in a small group of children admitted for long stays to a chronic care institution. A large double-blind randomized study in 220 children did not show a statistically significant protective effect of *Lactobacillus* GG for nosocomial rotaviral infection [48]. Another more recent study included 90 healthy infants living in residential nurseries or foster care centers and failed to demonstrate a reduction in the prevalence of diarrhoea with the administration of a formula supplemented with the viable *B. lactis* strain BB12 when compared with placebo (28.3% vs 38.7%; RR 0.7; 95% confidence interval 0.4–1.3) [14]. A formula fermented with *B. breve* c50 and *Str. thermophilus* 065 was well accepted and resulted in normal growth of infants [67]. However, incidence, duration of diarrhoea episodes, and number of hospital admissions did not differ significantly between groups. Episodes were less severe in the fermented formula group with fewer cases of dehydration, fewer medical consultations and fewer prescriptions of oral rehydration solutions [67]. Table 1 summarizes a selection of studies on prevention of acute gastroenterities. Seven children would need to be treated with a probiotic to prevent one patient from developing nosocomial rotaviral gastroenteritis [59]. However, the protective effect on prevention of diarrhoea becomes far less significant if the incidence of diarrhoea (episodes per patient-month) rather than the percentage of patients with diarrhoea is taken into account [60]. Three large, randomized controlled trials provide evidence of a very modest effect (statistically significant, but of questionable clinical importance) of some probiotic strains (*Lactobacillus* GG, *L. reuteri*, *B. lactis*) on the prevention of community-acquired diarrhoea [61]. Today, there is not enough evidence to recommend the routine use of probiotics to prevent nosocomial diarrhea [61].

Traveller's diarrhoea can be considered as a high-risk situation for infectious gastroenteritis, but the data currently available are not convincing for preventive use of probiotics. At least three placebo-controlled studies with lactobacilli have been performed, all with negative results [25, 32, 45]. One trial with *S. boulardii* reported a clinically small but statistically significant preventive effect in a specific subgroup, suggesting geographical differences in efficacy [34].

Treatment of infectious gastroenteritis

Treatment of acute infectious gastroenteritis should focus on the pathophysiological consequences of the condition: loss of water and electrolytes and a disturbance of the gastrointestinal ecosystem. Several studies on treatment of acute gastroenteritis can be found in a summary in Table 2. Probiotics address the second pathophysiological aspect of acute gastroenteritis: abnormal gastro-intestinal flora. Bacterial biotherapeutic strains comprise different lactobacilli and bifidobacteria, but to a certain extent also non-pathogenic *E. coli* (*E. coli* Nissle 1917) and some strains of enterococci (although relevant transfer of plasmid induced resistance was reported with enterococci). The yeast *S. boulardii* is the only non-bacterial biotherapeutic strain known.

L. caseii GG compared to placebo reduced significantly the duration of hospitalization in rotavirus diarrhoea (1.4 vs

Table 1 Prevention of acute gastroenteritis (mainly by addition of probiotics to infant formula)

Author (ref)	Probiotic	Country	Age	No. patients	Reduction diarrhoea
Saran et al. [51]	Fermented milk	India	2–5 years	100	Yes
Saavedra et al. [48]	*Str. thermophilus* and *B.lactis*	USA	5–24 months	55	Yes
Szajewska et al. [59]	*L.* GG	Poland	1–36 months	81	Yes (rotavirus)
Mastretta et al. [42]	*L.* GG	Italy	1–18 months	220	No
Chouraqui et al. [14]	*B. lactis* BB12	France	0–8 months	90	No
Thibault et al. [67]	*B. breve* c50, *Str. thermophilus* 065	France	4–6 months	971	No

Str: Streptococcus; *L: Lactobacillus*; *B: Bifidobacterium*

2.4 days) in 71 children treated with ORS [29]. The efficacy of *Lactobacillus* GG was confirmed in a study of 40 Pakistani children admitted for severe diarrhoea and malnutrition compared to controls in reducing the duration of non-bloody diarrhoea (31% vs 75% at 48 hours) [47]. Shornikova et al. showed similar results in a trial of 123 hospitalized children (33% with rotavirus and 21% with bacterial diarrhoea) with *Lactobacillus* GG in reducing the duration of viral diarrhoea (2.7 vs 3.7 days) [55]. The same group assessed the efficacy of *L. reuteri* in 66 hospitalized children with rotavirus diarrhoea, randomized into 3 groups: placebo in one group and two groups with different doses of *L. reuteri* (10^7 and 10^{10} cfu/g once a day for 5 days). The probiotic reduced the duration of diarrhoea with a dose-dependent effect (2.5 days in the placebo group vs 1.9 and 1.5 in the *L. reuteri* groups, respectively) [56]. *Lactobacillus* GG halved the duration of diarrhoea in outpatient children and significantly reduced rotavirus shedding [24]. A multi-center European prospective, randomized controlled trial of 287 children with acute diarrhoea with *L. casei* GG as an add-on to ORS, showed a significant decrease of the duration of diarrhoea by about 10% (a mean duration of diarrhoea of 123 hours in the placebo group vs 110 hours in the intervention group) [23]. A more detailed analysis showed that the difference was greatest in the rota-positive group (115 vs 136 hours) and that there was no difference in the subgroup with invasive pathogens (about 1/5th of all inclusions; 124 vs 121 hours duration of diarrhoea) [23]. *L. acidophilus* LB (Lacteol Fort, a product containing heat-killed lactobacilli) was tested in 73 children with acute diarrhoea (50% rotavirus positive) resulting in a similar reduction of duration (43 vs 57 hours) [57]. Comparable results have been recently obtained in a double-blind (DB) RCT involving 87 Polish children with infectious diarrhoea with a mixture of three *Lactobacillus rhamnosus* strains (573L/1; 573L/2; 573L/3). *L. rhamnosus* strains significantly shortened the duration of rotavirus diarrhoea (76 +/− 35 h vs 115 +/− 67 h; $p=0.03$) but not of diarrhoea of other aetiology. Gut colonization with administered strains was 80% and 41% at 5 and 14 days, respectively. Intervention also shortened the time of intravenous rehydration (15±14 h vs 38±33 h; $p=0.006$) although factors such as physician variability may have influenced the outcome [64]. The examined strains were detected in 37/46 (80.43%) patients after 5 days and in 19/46 (41.3%) patients after 14 days after the start of the treatment [65]. *L. rhamnosus* 573L/1 strain colonized the G.I. tract more persistently [65]. Persistence of colonization is dependent on the properties of administered probiotic strains [65]. However, lactobacilli also failed to shorten the duration of diarrhoea. At least three randomized controlled trials (RCTs) in developing countries negated the beneficial effect of *Lactobacillus* GG and *L .acidophilus* in acute diarrhoea, likely related to the distinct aetiological profile [16, 33, 50]. In children with more severe diarrhoea, there was no demonstrable benefit of *L. casei* GG [16, 50]. Absence of shortening of the duration of diarrhoea was also reported for a mixture of *L. acidophilus*, *B. bifidum* (later renamed *B. lactis*) and *L. bulgaricus* [35]. *L. paracasei strain* ST11 did not reduce the volume of stool output in rotavirus infection but improved the outcome of non-rotavirus diarrhoea in children from Bangladesh [52]. Three meta-analyses concluded that the majority of the studies had been performed in the developed world, and that there was efficacy for *L. rhamnosus* GG, *acidophilus* and *bulgaricus* [27, 62, 69]. In particular, the duration of (viral) diarrhoea was significantly reduced (about 17 hours or 0.7 days; relative risk (RR) 0.40 and 4 children need to be treated (NNT) to protect one subject from diarrhoea) compared to controls [62]. The efficacy of *Lactobacillus* GG appeared related to the logarithm of the dose (>10^{11} as the most efficient dose) [69]. A Cochrane review examined 23 RCTs and 1,917 participants (1,449 children) and highlighted the beneficial effect of probiotics as an add-on treatment to ORS in reducing the duration of diarrhoea (of about 30 hours with

Table 2 Treatment of acute gastroenteritis

Author (ref)	Probiotic	dose	Duration (days)	Country	Age	No. patients	Shortening diarrhoea
Isolauri et al. [29]	*L.* GG	$2\times10^{10-11}$ cfu 2×/day	5	Finland	4–45 months	71	Yes
Raza et al. [47]	*L.* GG	$2\times10^{10-11}$ cfu	2	Pakistan	Mean 13 months	40	More cured day 2
Shornikova et al. [55]	*L.* GG	5×10^{9} cfu/g b.d	5	Karelia (Russia)	1–36 months	123	Yes (rota)
Shornikova et al. [55]	*L. reuteri*	10^{7} or 10^{10} cfu/g	5	Finland	6–36 months	66	Yes (rota)
Guarino et al. [24]	*L.* GG	3×10^{9}CFU 2×/day	6	Italy	3–36 months	100	Yes
Guandalini et al. [23]	*L.* GG	10^{10} cfu /250 ml 2×/day	5	Europe	1–36 months	287	Yes
Simakachorn et al. [57]	Heat-killed *L. acidophilus* LB	10^{10} cfu 2×/day	2.5	Thailand	3–24 months	73	Yes
Szymanski et al. [64]	Mixture 3 *L. rhamnosus* strains	1.2×10^{10} cfu 2×/day	5	Poland	2–72 months	87	Yes (rota)
Costa-Ribeiro et al. [16]	*L.* GG	10^{10} cfu	?	Brazil	0–24 months	124	No
Khanna et al. [33]	*L. acidophilus*	1.5×10^{10} cfu	3	India	6–144 months	98	No
Salazar-Lindo et al. [50]	*L.* GG	$5-10^{11}$ cfu	5	Peru	3–36 months	89	No
Sarker et al. [52]	*L. paracasei* strain ST11	5×10^{9} cfu 2×/day	5	Bangladesh	4–24 months	230	No
Shamir et al. [54]	*Str. thermophilus* (a), *B. lactis* (b), *L. acidophilus* (b), zinc (10 mg) and FOS	6×10^{9} cfu (a) and 2×10^{9} cfu (b)	5	Israel	6–12 months	65	Yes
Cetina-Sauri and Sierra Basto [13]	*S. boulardii*	600 mg (1.2×10^{10} CFU)	4	Mexico	3–36 months	130	Yes
Kurugol [36]	*S. boulardii*	250 mg (5×10^{9} CFU)	5	Turkey	3–84 months	200	Yes
Villaruel [70]	*S. boulardii*	< 1 yr: 250 mg (5×10^{9} CFU) > 1 yr: 500 mg (1×10^{10} CFU)	6	Argentina	3–24 months	100	Yes
Billoo et al. [5]	*S. boulardii*	500 mg (1×10^{10} CFU)	5	Pakistan	2–144 months	100	Yes

L. GG: *Lactobacillus* (*caseii* GG); *B*: *Bifidobacterium*; *Str*: *Streptococcus*; FOS: fructo-oligosaccharides; *S. boulardii*: *Saccharomyces boulardii*

an RR 0.7) without significant side effects in immune-competent subjects [3]. Regarding the other bacterial strains evaluated (*Streptococcus thermophilus, L.acidophilus* and *bulgaricus*) more studies are needed [3]. More studies on the mechanisms of action in clinical situations are also needed [3]. Shamir and coworkers showed a reduction in duration of acute gastroenteritis from 1.96±1.24 to 1.43± 0.71 days (p=0.017) with the addition of 10^{9} CFU *Streptococcus thermophilus, B. lactis, L. acidophilus*, 10 mg zinc and 0.3 gram fructo-oligosaccharides per day [54].

Saccharomyces boulardii is a non pathogenic yeast isolated from the lychee fruit in Indonesia and introduced in France for the treatment of diarrhoea since 1950. The first double-blind, prospective, randomized trials of *S. boulardii* were performed more than 15 years ago: diarrhoea persisted for more than 7 days in 12% in the placebo group and in 3% in the *S. boulardii* group [26]. Since then, several double-blind, prospective, randomized trials performed with *S. boulardii* in children with acute gastro-enteritis have systematically shown a significant improvement in comparison to placebo. A consecutive series of 130 Mexican children, 3 months to 3 years old, with acute infectious diarrhoea were treated with ORS and placebo or *S. boulardii* (600 mg/d or 1.2×10^{10} CFU/day) for 5 days [13]. A significant decrease in the number of stools was apparent from day 2 onward [13]. After 48 hours, the percentage of children considered cured was almost 50% in the *S. boulardii* group compared to 8% in the placebo group;

on day 4, resolution was up to 95% in the intervention group compared to just almost 50% in the placebo group [13]. Kurugol treated 200 children with acute diarrhoea with 250 mg (or 5×10^9 CFU/day) *S. boulardii* or placebo for 5 days: duration of both diarrhoea and hospital stay decreased in approximately 24 hours [36]. Villaruel and coworkers showed similar results in ambulatory care in Argentina: diarrhoea persisted for more than 7 days in 27% of a placebo group compared to 7% of a group treated with *S. boulardii* for 6 days, with a greater effect if treatment was started within the first two days of the disease [70]. *S. boulardii* improved tolerance of feeding in children with chronic Giardia Lamblia infection [12]. *S. boulardii* is also effective in amoebiasis and HIV-diarrhoea [40, 49]. A randomized controlled open-label trial in Pakistani children with acute infectious gastroenteritis showed that administration of 500 mg (or 1×10^9 CFU/day) *S. boulardii* for 5 days significantly reduced the frequency of stools and duration of diarrhoea (3.5 days versus 4.8 days, $p=0.001$) and resulted two months later in a 50% decrease in re-infection rates and 30% better weight gain [5]. Szajewska and coworkers recently concluded that *S. boulardii* has a moderate clinical benefit in otherwise healthy infants and children with acute gastroenteritis, mainly by shortening the duration of diarrhoea [63]. Since most of the studies with *S. boulardii* have methodological limitations, results should be interpreted with caution [63].

A shortening of the duration of diarrhoea, as well as a reduced hospital stay suggests a relevant social and economic benefit of biotherapeutic treatment in adjunction to ORS in acute infectious gastroenteritis in children.

Numerous clinical trials have been published evaluating different probiotics in the treatment of acute gastroenteritis but vary in relation to strains tested, dosage, methodological quality, diarrhoea definitions and outcomes. Most studies show a statistically significant effect that is of only moderate clinical benefit, with the greatest effect in viral and watery diarrhea [61]. In general, meta-analyses of published trials conclude in a reduction of diarrhoeal duration of approximately 24 hours (17–30 hours) for selected strains of lactobacilli (such as *L. casei* GG, *L. acidophilus, L. Bulgaricus* and *L. reuteri*) and *S. boulardii* [3, 27, 53, 59, 61, 63, 69]. One should be aware that the available literature is biased since not all negative trials are reported. Greater efficacy has been shown if the probiotic is administered early in the disease. Probiotics in acute diarrhoea of diverse causes reduced the duration in children with about 57% (35–71%) [53]. In general, there is a lack of data from community-based trials and from developing countries, except for *S. boulardii*. However, some authors stress that business pressures may force usage of probiotics (and antisecretory drugs such as racecadotril) as important in the management of acute diarrhoea while their relevance has yet to be established [2].

Safety and side effects

Probiotics are "generally regarded as safe" and side-effects in ambulatory care are rarely reported. Large scale epidemiological studies in countries where probiotic use is endemic demonstrate (in adults) low rates of systemic infection, between 0.05% and 0.40% [22]. Invasive infections have been primarily noted to occur in immunocompromised adults [6]. Lactobacilli have been reported (in adults) to cause cases with sepsis, meningitis and infections localized in different organs [37, 39, 46]. Invasive infections in infants and children are exceedingly rare [6]. Two cases of bacteriaemia attributable to lactobacillus supplementation, with identical molecular clinical and supplement isolates, were recently reported in an infant and a child without underlying gastrointestinal disease or immunocompromised status [9]. Sepsis with probiotic lactobacilli has been reported in children with short gut. Probiotic enterococci may be of higher risk given possible plasmid transfer in immunocompromised patients. Fungaemia with *S. boulardii* has been reported in about 50 patients [21]. A central venous catheter is the main risk factor [21]. Fungaemia has even been reported in patients with deep central venous lines hospitalized in a bed next to a patient treated with the yeast [11]. Translocation from the gastrointestinal tract in the systemic circulation has not been reported. These case reports emphasize that probiotic supplementation should be used with caution in children with indwelling central venous catheters, prolonged hospitalizations, and a recognized or potential compromise of gut mucosal integrity [9]. The potential benefits of supplementation should be weighed against the risk of development of an invasive infection resulting from probiotic therapy.

In order to minimize the risk for side-effects such as fungaemia and bacteriaemia, more research should be done with inactivated or non-viable preparations. These modified probiotic preparations may be the preferred product in at-risk situations. It may not be necessary to administer the intact probiotoc organisms to achieve benefits. At the basic research level, products of probiotics such as secreted proteins or DNA can block inflammation and stop the death of epithelial cells [30].

Conclusion

Although probiotics can be helpful for specific disorders, they have been broadly prescribed for disorders without clear evidence to support their use [44]. Rapid rehydration and realimentation remain the cornerstone of the treatment of acute gastroenteritis [2]. Biotherapeutic agents administered as add-on medication are likely to decrease the duration of acute infectious gastroenteritis in about 24 hours. Further-

more, with *S.boulardii*, a 24-hour reduction in hospital stay has been documented. Literature shows a statistically significant but clinically moderate benefit for some strains, mainly in infants and young children, in the treatment of acute watery diarrhoea, especially in rotavirus gastroenteritis. Not all negative trials are published. Both for lactobacilli and *S. boulardii* greater efficacy has been shown if the treatment is started early. Because of strain-specificity, only those organisms that have been clinically tested can be recommended—*L. casei GG* and *S.boulardii* being the most reported.

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