Probiotics and acute gastroenteritis in children – critical review of published evidence

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Introduction

Acute gastroenteritis is a major cause of infant morbidity and mortality worldwide [1]. In developing countries, an estimated overall incidence of acute gastroenteritis ranges from 6 to 12 episodes of diarrhoea per year in children under 5 years of age compared to 1.3 to 2.3 episodes in developed countries [2]. In developing countries, approximately 2.4 to 3.3 million children below 5 years of age die per year from diarrhoeal diseases. In developed countries, death from acute diarrhoea is uncommon but, even in an affluent and industrialized country such as the United States, 300-500 deaths are attributed annually to acute gastroenteritis; the majority of those deaths occur in infants under 12 months of age [2, 3].

The economic burden of acute gastroenteritis is enormous. In the United States alone, gastroenteritis accounts for more than 220,000 hospital admissions per year in children less than 5 years of age (10% of all hospitalizations in this age group), resulting in an estimated direct annual cost of $2 billion [2, 4].

Acute gastroenteritis

Acute gastroenteritis is characterized by the rapid onset of diarrhoea defined as the passage of ≥3 loose or watery stools in a 24 hour period, or the passage of one or more bloody stools, with or without vomiting, nausea, fever, and abdominal pain. Acute gastroenteritis usually refers to an illness lasting no longer than 10-14 days [4].

Worldwide, both in developed and developing countries, rotavirus is the major cause of severe gastroenteritis, but several other enteric viruses appear to affect children in their first years of life [1, 5-8]. These primarily include Norwalk virus and other human caliciviruses, astroviruses and enteric adenoviruses. Enteric bacterial pathogens are also important causes of diarrhoeal diseases, particularly in developing countries. The two main parasites causing diarrhoea worldwide are Giardia lamblia and Cryptosporidium parvum [9].

Acute gastroenteritis generally is a self-limited illness lasting few days. The main treatment aims are to prevent dehydration, metabolic acidosis and electrolyte disturbances. In the majority of cases of acute gastroenteritis with mild or moderate dehydration, these aims can be achieved with oral rehydration solutions (ORS). Severe dehydration, however, requires immediate admission to hospital and intravenous replacement of fluid and electrolytes. It is of vital importance to maintain adequate nutrition during diarrhoea. Nutritional support, i.e. avoidance of energy-restricted feeding regimens, is necessary in nearly all instances. There are no indications for the routine use of lactose-free formulae or formulae with a reduced amount of lactose, although they are indicated in cases of concomitant secondary lactose intolerance. Continuation of breastfeeding during diarrhoea, with additional oral rehydration solution, is recommended [10, 12].

Despite the proven efficacy of oral rehydration therapy, it remains underused. The main reason is that oral rehydration solutions neither
reduce the frequency of bowel movements and fluid loss, nor shorten the duration of illness. This appears to decrease their acceptance. Parents, caregivers, but also physicians demand safe, effective and inexpensive agents as an additional treatment that visibly will reduce the frequency and fluidity of stools during the illness. An important question is whether probiotics are beneficial option as an adjunct to the standard treatment and prevention of diarrhoeal diseases in childhood.

Probiotics

Probiotics have been defined recently as living microorganisms which, upon ingestion in certain numbers, exert health benefits beyond general nutrition [14]. The most commonly used probiotics are lactic acid bacteria, such as lactobacilli and bifidobacteriae, but other non-pathogenic bacterial strains, including *Streptococcus*, *Escherichia coli* and non-bacterial organisms, such as a non-pathogenic yeast *Saccharomyces boulardii* also have been used. Criteria for a bacterium to be designated a probiotic include: i) human origin; ii) non-pathogenic properties; iii) resistance to technologic processing, including viability in delivery vehicles; iv) stability in acid and bile; v) adhesion to target epithelial tissue; vi) ability to persist within the gastrointestinal tract; vii) production of antimicrobial substances; and viii) ability to positively influence immune function and positively influence metabolic activities [15].

Probiotics are available either in the form of fermented dairy foods such as yogurt and other dairy products, fruit juices and other drinks, or as powdered supplements containing freeze-dried bacteria. In some countries medicinal probiotic products that are sold for specific medical indications are available.

There is an increasing number of potential health benefits attributed to probiotics, including the prevention and treatment of diarrhoea, alleviation of lactose intolerance [16], prevention of vaginal infections [17, 18], enhancement of the immune system, prevention and treatment of allergic diseases [19-21], reduction of serum cholesterol [22] and prevention of cancer and tumor growth [23]. However, only a few of these effects have been confirmed in randomized placebo controlled trials.

Rationale for the use of probiotics in diarrheal diseases

The rationale for the use of probiotics in the treatment and prevention of diarrheal diseases is based on the assumption that they modify the composition of the colonic microflora and act against enteric pathogens. Although hypotheses mechanisms have been proposed, the exact mechanisms by which probiotics exert their putative effects in humans are unknown.

Candidate mechanisms include the synthesis of antimicrobial substances (e.g. *Lactobacillus* GG and *L. acidophilus* strain LB have been shown to produce substances that inhibit Gram-positive and Gram-negative pathogens) [24-26], competition for nutrients required for growth of pathogens [27, 28], competitive inhibition of adhesion of pathogens [29-32] and modification of toxins or toxin receptors [33-34]. Experimental studies have shown that probiotics stimulate or modify non-specific and specific immune responses to pathogens. It was demonstrated that certain probiotics increase the number of circulating lymphocytes, induce lymphocytic proliferation, increase specific antibody responses to rotavirus vaccine and cytokine secretion, including interferon-γ (IFN-γ), and stimulate phagocytosis [35-40]. Recently, Mack *et al.* [41] showed that some lactobacilli species (e.g. *L. rhamnosus* strain GG and *L. plantarum* strain 299v) inhibit, in a dose-dependent manner, binding of *E. coli* strains to intestine-derived epithelial cells grown in tissue culture. This inhibition is a result of stimulation of synthesis and secretion of mucins (glycoproteins known to have a protective effect in intestinal infections) (see M. Chapman, and Ian R. Sanderson, in this issue, pp 55-65.). Probiotics also enhance mucosal immune defenses and protect against structural and functional damage in the brush border of enterocytes often promoted by enterovirulent pathogens. Probiotics appear to interfere with the cross-talk between pathogens and host cells (i.e. inhibit pathogen-induced cell signalling) [42, 43]. Two or more mechanisms listed above likely operate simultaneously in any given instance.
Their combination and intensity likely depend on the properties of targeted enteric pathogens (e.g. bacterial or viral) and the specific probiotic [15]. We are merely at the beginning of our understanding of these protective mechanisms. Therefore, further studies are warranted.

Probiotics in the treatment of acute infectious diarrhoea

Three systematic reviews are particularly relevant to this discussion. The first is based on a search of MEDLINE and the Cochrane Library (search date April 2001) for randomized, double-blind placebo controlled clinical trials (RCT) [44]. Ten RCTs comparing probiotics versus placebo in children aged 1 to 48 months with acute infectious diarrhoea were identified [38, 45-53]. A qualitative assessment of the validity of studies was done using Jadad’s criteria [54]. All studies involved only inpatients, except one that also included a small outpatients group. Most were conducted in developed countries. The probiotic strains studied were L. GG, L. reuteri, L. acidophilus LB, L. acidophilus, L. bulgaricus, S. thermophilus lactis, and S. boulardii. The meta-analysis revealed that probiotics (L. GG, L. reuteri and S. boulardii) compared with placebo significantly reduced the risk of gastroenteritis lasting ≥3 days (relative risk [RR]: 0.40; 95% confidence interval (CI): 0.28-0.57) (Table I and II); however only L. GG showed a consistent effect. The reviewers calculated by conservative statistical means that on average four patients (95% CI: 3-9) would need to be treated with L. GG to prevent one from having diarrhoea lasting ≥3 days. The greatest effect was observed against rotavirus gastroenteritis. In contrast, no effect of L. GG was detected in a subset of children with invasive bacterial enteric infections. No adverse effects of probiotics were reported in the included trials.

In the second meta-analysis, all relevant literature published from 1966 to 2000 was searched [55]. Trials were identified by checking the traditional biomedical journals and the complementary and alternative medicine literature. Nine studies that compared placebo with treatments with the use of different L. species (L. GG, L.

<table>
<thead>
<tr>
<th>Author</th>
<th>Probiotic</th>
<th>Dose (CFU)*</th>
<th>Sample size</th>
<th>Probiotic (%)</th>
<th>Placebo (%)</th>
<th>#RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolauri et al., [45]</td>
<td>L. GG</td>
<td>2×10^10-11</td>
<td>71</td>
<td>17</td>
<td>58</td>
<td>0.29</td>
<td>0.1-0.6</td>
</tr>
<tr>
<td>Kaila et al., [38]</td>
<td>L. GG</td>
<td>10^10-11</td>
<td>39</td>
<td>9</td>
<td>53</td>
<td>0.17</td>
<td>0.05-0.6</td>
</tr>
<tr>
<td>Guandalini et al., [47]</td>
<td>L. GG</td>
<td>10^10-11</td>
<td>287</td>
<td>25</td>
<td>41</td>
<td>0.61</td>
<td>0.4-0.9</td>
</tr>
<tr>
<td>Shornikova et al., [48]</td>
<td>L. reuteri</td>
<td>10^10-11</td>
<td>40</td>
<td>10.5</td>
<td>52</td>
<td>0.20</td>
<td>0.05-0.7</td>
</tr>
<tr>
<td>Shornikova et al., [49]</td>
<td>L. reuteri</td>
<td>10^10-11</td>
<td>45</td>
<td>25</td>
<td>44</td>
<td>0.57</td>
<td>0.2-1.3</td>
</tr>
<tr>
<td>Simakachorn et al., [50]</td>
<td>L. acidophilus LB</td>
<td>10^10-11</td>
<td>73</td>
<td>3</td>
<td>25</td>
<td>0.11</td>
<td>0.02-0.6</td>
</tr>
<tr>
<td>Bouloche et al., [51]</td>
<td>L. acidophilus LB</td>
<td>10^10-11</td>
<td>46</td>
<td>12.5</td>
<td>13.6</td>
<td>0.92</td>
<td>0.2-3.7</td>
</tr>
<tr>
<td>Cetina-Sauri et al., [52]</td>
<td>S. boulardii</td>
<td>200 mg</td>
<td>130</td>
<td>29</td>
<td>80</td>
<td>0.37</td>
<td>0.2-0.5</td>
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<tr>
<td>Pooled RR (fixed effect)</td>
<td></td>
<td></td>
<td>731</td>
<td>20</td>
<td>48</td>
<td>0.43</td>
<td>0.34-0.53</td>
</tr>
<tr>
<td>Pooled RR (random effect)</td>
<td></td>
<td></td>
<td>731</td>
<td>20</td>
<td>48</td>
<td>0.40</td>
<td>0.28-0.57</td>
</tr>
</tbody>
</table>

#RR: relative risk
* colony forming units
** oral rehydration solution
were identified (8 also were identified in the first review described above) [38, 46-50, 53, 56, 57]. A significant reduction in the duration of diarrhoea of 16.8 h (95% CI: 7.2-28.8) and a reduction in stool frequency of 1.6 stool per day by day 2 of treatment (95% CI: 0.7-2.6) were observed in those who received lactobacilli compared with those who received placebo. A preplanned subgroup analysis suggested a dose-dependent, inverse relationship between the daily lactobacilli dose and the reduction in the duration of diarrhoea.

In the third meta-analysis, 18 studies were identified by searching MEDLINE, EMBASE and CINAHL, and reviewing abstracts from scientific meetings [58]. The studies selected for analysis were characterized by significant clinical and statistical heterogeneity. Both not blinded and double-blind randomized studies were included. Results from in- and out-patients were pooled, and the authors did not perform a methodological quality assessment of identified trials. However, subgroup analysis of nine double-blind, placebo-controlled studies (no details given) showed that in children who received probiotics the duration of diarrhoea was reduced significantly (by 14.4 hours [95% CI: 7.2 to 24]). These results were in agreement with both the previous meta-analyses.

Two small RCTs performed in Denmark and published subsequently to the three reviews described above, examined the effect of 2 newly identified probiotic strains, *L. rhamnosus* 19070-2 and *L. reuteri* DSM 12246, administered as a mixture of 10¹⁰ CFU (colony forming units) of each strain, twice daily for 5 days. The first study included 69 children aged 6-36 month-old hospitalized with acute watery diarrhoea; sixty-seven percent were rotavirus-positive; forty-six percent of the total sample had moderate dehydration; the remaining 54% had no signs of dehydration. In patients receiving probiotics, the diarrhoeal phase was reduced by 20%, although this difference did not reach statistical significance (82 h in the treatment group vs 101 in the control group; p=0.07). However, the probiotics reduced the risk of having loose stools on day 5 of treatment (10% vs 33% in the placebo group; RR: 0.3; 95% CI: 0.1-0.9). The beneficial effects of the probiotic mixture were most evident in patients treated within the first 60 h of illness. After the early intervention, the duration of diarrhoea was reduced significantly (by 14.4 hours [95% CI: 7.2 to 24]).

### Table II: Weighted mean difference (WMD) in the duration of diarrhoea between probiotics and placebo (based on reference [44]).

<table>
<thead>
<tr>
<th>Author</th>
<th>Probiotic</th>
<th>Dose (CFU)**</th>
<th>Sample size</th>
<th>Probiotic* (hours)</th>
<th>Placebo* (hours)</th>
<th>WMD (hours)#</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolauri et al., [45]</td>
<td><em>L. GG</em></td>
<td>2×10¹⁰¹¹ 10¹⁰¹¹</td>
<td>71</td>
<td>33.6±19.2</td>
<td>57.6±26.4</td>
<td>-24.0</td>
<td>-34.8 to -13.2</td>
</tr>
<tr>
<td>Kaila et al., [38]</td>
<td><em>L. GG</em></td>
<td>twice daily, 5 days</td>
<td>39</td>
<td>26.4±14.4</td>
<td>60±33.6</td>
<td>-33.6</td>
<td>-49.2 to -18.0</td>
</tr>
<tr>
<td>Shornikova et al., [46]</td>
<td><em>L. GG</em></td>
<td>twice daily, 5 days 5×10⁶</td>
<td>123</td>
<td>64.8±52.8</td>
<td>91.2±67.2</td>
<td>-26.4</td>
<td>-47.9 to -4.9</td>
</tr>
<tr>
<td>Guandalini et al., [47]</td>
<td><em>L. GG</em></td>
<td>10¹⁰ with ORS</td>
<td>287</td>
<td>58.3±27.6</td>
<td>71.9±35.8</td>
<td>-13.6</td>
<td>-21.0 to -6.2</td>
</tr>
<tr>
<td>Shornikova et al., [48]</td>
<td><em>L. reuteri</em></td>
<td>10¹⁰¹¹</td>
<td>40</td>
<td>40.8±38.4</td>
<td>69.6±55.2</td>
<td>-28.8</td>
<td>-58.6 to 0.96</td>
</tr>
<tr>
<td>Shornikova et al., [49]</td>
<td><em>L. reuteri</em></td>
<td>once daily, 5 days 10⁶</td>
<td>46</td>
<td>36±26.4</td>
<td>60±36</td>
<td>-24.0</td>
<td>-42.6 to -5.4</td>
</tr>
<tr>
<td>Simakahorn et al., [50]</td>
<td><em>L. acidophilus</em> LB</td>
<td>10¹⁰ 5 doses</td>
<td>73</td>
<td>43.4±25.9</td>
<td>57±36.3</td>
<td>-13.6</td>
<td>-28.1 to 0.8</td>
</tr>
<tr>
<td>Pooled WMD (fixed effect)</td>
<td></td>
<td></td>
<td>679</td>
<td>-19.1</td>
<td></td>
<td>-24.1</td>
<td>-14.2</td>
</tr>
<tr>
<td>Pooled WMD (random effect)</td>
<td></td>
<td></td>
<td>679</td>
<td>-20.1</td>
<td></td>
<td>-26.1</td>
<td>-14.3</td>
</tr>
</tbody>
</table>

# Negative values indicate that duration of diarrhoea was shorter in the probiotic than in the control group.
* Mean ± SD
** CFU: colony forming units

reuteri, *L. acidophilus/bulgaricus*) were identified (8 also were identified in the first review described above) [38, 46-50, 53, 56, 57]. A significant reduction in the duration of diarrhoea of 16.8 h (95% CI: 7.2-28.8) and a reduction in stool frequency of 1.6 stool per day by day 2 of treatment (95% CI: 0.7-2.6) were observed in those who received lactobacilli compared with those who received placebo. A preplanned subgroup analysis suggested a dose-dependent, inverse relationship between the daily lactobacilli dose and the reduction in the duration of diarrhoea.

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Rhoea was significantly shorter (80 h in the treatment group vs 130 in the control group; p=0.003) and the length of hospitalization was reduced by 48% (1.7 vs 3.5 days; p=0.03), however the number of patients in both subgroups were small (10 vs 18 respectively) [59].

The other RCT, performed by the same group of authors, revealed that the same probiotic mixture was effective in reducing the duration of diarrhoea (76 vs 116 h in the placebo group; p=0.05) in 43 children with mild gastroenteritis (63% rotavirus-positive; mild to moderate dehydration [16%] or no dehydration [84%]) who attended day-care centers. Again, the probiotics seemed to be the most effective when administered early in the disease’s course. The mixture of two probiotics significantly reduced the risk of having loose stools 120 h after the start of treatment (5% vs 46% in the placebo group; RR: 0.13; 95% CI: 0.02 to 0.7) [60].

The most recent RCT looked at the effect of L. GG in 124 boys, aged 1 to 24 months with acute, moderate to severe watery diarrhoea treated as inpatients in a tropical developing country. There was no significant reduction in the duration of the diarrhoea in subjects given L. GG compared with control subjects (38.3 ±3.8 vs 39 ±4.6 h, p=0.59). The study was the first to include stool output as an outcome. The intervention did not result in any statistically significant difference (140 ±171 ml/kg in L. GG group vs 185 ±274 in the placebo group; p=0.81). The lack of efficacy of L. GG in this study differs from the results of previous trials. However, it is noteworthy that the mean duration of diarrhoea in controls in this study was significantly shorter than that reported by others and the dose used (10^6 CFU per day) was lower. The dose-effect relationship described above suggested that lactobacilli are most effective above a threshold dose 10^9–10^10 CFU during the first 48 hours [61].

Two more RCTs appeared after the publication of the trials cited previously. They were excluded from this review because they had either no placebo group [62] or an otherwise inadequate design [63].

In summary, the evidence from two systematic reviews and two RCTs suggests statistically significant beneficial effects of some probiotic strains in the treatment of acute gastroenteritis, mainly rotaviral, in infants and young children.

Other probiotic strains also may be effective but each should be evaluated in properly performed RCTs to assess their efficacy and efficiency [64]. The beneficial effects of probiotics against acute diarrhoea in children seem to be moderate, strain- and dose-dependent (greater for doses >10^9–10^11 CFU), and significant in watery diarrhoea caused by some viruses. Probiotics appear ineffective against invasive, bacterial diarrhoea. The beneficial effects are more evident when treatment with probiotics is initiated early in the course of disease.

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Probiotics in the prevention of community acquired diarrhoea

Prevention is the most important challenge posed by childhood diarrhoeal diseases, particularly in developing countries. Over the past several years, enormous efforts have been put into the development of safe and effective vaccines against enteric infections, mainly rotaviral [65]. Although early finding are encouraging, the goal has not been attained. To date, only two published RCTs have attempted to assess the role of probiotics in the prevention of diarrhoea at a community level [66, 67].

One study performed in Peru involved 204 undernourished infants. Their community was characterized by a high burden of diarrhoeal
diseases. Fewer episodes of diarrhoea in children were observed in those who received \textit{L. GG} (5.21 vs 6.02 episodes/child/year in the placebo group; \( p=0.028 \)). This benefit was particularly evident in non-breastfed children 18-29 months-old (4.69 vs 5.86 episodes/child/year; \( p=0.005 \)) [66].

The second placebo controlled RCT was performed in Finland. It examined the effects of the long-term consumption of probiotic milk containing \textit{L. GG} (in a dose \( 2 \times 10^8 \text{ CFU/day} \)) on the incidence of diarrhoea and respiratory infections in 571 healthy children aged 1-6 years who attended day-care centers. No significant differences were noted in the number of days with diarrhoeal symptoms, nor in the proportion of children without diarrhoea during the 7-month study period. However, the group treated with \textit{L. GG} seemed to have a less severe disease, as measured by a 16% (95% CI: 2-27) reduction in the number of days of absence due to gastrointestinal and respiratory illness in the study period (4.9 vs 5.8 days; \( p=0.03 \)) [67]. Thus, these two large RCTs provide some evidence of modest beneficial effects of \textit{L. GG} on the prevention of community acquired diarrhoea in the developing country and no effect of such prevention in developed country.

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**Probiotics in the prevention of nosocomial diarrhoea**

In children, nosocomial diarrhoea is caused commonly by enteric pathogens, especially rotavirus [68]. Depending on population, type of hospital and standards of care, reported incidence rates range from 4.5 [69] to 22.6 [70] episodes per 100 hospital admissions. Nosocomial diarrhoea may prolong hospital stays and increase medical costs. Thus, there is a strong need for cost-effective measures to prevent it.

Three RCTs were identified that examined the prevention of diarrhoea in infants and young children admitted to hospitals for reasons other than diarrhoea (Table III). Two studies of \textit{L. GG} in young children admitted for relatively short stays reported conflicting results [71, 72]. One double-blind RCT involved 81 children aged 1 to 36 months-old. It reported that \textit{L. GG} at a dose \( 6 \times 10^9 \text{ CFU} \) given orally twice daily reduced significantly the prevalence of nosocomial diarrhoea in comparison with the placebo group (6.7% vs 33.3%). Rotavirus was the predominant identified aetiologic agent in this study. The prevalence of rotaviral infection did not differ significantly in the treatment and control groups (20% vs 27.8%). However, the use of probiotics significantly reduced the risk of rotaviral gastroenteritis (2.2% vs 16.7%). This finding suggests that seven patients (95% CI: 3-40) must be treated to prevent one episode of nosocomial rotaviral gastroenteritis [71].

The second RCT involved 220 children aged 1 to 18 months. It reported no significant protective effects of \textit{L. GG} at a dose \( 10^{10} \text{ CFU} \) given orally once daily in preventing nosocomial rotavirus infection (25.4% vs 30.2%). In contrast breastfeeding was effective. Symptomatic rotaviral infections (gastroenteritis) occurred in 13% of children receiving \textit{L. GG} vs 21% in the placebo group [72]. However, this study was not powered enough to detect significant effect at the 5% level (with an 80% power).

We pooled the data from these two studies (301 children) and found that the proportion of patients with nosocomial rotavirus diarrhoea was lower in \textit{L. GG} group compared to the placebo group (10% vs 20%). However, the pooled results did not provide strong support for the routine use of \textit{L. GG} in the prevention of nosocomial rotaviral diarrhoea in infants and toddlers (RR 0.4; 95% CI: 0.09-1.6). Further research is needed. The effect of twice daily \textit{vs} once daily dose should be studied since this is one of the main differences between the two RCTs described above.

Other probiotic strains used to assess potential effectiveness in preventing nosocomial in-
Infections were *B. bifidum* (recently renamed *B. lactis*) and *S. thermophilus*. One double-blind RCT in 55 infants aged 5 to 24 months who were admitted to a chronic medical care hospital (relatively long stay) found that administration of standard infant formula supplemented with *B. bifidum* and *S. thermophilus* reduced the prevalence of nosocomial diarrhoea in comparison with the administration of non-supplemented formula (7% vs 31%; RR: 0.2; 95% CI: 0.06-0.6). These results suggest that five (95% CI: 3-20) patients must be treated with these two probiotic strains to prevent one of having nosocomial diarrhoea. The risk of rotaviral gastroenteritis was significantly lower in those receiving probiotics supplemented formula (RR: 0.3; 95% CI: 0.09-0.8). Furthermore, it was found that feeding *B. bifidum* and *S. thermophilus* led to a significantly lower rate of rotaviral shedding [73]. If confirmed, this is an important effect. A decrease in rotaviral shedding may lead to less environmental exposure and thus lower rates of rotaviral transmission in hospitalized children. However, when incidence rates (number of episodes per patient-month) rather than percentages of patients with diarrhoea were examined, the difference between the probiotic treated and control groups was not statistically significant (2 episodes per 76.5 patient-month vs 8 per 71.8, respectively). Therefore, results of this study should be interpreted cautiously. A large randomized trial is necessary to assess accurately the role of probiotics in the prevention of nosocomial diarrhoea in children.

In summary, conflicting evidence from two RCTs on the efficacy of *L. GG* in the prevention of nosocomial diarrhoea in infants and toddlers were found. One small RCT suggests beneficial effects of *B. bifidum* and *S. thermophilus* treatment. Clearly, these interventions need to be studied further before they are recommended routinely for the prevention of nosocomial diarrhoea.

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**Table III: Summary of randomized controlled trials on efficacy of probiotics in the prevention of nosocomial diarrhoea in infants and toddlers.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Probiotic</th>
<th>Dose (CFU)</th>
<th>Intervention</th>
<th>Probiotic (%)*</th>
<th>Placebo (%)*</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szajewska et al., [71]</td>
<td><em>L. GG</em></td>
<td>6×10⁹</td>
<td>Twice daily for the duration of hospital stay (mean: 8.97 days)</td>
<td>3/45 (7)</td>
<td>12/36 (33)</td>
<td>0.2 (0.06-0.6)</td>
<td>4</td>
</tr>
<tr>
<td>(2-10) Mastretta et al., [72]</td>
<td><em>L. GG</em></td>
<td>10¹⁰</td>
<td>Once daily for the duration of hospital stay (mean: 5.2 days)</td>
<td>15/114 (13)</td>
<td>22/106 (21)</td>
<td>0.6 (0.4-1.2)</td>
<td>NS #</td>
</tr>
<tr>
<td>Saavedra et al., [73]</td>
<td><em>B. bifidum</em> BB 10⁹/g S. thermophilus ST 10⁷/g</td>
<td>For the duration of hospital stay (mean: 80.9 days)</td>
<td>2/29 (7)</td>
<td>8/26 (31)</td>
<td>0.2 (0.06-0.8)</td>
<td>5 (3-20)</td>
<td></td>
</tr>
</tbody>
</table>

NNT: number needed to treat; calculated using data from original publications.
# NS: non significant
*Percentage of patients with diarrhoea
Probiotics in the prevention of antibiotic associated diarrhoea

Diarrhoea is a well-known complication of antibiotic treatment. The spectrum of clinical illness of antibiotic-associated diarrhoeas ranges from mild, self-limited diarrhoea to severe, life-threatening pseudomembranous colitis. The prevalence of antibiotic-associated diarrhoea ranges from 8 to 30% in children [74, 75], and 5 to 25% in adults [75] and depends on the definition of diarrhoea, the antimicrobial agents and host factors. Virtually any antimicrobial agent may cause diarrhoea and pseudomembranous colitis, but ampicillin, amoxicillin-clavulanate, cephalosporins, and clindamycin are incriminated most often [75]. Antibiotic-associated diarrhoea has been associated with an increased number of days of hospitalization and higher medical costs. Its mechanism presumably is related to alterations in the intestinal microflora and colonization by antibiotic resistant flora, including Clostridium difficile. Based on this assumption, probiotics are used widely to prevent and treat antibiotic associated diarrhoea.

Two systematic reviews of RCTs were found. Both searched MEDLINE and the Cochrane Library to identify relevant studies. The first [76] (search date 2000) identified nine trials with 1,214 patients. Their search yielded only two trials involving children [77, 78]. The pooled odds ratio (OR) showed that probiotic treatment was more effective than placebo in the prevention of diarrhoea (OR: 0.37; 95% CI: 0.26-0.53). The combined odds ratios for four trials that used S. boulardii also favored probiotic treatment (OR: 0.39; 95% CI: 0.25-0.62), as did studies that used lactobacilli or enterococci (OR: 0.34; 95% CI: 0.19-0.61) [76].

The second meta-analysis [79] (search date 2001) identified seven studies with 881 patients (5 of those also were identified in the meta-analysis discussed in the previous paragraph). Two of the 7 studies involved children [77, 80]. The others were performed in adults. These studies also found a significant reduction in risk of diarrhoea. The pooled relative RR was 0.4 (95% CI: 0.3-0.6).

The main questions for a paediatrician relate to the clinical applicability and clinical significance of the results of these meta-analyses. With few exceptions, the trials were carried out mainly in adults, and the authors’ conclusions may not be applicable directly to children. Hence, we have analysed four RCTs that involved children. One small RCT (38 children treated with L. acidophilus and L. bulgaricus) found no significant effect in the prevention of antibiotic associated diarrhoea (OR: 0.88; 95% CI: 0.22-3.52) [78]. One other double-blind RCT assessed the effects of treatment with L. acidophilus and B. infantis [81], but methodological limitations (i.e. small sample size, lack of the definition of diarrhoea as an end-point) preclude from drawing reliable conclusions from its findings.

No RCTs evaluating the effects of probiotics in antibiotic-associated diarrhoea caused by C. difficile in children were identified. Two RTCs in children provided evidence of a moderate beneficial effect of L. GG in the prevention of mild antibiotic-associated diarrhoea, but results in adults are conflicting. Data on the efficacy of other probiotic strains in children are very limited.

Two RCTs studied L. GG in children during a short term (7-10 days) antibiotic therapy for respiratory tract infections in an ambulatory setting. The first RCT found that in children receiving antibiotics (93 in the intervention and 95 in the control group), co-administration of L. GG reduced both the prevalence of diarrhoea defined as ≥2 liquid stools/day on ≥2 days (8% vs 26%; RR: 0.29; 95% CI: 0.13-0.61), and its duration (4.7 vs 5.9 days; p=0.05). By day 10, stool frequency was statistically significantly lower in the L. GG group than in the placebo group (mean number of stools/day: 1.4 vs 2.0; p<0.02). Diarrhoeal episodes in both intervention and control group were, however, mild, did not lead to dehydration or hospitalization, and resolved shortly after the cessation of antibiotic therapy [77].
The authors of the second RCT defined diarrhoea more conservatively as ≥3 liquid stools per day for ≥2 consecutive days. They recruited 119 children (61 in the intervention group and 58 as controls). The authors reported that *L. GG* reduced the risk of diarrhoea from 16% to 5%, but the difference did not reach statistical significance (RR: 0.32; 95% CI: 0.1-1.02). The severity of diarrhoea as measured by stool frequency (mean: 5 per day; range: 3-6) and the duration of diarrhoea (mean: 4 days; range: 2-8) also did not differ significantly between groups. The episodes of diarrhoea in this study also were mild, did not lead to dehydration or hospitalization, did not require additional treatment and resolved shortly after cessation of antibiotic therapy [80].

The pooled results of these two trials (307 children) showed that *L. GG* administered during short-term (7-10 days) antibiotic therapy in an ambulatory setting reduced the risk of mild antibiotic-associated diarrhoea in comparison with placebo (6% vs 22%; RR: 0.29; 95% CI: 0.15-0.57). These results suggest that out of 7 (95% CI: 5-13) children receiving *L. GG*, one will be protected from antibiotic-associated diarrhoea. Thus the pooled results may suggest a moderate clinical benefit from *L. GG*. However, these results should be interpreted cautiously. A recent large study in hospitalized adults failed to confirm the efficacy of *L. GG* [82]. The lower dosages of *L. GG* used in adults, differences in administered antibiotics and/or age-related differences in the pathomechanism of antibiotic-associated diarrhoea may be responsible for conflicting results. Therefore, further research is needed to elucidate this difference. One should not forget, however that probiotics are not a substitute for judicious use of antibacterial agents.

No RCTs evaluating the effects of probiotics in antibiotic-associated diarrhoea caused by *C. difficile* in children were identified. RCTs in adults suggest that *S. boulardii* is effective in reducing the risk of recurrent *C. difficile* colitis [83].

In conclusion, two RTCs in children provided evidence of a moderate beneficial effect of *L. GG* in the prevention of mild antibiotic-associated diarrhoea, but results in adults are conflicting. Data on the efficacy of other probiotic strains in children are very limited.

### Probiotics in the prevention of traveller’s diarrhoea and acute diarrhoea in immunocompromised host

Traveller’s diarrhoea is caused commonly by enterotoxigenic *E. coli*, campylobacter, shigellae and salmonellae [84, 85]. Options for the prevention of traveller’s diarrhoea include dietary and hygienic precautions, bismuth preparations and antibiotics [86]. All are controversial and not recommended for children. No RCTs addressing the efficacy of probiotics for the prevention or treatment of traveller’s diarrhoea in paediatric populations were found. In adults, several trials evaluating the use of probiotics in the prevention of traveller’s diarrhoea report conflicting results [87, 88].

No RCTs addressing the efficacy of probiotics in the prevention or treatment of diarrhoea in high-risk populations, such as immunocompromised children, were found. Further research is needed, although safety is a significant concern in these populations.

No RCTs addressing the efficacy of probiotics for the prevention or treatment of traveler’s diarrhoea in paediatric populations were found in the prevention or treatment of diarrhoea in high-risk populations, such as immunocompromised children, were found.

### Conclusions

Enthusiasm for probiotics in the prevention and management of diarrhoeal diseases in children is based mainly on the results of *in vitro* and animal studies. Convincing evidence obtained in clinical setting remains limited. Very few probiotic strains have been tested rigorously in randomized, controlled trials. Optimal doses and treatment duration have not been established clearly but the minimum effective dose for the-
rapeutic purposes seems to be a daily intake of 10⁹ CFU [89]. So far, the best documented is the efficacy of certain probiotic strains in children with rotaviral gastroenteritis, although the clinical significance of this effect is still debatable. Perhaps the most important message is that the effects of distinct probiotic microorganisms are not equal. Therefore, future clinical trials should evaluate carefully selected, precisely defined probiotic strains and address clinically important end-points. Comparative studies of minimal effective and optimal doses, different dosing regimens (e.g. once vs twice or more frequent administration per day) delivery vehicles, optimal treatment duration are needed. Furthermore, the microbiological quality and labeling of probiotics must be improved [90-92]. Health care professionals and patients should be aware of possible inappropriate labelling and quality control of diverse formulation.

References


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