# Probiotics as prevention and treatment for diarrhea

Alfredo Guarino, Andrea Lo Vecchio and Roberto Berni Canani

Department of Pediatrics, University of Naples 'Federico II', Naples, Italy

Correspondence to Alfredo Guarino, Professor of Pediatrics, University of Naples 'Federico II', Via Pansini 5, Naples, Italy
Tel: +39 0817464232; e-mail: alfguari@unina.it

**Current Opinion in Gastroenterology** 2008, 25:18–23

**Purpose of review**

To critically appraise evidence on probiotic use for prevention and treatment of diarrhea in children and adults.

**Recent findings**

Several randomized controlled trials and meta-analyses suggested that probiotics are effective in primary and secondary prevention of gastroenteritis and its treatment. Selected *Lactobacillus* strains had a modest, although significant effect in primary prevention. *Saccharomyces boulardii* was effective in antibiotic-associated and in *Clostridium difficile* diarrhea. There is evidence that it might prevent diarrhea in day-care centers. *Lactobacillus rhamnosus GG* was associated with reduced diarrheal duration and severity, more evident in case of childhood Rotavirus diarrhea. Similar, although weaker, evidence was obtained with *S. boulardii*. Both strains are included in evidence-based recommendations for gastroenteritis management in children. Data on other *Lactobacillus* strains are preliminary. Probiotic efficacy was related to cause, early administration and bacterial load, and their mechanisms were associated with antiinfectious action in the intestine or, indirectly, to modulation of innate and adaptive immunity.

**Summary**

Probiotics have gained a role as adjunctive treatment of infantile gastroenteritis together with rehydration. Their efficacy is less convincing in adults, but promising in antibiotic-associated diarrhea. However, evidence of efficacy is limited to a few strains.

**Keywords**

gastroenteritis, guidelines, *Lactobacillus*, probiotics

Curr Opin Gastroenterol 25:18–23

0267-1379

## Introduction

Probiotics may have preventive or therapeutic effects on diarrhea of various etiologies. However, not all probiotics are effective and physicians must select preparations with proven efficacy. Here, we critically appraise recent data on the prevention and treatment of diarrhea in relation to cause. We also briefly discuss new data impinging on the mechanisms governing the effects of probiotics. The role of probiotics in diarrhea associated with inflammatory bowel diseases and irritable bowel syndrome is not taken into account in this review.

### Primary prevention

As diarrhea is a very frequent problem in young infants and children, probiotics have been proposed for the prevention of community-acquired diarrhea. Six randomized controlled trials (RCTs) are available. The probiotics tested were *Lactobacillus* GG (LGG), *Streptococcus thermophilus* in association with *Bifidobacterium breve* or with *Bifidobacterium lactis*, *B. lactis* alone, *Lactobacillus casei DN-114* and *Lactobacillus reuteri*. The results were not always statistically significant and were of questionable clinical relevance. A double-blind RCT performed in a large pediatric population in France reported fewer episodes of dehydration, medical consultation and need for formula shift in infants fed probiotic-supplemented formula, although the incidence of diarrhea was similar to that of the control group [1]. A smaller RCT in Israel found a reduction in the frequency and duration of diarrhea in treated children [2]. These trials provided evidence of a modest protective effect of specific strains. Indirect evidence that targeting intestinal microecology is effective in preventing diarrhea is the finding of fewer intestinal infections in a cohort of healthy infants fed prebiotics in the first year of life [3]. The cost efficacy of such interventions remains to be established.

### Secondary prevention

Secondary prevention involves selected conditions, limited in duration, that are associated with an increased risk of diarrhea rather than with host-related factors.

*Antibiotic-associated diarrhea*

Antibiotic-associated diarrhea (AAD) occurs in about 5–25% of adult patients and 11–40% of children upon administration of broad-spectrum antibiotics. *Clostridium difficile* is a major agent, although diarrhea may be related to general changes in intestinal microflora. A systematic review [4] and a meta-analysis of RCTs [5] provided evidence of a moderate beneficial effect of LGG, *Saccharomyces boulardii* and a combination of *B. lactis* and *S. thermophilus* in preventing AAD. A recent Cochrane review of 10 RCTs carried out in 1015 treated and 971 control children reported a significant reduction in the incidence of AAD [Relative risk (RR) 0.49; 95% confidence interval (CI) 0.32–0.74], confirming the efficacy of LGG and *S. boulardii* [6••]. The subgroup analyses provided evidence that probiotic dose may be responsible for the observed clinical and statistical heterogeneity of results. Interestingly, of the eight studies that provided dosage information, five studies in which children received 5–40 billion bacteria/yeast/day showed that probiotics had preventive effects (RR 0.35; 95% CI 0.25 to 0.47), whereas the combined results of three studies using less than 5 billion colony-forming unit (CFU) bacteria/yeast/day were not significant (RR 0.89; 95% CI 0.53 to 1.48, $I2 = 61.4\%$). The number-needed-to-treat was between seven and 10. As suggested by the Cochrane review, more data are needed to consider the routine use of probiotics to prevent AAD in children started on large spectrum antibiotics. In particular, cost-benefit data are strongly needed.

Two recent double-blind RCTs suggested that other strains were effective in preventing AAD. The first, conducted on 135 adults, showed that a drink containing *L. casei*, *Lactobacillus bulgaricus* and *S. thermophilus* twice daily prevented AAD and diarrhea caused by *C. difficile* (number-needed-to-treat five and seven, respectively) [7]. The second was a pediatric trial in which *Lactobacillus rhamnosus* (strains E/N, Oxy and Pen) reduced the risk of any diarrhea in children undergoing antimicrobial therapy for common infectious diseases [8•].

The role of probiotics in *C. difficile*-associated diarrhea is still unclear. *S. boulardii* was found to be significantly effective in treating *C. difficile* diarrhea [9]. The benefit of probiotics in *C. difficile* diarrhea was mostly seen in adults and, particularly, in subgroups characterized by severe disease [10]. Despite the moderate evidence obtained in adults, the use of probotics to specifically treat or prevent *C. difficile* diarrhea has not been evaluated in a RCT in children. A recent meta-analysis showed that LGG and *S. boulardii* might be useful in treating or preventing recurrences of *C. difficile* diarrhea [11]. Nonetheless, the heterogeneity of the studies makes it difficult to draw definite conclusions.

*Nosocomial and day-care center diarrhea*

Nosocomial diarrhea may prolong hospital stay and increase medical costs. It is commonly caused by Rotavirus and less frequently by *C. difficile*. Earlier and inconsistent data suggesting that probiotics may reduce the risk of nosocomial diarrhea were summarized in a recent review, and the conflicting results may have been related to the strain and dose of probiotic used [12•]. Five RCTs have been published on the prevention of diarrhea in day-care centers. The probiotics tested were LGG, *B. lactis* (alone or combined with *S. thermophilus*) and *Lactobacillus thermophilus*. Efficacy was modest and inconsistent and was detected for some strains only. A narrative review [12•] and a recent systematic review [13] agreed that evidence in favor of probiotics for prevention of diarrhea in day-care centers and for nosocomial diarrhea is not sufficient to recommend their routine use.

*Traveler's diarrhea*

Travel is a risk factor for infectious gastroenteritis. A recent meta-analysis revealed evidence of a protective effect by *S. boulardi* and by mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* [14]. However, evidence of the efficacy of probiotics in the prevention of traveler's diarrhea is preliminary.

*Diarrhea related to nonantibiotic treatment*

Drugs and other treatment administered for noninfectious diseases such as cancer may induce diarrhea. A novel field of application of probiotics is prevention of iatrogenic diarrhea related to treatment toxicity. Lactic acid producing bacteria reduce the risk of radiation-induced diarrhea. Prophylactic administration of VSL#3 (a mixture of four species of lactobacilli, three species of bifidobacteria and *S. thermophilus*) reduced the incidence of radiation-associated enteritis in a placebo-controlled trial that included 500 patients who underwent postoperative radiation therapy [15]. Some probiotic strains were found to be beneficial in cancer drug-induced diarrheas, namely, VSL#3 prevented irinotecan-related diarrhea (in rats) and LGG reduced the frequency of severe diarrhea caused by 5FU-based chemotherapy [16].

## Treatment of intestinal infections

Although the standard treatment of acute diarrhea remains to be an oral rehydration solution (ORS), probiotics have gained an important role as adjuvant therapy. A large number of trials, including randomized and controlled, and several accurate meta-analyses reported that probiotics exerted antidiarrheal effects particularly in children. A wide pattern of strains, schedules, doses and conditions have been tested. The outcomes most widely considered were duration of diarrhea, duration of hospitalization and severity of diarrhea, with some trials evaluating ORS intake, number of vomiting episodes and

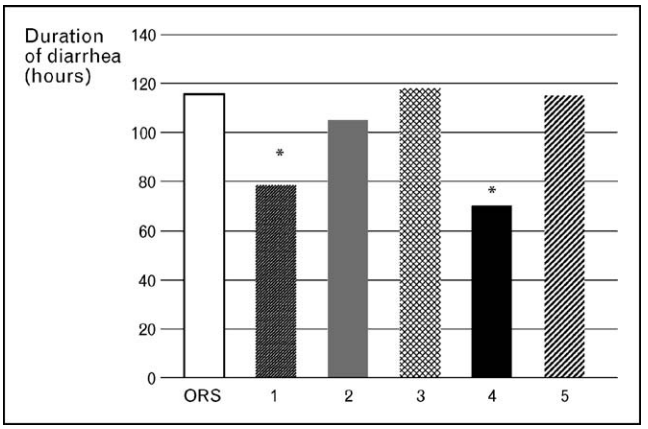
stool volumes. Despite the broad spectrum of design and conditions, nearly all studies showed some positive effects on diarrhea, with statistically significant benefits or moderate clinical benefits mainly in infants and young children. A number of strains have been tested, but proof of efficacy is compelling only for a few. LGG and *S. boulardii* are the strains most widely tested and also are the most effective. The efficacy of LGG as an adjunctive treatment of diarrhea is now considered conclusive.

A recent meta-analysis of RCTs [17•] showed that LGG is associated with a reduced duration of diarrhea, particularly that induced by Rotavirus. LGG also reduced the risk of persistent diarrhea (lasting >7 days) and shortened the duration of hospitalization compared with placebo. Interestingly, probiotic administration is generally effective in a population irrespective of the cause of diarrhea. However, when the cause of diarrhea is known, the efficacy tends to be confined to viral diarrhea and, less commonly, to 'unknown etiology', whereas it does not extend to bacterial diarrhea. An exception is a recent double-blind RCT conducted in parallel with an experimental study of *L. acidophilus* strain LB, which showed a reduction by 1 day of bacteria-induced diarrhea [18]. This trial was performed with a probiotic preparation containing heat-killed strains.

Five RCTs testing *S. boulardii* in a total of 619 patients were included in a recent meta-analysis [19•], and the authors concluded that *S. boulardii* exerts a moderate clinical benefit by significantly reducing the duration of diarrhea and the risk of diarrhea longer than 1 week. Other strains have been tested including *Lactobacillus reuteri*, *L. acidophilus* LB, a mixture of *S. thermophilus*, *Lactobacillus bulgaricus* and others. Two recent multicenter RCTs, each of which included more than 100 children treated with *Escherichia coli* strain Nissle 1917, reported a significant reduction of the duration of acute diarrhea [20,21].

The only head-to-head comparative trial performed with different strains was a single-blind RCT performed in Italy on children aged from 3 to 36 months with acute gastroenteritis [22••]. The trial compared the effects of five probiotic preparations, namely, LGG, *S. boulardii*, *Bacillus clausii*, a mixture of *L. bulgaricus*, *S. thermophilus*, *L. acidophilus* and *B. bifidum* and finally *Enterococcus faecium* SF68. The control group received oral rehydration solution only. Diarrhea duration and severity were significantly reduced after the administration of LGG and the mix of four strains versus children who received ORS alone (Fig. 1). LGG was more effective than the mix, but the difference was not significant. The other three preparations did not affect symptom duration. These results confirm that the efficacy of probiotics is related to the strain, however, dosage is also important.

**Figure 1 Effects of different probiotic strains on the duration of acute diarrhea in children**




*$=P<0.001$ compared with oral rehydration solution alone (Mann–Whitney *U* test). The figure shows the effects on the duration of diarrhea of five different probiotic preparations administered in addition to oral rehydration solution. The control group received oral rehydration solution only. The total duration of diarrhea is significantly lower in children receiving *Lactobacillus rhamnosus GG* (group 1) and in those receiving the bacterial mix (group 4) than in patients receiving oral rehydration solution alone. These results demonstrate that not all commercially available probiotic preparations are effective in children with acute diarrhea. □, Oral rehydration solution (ORS) alone; ▨, *Lactobacillus casei* subsp. *rhamnosus GG*; ■, *Saccharomyces boulardi*; ▩, *Bacillus clausii*; ■, *Lactobacillus delbrueckii* var. *bulgaricus*, *Lactobacillus acidophilus*, *Streptococcus thermophilus*, *Bifidobacterium bifidum*; ▨, *Enterococcus faecium* Sf 68. Reproduced with permission [22••].

An early meta-analysis reported dose-related efficacy for lactobacilli preparations against gastroenteritis [23]. This important concept emerged again from a recent review [12•]. Probiotic efficacy was correlated in a linear fashion with bacterial load, the minimal effective dose being at least 10 billions CFU/day. An example of the importance of the dose comes from a RCT conducted in India [24], in which a dose of only 60 million CFU of LGG, one of the lowest ever used in a clinical trials, was administered twice a day and did not affect the frequency and duration of diarrhea or vomiting in children with acute diarrhea. However, interestingly, the same dose significantly reduced the risk of persistent diarrhea, thus showing that efficacy is not merely a matter of dose, but also depends on the outcome parameter considered [25].

In conclusion, data from several meta-analyses show that the effects of probiotics in acute diarrhea in children are strain-dependent and dose-dependent, being generally greater with doses more than $10^{10}$–$10^{11}$ CFU, highly significant for watery diarrhea and viral gastroenteritis, but not for invasive bacterial diarrhea, more evident when treatment is initiated early in the course of disease and more evident in children in developed than in developing countries.

In May 2008, probiotics were included in a guideline document, namely the Guidelines For the Management of Acute Gastroenteritis produced by a joint committee from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Pediatric Infectious Disease (ESPID) [26••]. The document was developed through an evidence-based systematic review approach that incorporated tables of evidence with their grading. The guidelines state that 'probiotics may be an effective adjunct to the management of diarrhea. However, because of the lack of efficacy for many preparations, only the use of probiotic strains with proven efficacy and in appropriate doses is suggested for the management of acute diarrhea in European children as an adjunct to rehydration therapy'. The evidence of efficacy for LGG was rated as IA, which is the maximum, and that for *S. boulardii* IIB, corresponding to a strong level of evidence based on meta-analysis of RCTs and properly designed RCTs of appropriate size, respectively. A similar conclusion appears in the recent recommendations for the clinical use of probiotics based on the Yale University Workshop update of 2007 in which the recommendations were graded 'A', 'B', 'C' or no category, based on expert opinion [27].

Probiotics have also been tested in HIV/AIDS patients, many of whom suffer from debilitating infectious and noninfectious diarrhea. Although probiotics did not significantly affect gastrointestinal symptoms in a well designed RCT that included HIV-infected patients undergoing antiretroviral therapy [28], a recent clinical trial showed that probiotic yogurt containing some *Lactobacilli* strains resolved moderate diarrhea and increased CD4 cells/μl in HIV/AIDS patients [29].

## Safety issues

Probiotics are generally regarded as being safe, and side effects in ambulatory care have rarely been reported. Safety issues are related to bacterial translocation and sepsis, and to the risk of carrying antibiotic resistance transposons that may spread resistance to antibiotics. The latter has been reported for some probiotics, among which are *L. reuteri* ATCC 55730 and *Enterococcus faecium* [30,31].

## Mechanisms of action of probiotics

The rationale for using probiotics is based on the assumption that they modify the composition of colonic microflora and counteract enteric pathogens. However, there are two main views as to how probiotics counteract diarrhea. According to one theory, probiotics act locally (at intestinal level). According to the other theory, probiotics act by modulating the immune response.

At local level, probiotics:

(1) compete with pathogens for nutrients and receptors [32];
(2) induce hydrolysis of toxins and receptors [32];
(3) induce production of antimicrobial substances (including peptides of the innate immune system) [32];
(4) induce production of organic acids and modulation of nitric oxide synthesis [32];
(5) regulate intestinal permeability by modulating the epithelial tight junctions [33];
(6) exert a trophic action on the intestinal mucosa, which leads to brush border enzyme activation, stimulation of glucose absorption and antiapoptotic effects on the enterocyte [34];
(7) inhibit selected intracellular mechanisms involved in viral replication (such as MEK, PKA, p38 MAPK) [34].

On the other hand, an increasing body of evidence supports the concept that probiotics modulate the immune response. Dendritic cells and toll-like receptor molecules are crucial factors in this process. These cells receive signals from structural lipopolysaccharides, glycopeptides and CpG DNA of probiotic strains and transduce them in order to regulate the production of innate immunity peptides that, in turn, exert antimicrobial activity or modulate adaptive immunity [35•]. Selected probiotics promote specific antibody responses against given pathogens. This is the case of *S. boulardii* that, apart from producing a 54-kD protease that hydrolyzes the A and B toxins of *C. difficile* and their intestinal receptors, also stimulates the production of specific IgG and IgA antitoxin A produced by the same pathogen [35•]. LGG increases the mucosal production of specific antirotavirus sIgA and modulates the mucosal inflammatory response to pathogens by stimulating the production of anti-inflammatory IL-10 and IL-4 and by inhibiting the production of proinflammatory TNF-α, IL-6 and IFN-γ [36••]. This process affects transepithelial ion fluxes, and hence diarrhea, as proinflammatory cytokines induce a potent ion secretory effect at intestinal level and their inhibition reduces fluid losses in children with inflammatory diarrhea.

Specific *Lactobacillus* strains activate muciparous cell genes, which leads to an increase in the thickness of the enterocyte mucus layer, thereby preventing the adhesion of pathogenic *E. coli*. LGG negatively modulates Shiga toxin 2A production by enterohemorrhagic *E. coli* (EHEC) 0157:H7 through a mechanism that involves pH changes mediated by the production of organic acids [37]. Finally, strains of the same probiotic species may have different mechanisms of action depending on the pathogen.

Most probiotic effects have been demonstrated in experimental studies and only a few in clinical studies. However, it remains to be established whether the antidiarrheal effects of different probiotic strains are governed by a single mechanism.

## Conclusion

The evaluation of the effects of probiotics has progressed from empiricism to science, and the efficacy of specific strains in acute gastroenteritis is demonstrated in several RCTs and meta-analyses. The increasing use of probiotics is linked to the concept of 'naturality', which fulfills the desire of customers to take medicines free from side effects that is largely true for probiotics. Novel fields of application for probiotics may emerge, including functional bowel disorders and inflammatory or allergic diseases that are responsible for chronic, potentially severe diarrhea in both adults and children. This is likely to support the concept of using specific strains for specific conditions.

## Acknowledgements

We are grateful to Jean Ann Gilder for editing the text.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 77).

**1** Thibault H, Aubert-Jacquin C, Goulet O. Effects of long-term consumption of a fermented infant formula (with *Bifidobacterium breve* c50 and *Streptococcus thermophilus* 065) on acute diarrhea in healthy infants. J Pediatr Gastroenterol Nutr 2004; 39:147–152.

**2** Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. Pediatrics 2005; 115:5–9.

**3** Bruzzese E, Volpicelli M, Squaglia M, *et al.* Impact of prebiotics on human health. Dig Liver Dis 2006; 38 (Suppl 2):S283–S287.

**4** Szajewska H, Setty M, Mrukowicz J, *et al.* Probiotics in gastrointestinal diseases in children: hard and not-so-hard evidence of efficacy. J Pediatr Gastroenterol Nutr 2006; 42:454–475.

**5** Szajewska H, Ruszczynski M, Radzikowski A. Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. J Pediatr 2006; 149:367–372.

**6** •• Johnston BC, Supina AL, Ospina M, *et al.* Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev 2007; 2:CD004827.
A recent and complete systematic review that reports the efficacy of selected probiotics in the prevention of antibiotic-associated diarrhea and underlines the important role of the dose-response effect.

**7** Hickson M, D'Souza AL, Muthu N, *et al.* Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. BMJ 2007; 335:80.

**8** • Ruszczynski M, Radzikowski A, Szajewska H, *et al.* Clinical trial: effectiveness of *Lactobacillus rhamnosus* (strains E/N, Oxy and Pen) in the prevention of antibiotic-associated diarrhoea in children. Aliment Pharmacol Ther 2008; 28:154–161.
A well designed randomized controlled trial that demonstrates the beneficial effects of new probiotic strains for the prevention of antibiotic-associated diarrhea in children.

**9** Czerucka D, Piche T, Rampal P. Review article: yeast as probiotics – Saccharomyces boulardii. Aliment Pharmacol Ther 2007; 26:767–778.

**10** Dendukuri N, Costa V, McGregor M, *et al.* Probiotic therapy for the prevention and treatment of Clostridium difficile disease: a systematic review. CMAJ 2005; 173:167–170.

**11** Segarra-Newnham M. Probiotics for *Clostridium difficile*-associated diarrhea: focus on *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. Ann Pharmacother 2007; 41:1212–1221; Review.

**12** • Guandalini S. Probiotics for children with diarrhea: an update. J Clin Gastroenterol 2008; 42 (Suppl 2):S53–S57.
A complete and useful review that focuses on the efficacy of probiotics for diarrhea of different etiologies in children in different settings.

**13** Mrukowicz J, Szajewska H, Vesikari T. Options for the prevention of rotavirus disease other than vaccination. J Pediatr Gastroenterol Nutr 2008; 46 (Suppl 2):S32–S37.

**14** McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhea. Travel Med Infect Dis 2007; 5:97–105.

**15** Delia P, Sansotta G, Donato V, *et al.* Use of probiotics for prevention of radiation-induced diarrhea. World J Gastroenterol 2007; 13:912–915.

**16** Osterlund P, Ruotsalainen T, Korpela R, *et al. Lactobacillus* supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. Br J Cancer 2007; 97:1028–1034.

**17** • Szajewska H, Skorka A, Ruszczynski M, *et al.* Meta-analysis: Lactobacillus GG for treating acute diarrhoea in children. Aliment Pharmacol Ther 2007; 25:871–881.
A complete meta-analysis of the role of LGG in the therapy of acute diarrhea in children.

**18** Lievin-Le Moal V, Sarrazin-Davila L, Servin AL. An experimental study and a randomized, double-blind, placebo-controlled clinical trial to evaluate the antisecretory activity of *Lactobacillus acidophilus* strain LB against nonrotavirus diarrhea. Pediatrics 2007; 120:e795–e803.

**19** • Szajewska H, Skorka A, Dylag M. Meta-analysis: *Saccharomyces boulardii* for treating acute diarrhoea in children. Aliment Pharmacol Ther 2007; 25:257–264.
A complete meta-analysis on the role of *S. boulardii* in the therapy of acute diarrhea in children.

**20** Henker J, Laass M, Blokhin BM, *et al.* The probiotic *Escherichia coli* strain Nissle 1917 (EcN) stops acute diarrhoea in infants and toddlers. Eur J Pediatr 2007; 166:311–318.

**21** Henker J, Laass M, Blokhin BM, *et al.* Probiotic *Escherichia coli* Nissle 1917 versus placebo for treating diarrhea of greater than 4 days duration in infants and toddlers. Pediatr Infect Dis J 2008; 27:494–499.

**22** •• Canani RB, Cirillo P, Terrin G, *et al.* Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. BMJ 2007; 335:340.
The only head-to-head trial with different probiotic preparations. It shows that many probiotic strains are effective and not all probiotics are interchangeable in their efficacy.

**23** Van Niel CW, Feudtner C, Garrison MM, *et al. Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. Pediatrics 2002; 109:678–684.

**24** Basu S, Chatterjee M, Ganguly S, *et al.* Efficacy of *Lactobacillus rhamnosus* GG in acute watery diarrhoea of Indian children: a randomised controlled trial. J Paediatr Child Health 2007; 43:837–842.

**25** Basu S, Chatterjee M, Ganguly S, *et al.* Effect of *Lactobacillus rhamnosus* GG in persistent diarrhea in Indian children: a randomized controlled trial. J Clin Gastroenterol 2007; 41:756–760.

**26** •• Guarino A, Albano F, Ashkenazi S, *et al.* European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for paediatric infectious diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: executive summary. J Pediatr Gastroenterol Nutr 2008; 46:619–621.
This is the most recent and complete evidence-based document for the management of acute gastroenteritis in pediatric age and the first guideline to recommend probiotics as an effective adjunct to the management of diarrhea.

**27** Floch MH, Walker A, Guandalini S, *et al.* Recommendations for probiotic use-2008. J Clin Gactroenterol 2008; 42 (Suppl 2):S104–S108.

**28** Salminen MK, Tynkkynen S, Rautelin H, *et al.* The efficacy and safety of probiotic *Lactobacillus rhamnosus* GG on prolonged, noninfectious diarrhea in HIV Patients on antiretroviral therapy: a randomized, placebo-controlled, crossover study. HIV Clin Trial 2004; 5:183–191.

**29** Anukam KC, Osazuwa EO, Osadolor HB, *et al.* Yogurt containing probiotic *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 helps resolve moderate diarrhea and increases CD4 count in HIV/AIDS patients. J Clin Gastroenterol 2008; 42:239–243.

**30** Egervarn M, Danielsen M, Roos S, *et al.* Antibiotic susceptibility profiles of *Lactobacillus reuteri* and *Lactobacillus fermentum*. J Food Prot 2007; 70:412–418.

**31** Kayser FH. Safety aspects of enterococci from the medical point of view. Int J Food Microbiol 2003; 88:255–262.

**32** Lemberg DA, Ooi CY, Day AS. Probiotics in paediatric gastrointestinal diseases. J Paediatr Child Health 2007; 43:331–336.

**33** Seth A, Yan F, Polk DB, Rao RK. Probiotics ameliorate the hydrogen peroxide-induced epithelial barrier disruption by a PKC- and MAP kinase-dependent mechanism. Am J Physiol Gastrointest Liver Physiol 2008; 294:G1060–G1069.

**34** Yan F, Cao H, Cover TL, *et al.* Soluble proteins produced by probiotic bacteria regulate intestinal epithelial cell survival and growth. Gastroenterology 2007; 132:562–575.

**35** Walker WA. Mechanisms of action of probiotics. Clin Infect Dis 2008; • 46:S87–S91.
A very interesting review of the mechanisms of action of probiotics.

**36** Jonkers D, Stockbrügger R. Review article: probiotics in gastrointestinal and •• liver diseases. Aliment Pharmacol Ther 2007; 26:133–148.
This is an exhaustive review of the effects of probiotics in gastrointestinal and liver diseases.

**37** Carey CM, Kostrzynska M, Ojha S, Thompson S. The effect of probiotics and organic acids on Shiga-toxin 2 gene expression in enterohemorrhagic *Escherichia coli* O157:H7. J Microbiol Methods 2008; 73:125–132.