The role of probiotics in the prevention and treatment of childhood infectious diarrhea

Vloga probiotikov pri preprečevanju in zdravljenju infekcijske diareje pri otrocih

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Ključne besede:
Probiotics, infectious diarrhea, Clostridium difficile diarrhea, community acquired diarrhea,traveler's diarrhea, children

Key words:
probiotiki, infekcijska driska, driska povzročena s Clostridium difficile, driska v domačem okolju, driska na potovanjih

Citirajte kot/Cite as:
Zdrav Vestn 2013; 82 supl 1: I-94–102

Prispelo: 21. jun. 2013,
Sprejeto: 24. jul. 2013

Abstract

Probiotics are beneficial bacteria that colonize and replicate in the human intestinal tract providing a positive benefit to the host. Several clinical trials support the efficacy of certain probiotics in the prevention and treatment of various diarrheal illnesses. This paper reviews published clinical trials assessing the efficacy of various probiotic species and strains in preventing and treating acute diarrhea in children. The available evidence shows that few probiotic species (mostly *Lactobacillus GG and Saccharomyces boulardii*) are efficacious in decreasing the duration and the severity of acute gastroenteritis, with the most prominent of the reported benefits, the reduction of the duration of diarrhea by approximately 1 day. With regard to the prevention of acute diarrhea in the community and the hospital, there is modest evidence that some probiotic species may be efficacious in preventing community acquired diarrhea (*Bifidobacterium lactis, Lactobacillus reuteri, Lactobacillus GG)*, nosocomial acquired diarrhea (*Lactobacillus GG)* and Clostridium difficile diarrhea *(Lactobacillus GG* and *Saccharomyces boulardii)*. In conclusion, the available evidence suggests that probiotics are safe when used in healthy children and effective in reducing the duration of acute infectious diarrhea. Further studies are required to assess the efficacy of selected probiotic species and strains at different dosages for different clinical indications and patient groups.

Izvleček

Probiotiki so koristne bakterije, ki se naseljujejo in razmnožujejo v človeškem prebavnem traktu in ugodno delujejo na gostitelja. Mnogi klinični preskusi potrjujejo učinkovitost nekaterih probiotikov pri preprečevanju in zdravljenju različnih vrst driske. Ta pregledni članek obravnava objavljena klinična preskušanja, ki ocenjujejo učinkovitost različnih vrst in sevov probiotikov pri preprečevanju in zdravljenju akutne diareje pri otrocih. Iz razpoložljivih dokazov je razvidno, da nekaj vrst probiotikov (predvsem *Lactobacillus GG* in *Saccharomyces boulardii*) učinkovito zmanjšuje trajanje in resnost akutnega gastroenteritisa, pri čemer je med navedenimi koristmi najočitnejše skrajšanje trajanja driske za približno 1 dan. V zvezi s preprečevanjem akutne diareje v skupnosti in bolnišnicah obstajajo skromni dokazi, da lahko nekatere vrste probiotikov učkovito preprečujejo pojav okužb z drisko v skupnosti (*Bifidobacterium lactis, Lactobacillus reuteri, Lactobacillus GG*), bolnišničnih okužb z drisko (*Lactobacillus GG*) in drisk, ki jih povzroča bakterija Clostridium difficile (*Lactobacillus GG* in *Saccharomyces boulardii*). Skratka, razpoložljivi podatki kažejo, da je uporaba probiotikov, kadar se uporabljajo pri zdravih otrocih, varna in učinkovito skrajša trajanje akutne infekcijske driske. Za oceno učinkovitosti izbranih vrst in sevov probiotikov v različnih odmerkih pri različnih kliničnih indikacijah in skupinah bolnikov so potrebne nadaljnje raziskave.

Introduction

Acute gastroenteritis is one of the most common infectious diseases in childhood. Viruses (rotaviruses, noroviruses), bacterial pathogens (Escherichia coli, toxigenic Clostridium difficile, Campylobacter jejuni and Vibrio cholerae) and parasites can all cause acute gastroenteritis. However, the most common cause of gastroenteritis in children, especially in young children aged 3–24 months, is rotavirus infection. Around 1.4

million of the 9 million child deaths reported in 2008 were due to acute diarrhea, with 49 % of the deaths occurring in the following five countries: India, Nigeria, Democratic Republic of the Congo, Pakistan and China.[1,2] In the countries with low and middle socioeconomic status, the incidence of acute diarrhea was estimated in 2010 to be around 2.9 episodes per child annually, mostly affecting infants aged 6–11 months (4.5 episodes per child annually).[3] In Europe, the incidence of diarrhea in children up to 3 years of age ranges from 0.5 to 1.9 episodes per child per year.[4] Furthermore, infectious agents, such as enteropathogenic E. coli (EPEC), may cause protracted diarrhea in children, increasing the risk of long-term morbidities.[4] Furthermore, some studies have shown that an early onset of episodes of diarrhea predisposes children to lasting disabilities, stunted growth and impaired cognition and school performance.[5] In 2008, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Pediatric Infectious Diseases (ESPID) developed management guidelines in acute gastroenteritis for pediatricians practicing in Europe.[6] The above Societies in collaboration with the National Institute for Health and Clinical Excellence (NICE) agree that the primary management of acute gastroenteritis is the rehydration using an oral rehydration solution (ORS). It should be noted however, that ORS neither reduces the frequency of fluid loss, nor shortens the duration of diarrhea. Due to a need for alternatives to routine treatment, the use of probiotics has gained favor in the past decade, although the concept of using them for prevention and treatment of some human illnesses has been around for more than a century.[7] Up to now, numerous studies assessing the efficacy and safety of various probiotic species and strains in preventing and treating childhood infectious diarrhea are available as well as several meta-analyses. The ESPGHAN/ESPID evidence-based guidelines for the management of acute gastroenteritis in children in Europe summarized data from several meta-analyses consistently showing a significant effect and moderate clinical benefit of selected probiotic strains in the treatment of acute watery diarrhea (primarily rotaviral), mainly in infants and young children.[6] In 2011, the consensus opinion of 10 experts participating at the third Yale Workshop updated recommendations on probiotic use of the previous two meetings that were published in 2005 and 2008.[8] The concept of probiotic use in acute diarrheal diseases is based on the assumption that they act against enteric pathogens with various mechanisms. They may be involved in immune signaling pathways, stimulate immunity, produce factors against enteric pathogens, and/or induce the host to secrete antipathogenic factors.[9] The "defense and protection" function of the microflora is mediated by a number of mechanisms, including competition with pathogenic bacteria for binding sites and nutrients, increased production of secretory IgA and mucin, increased gut barier function and production of antimicrobial substances.[10-12] While various bacteria in various daily doses have been studied, specific species of bifidobacteria (B. *breve, B. lactis*) and lactobacilli (*LGG, L. casei, L. reuteri*) are better documented than others in terms of beneficial effects in infants and children.

The aim of this paper is to review studies addressing the efficacy of probiotics in the treatment and prevention of infectious diarrhea occurring in the community, of the hospital-acquired acute diarrhoea, and the traveler's diarrhea, as well as their efficacy in the prevention or treatment of Clostridium difficile–associated diarrhea.

1. Prevention of community-acquired diarrhea

Several studies have examined the efficacy of probiotics in preventing acute diarrheal episodes occurring in the community settings (Table 1). In 2000, Pedone CA et al.[13] compared the incidence of diarrhea in 779 healthy children aged 6 to 24 months. The study consisted of 2 periods (supplementation period and observation period) and 2 groups (placebo and supplemented group). Subjects of the supplemented group consumed *L. casei* strain DN-114 001 in a standard yogurt, while the placebo group consumed

yogurt without probiotic. The study showed that at least one episode of diarrhea occurred in 22 % of placebo consuming children compared to 15.8 % of children receiving yogurt supplemented with probiotic.[13] Since then, several studies have been published in Europe,[14-17] in Israel,[18] in Australia,[19] in Asia[20] and in other countries assessing the efficacy of probiotics in this context. In some studies, the efficacy of a formula supplemented with a specific strain of probiotic[21] was evaluated, while other studies compared two different concentrations of a formula containing a mixture of two probiotics.[22] Weitzman et al.,[18] studied 201 infants aged 4–10 months attending several care-centers in Israel, for a period of 12 weeks. Children were randomized to three groups: the 1st group received a formula enriched with *Bifidobacterium lactis BB12*, the 2nd group, a formula enriched with *L. reuteri (American Type Culture Collection 55730)* and the 3rd group, a formula with no probiotics. The results showed fewer febrile illnesses as well as diarrheal episodes in infants receiving probiotics compared to the control group, with *L. reuteri* showing greater efficacy.[18] In 2007, a placebo controlled trial, conducted in 496 children in Australia, evaluated a milk product containing probiotics B. lactis

Table 1: Studies assessing the preventive effect of probiotics on the incidence of acute diarrhea in community and in hospitals

Reference	Patients	Age	Probiotics used	Source	Benefit in patients receiving probiotic
Pedone CA et al.[13]	779 healthy children, attending day-care	age 6 to 24 months	L. casei DN114 001, 3.2×10^8 CFU, 5 days per week	Supplemented yogurt	↓ incidence of diarrhea
Thibault et al.[15]	900 healthy infants	Age 4 to 6 months	Bifidobacterium brevis plus Streptococcus thermophilus 065	Reconstituted formula	No difference in incidence or duration of diarrheal episodes or hospital admissions Less severe the diarrheal episodes
Weitzman et al.[18]	201 infants in 14 child care centers in Israel	Age 4 to 10 months	1st group Bifidobacterium lactis Bb-12 (1×10^7 CFUs/mL) 2nd group L.reuteri ATCC 55730 (1×10^7 CFUs/mL) 3rd group No probiotics	Supplemented formula	↓ diarrheal episodes ↓ febrile illnesses Effects more prominent with L.reuteri
Chouraqui JP et al.[21]	90 healthy children	Age < 4 months	Bifidobacterium lactis Bb-12 (1×10^6 CFU/g) Powder formula resulting in 1.5×10^8	Supplemented formula	↓ probability of diarrhea ↓ number of days with diarrhea per child-year
Oberhelman RA et al.[23]	204 undernourished infants and children	6 to 24 months	LGG, 3.7×10^{10} CFU, 6 days/week	Added to liquid gelatin	↓ episodes of diarrhea
Szajewska H et al. [24]	81 children hospitalized for reasons other than diarrhea	age 1 to 36 months	LGG, 6×10^9 CFU; twice daily	Reconstituted sachet	↓ incidence of diarrhea ↓ incidence of rotavirus gastroenteritis

CNCM and prebiotics (CUPDAY milk formula). The study showed no difference with regards to the frequency of diarrhea, but the duration of diarrhea in the study group was shorter compared to the control group. The children receiving the CUPDAY milk formula presented fewer diarrheal episodes compared to those receiving placebo.[19] In a study conducted in Peru, 200 malnourished infants and children were randomized to receive either *Lactobacillus GG* (LGG) or placebo for 15 months. Children in the LGG group had significantly fewer diarrheal episodes (5.2 per child per year versus 6.0 in the placebo group, $P < .03$).[23]

In summary, there is modest evidence that some probiotics (*Bifidobacterium lactis, L. reuteri, LGG*) are efficacious in preventing community acquired diarrheal episodes in infants and children.

2. Prevention of nosocomial diarrhea

Development of acute diarrhea is common in hospitalized children, especially due to rotavirus infection. Two trials conducted in 2001 and 2002 assessed *LGG* in children hospitalized for reasons other than diarrhea and showed that children who were administered *LGG* had significantly fewer episodes of rotavirus diarrhea, but there was no difference with regards to the prevalence of the infection.[24,25] Recently, Hojsak et al.[26] in a randomized, double-blind, placebo controlled trial, examined 742 children admitted in the hospital, randomly allocated to receive either milk supplemented with *LGG* (at a dose of 10^9 CFU in 100mL milk) or placebo. The study showed that the risk for developing gastroenteritis was reduced as well as the number of vomiting episodes and the duration of the infection.[26] No differences were reported with regard to the duration of hospital stay between the two groups.[26]

In summary, *Lactobacillus GG* may be useful as a measure for the prevention of nosocomial-acquired diarrhea.

3. Prevention of traveler's diarrhea

Acute diarrhea occurs in about half of travelers who visit high-risk areas. Several studies were performed using probiotics for prevention. McFarland et al.,[27] analyzed numerous studies in a recent meta-analysis and concluded that *L. acidophilus* and *B. bifidum* as a mixture, and *S. boulardii* as a single strain, were both effective in preventing traveler's diarrhea in adults (RR = 0.85, 95 % CI 0.79, 0.91; $P < .001$). In children, however, the role of probiotics in preventing traveller's diarrhea needs further investigation.

4. Prevention of Clostridium difficile infection

Clostridium difficile (*C. difficile*) is a relatively common finding in healthy infants, suggesting it may be an incidental finding and forms part of the normal intestinal flora in this age group. On the other hand, particularly in children with significant co--morbidities, C. difficile may cause severe disease. Moreover, 25–35 % of patients with *C. difficile* infection manifest recurrent *C. difficile* colitis within few days to 4 weeks and a smaller percentage of them may develop complications such as toxic megacolon or pseudomembranous colitis. For all these reasons, scientists have been driven to developing new therapeutic strategies for the prevention and treatment of *C. difficile*-associated diarrhea.

C. difficile--associated diarrhea (CDAD) occurs primarily in patients who have been treated with anti-microbial therapy and is considered as complication in 25 % of cases. The use of broad-spectrum antibiotics and a prolonged duration of antibiotic treatment result in an increasing incidence of *C. difficile*-associated diarrhea, as well as in developing strains resistant to metronidazole and/or vancomycin.[28] Furthermore, the use of proton-pump inhibitors was associated with a two-fold increase in risk for CDI.[29]

Several randomized placebo-controlled studies support the efficacy of probiotics in the prevention of antibiotic-associated diarrhea and, secondary, of *C. difficile* infec-

tion. Hickson et al.[30] included 135 hospitalized patients in a randomized double–blind, placebo-controlled trial (69 in the probiotic group and 66 in the placebo group). The authors assessed the efficacy of a yogurt milk supplemented with a mixture contain-

TABLE 2: Studies assessing the effect of probiotics on the treatment of acute diarrhoea in children

Reference	Patients	Age	Probiotics use/dosage	Source	Benefit in patients receiving probiotics
Isolauri E et al.[36]	71 hospitalized infants and children with acute diarrhea	4 to 45 months	LGG, 2×10^{10} to 2×10^{11} CFU, twice daily	Supplemented formula	↓ duration of diarrhea
Guandalini S et al.[39]	287 children with acute diarrhea	1 to 36 months	LGG, 4×10^{10} CFU, daily	Supplemented formula	↓ duration of diarrhea ↓ duration of hospital stay
Boudraa G et al. [44]	112 hospitalized infants and children with acute diarrhea	3 to 24 months	L. bulgaricus, 1×10^{8} CFU/day; S. thermophilus, 1×10^{8} CFU/day	Supplemented formula	↓ duration of diarrhea ↓ stool frequency
Canani RB et al.[45]	571 children with acute diarrhea	15 to 20 months	L. casei rhamnosus GG, 6×10^{9} CFU, twice daily; or S. boulardii, 5×10^{9} CFU, twice daily; or Bacillus clausii, 1×10^{9} CFU, twice daily; or Mixture of L. delbrueckii bulgaricus (LMG-P17550), 1×10^{9} CFU, twice daily; L. acidophilus (LMG-P 17549), 1×10^{9} CFU, twice daily; S. thermophilus, (LMG-P 17503), 1×10^{9} CFU, twice daily; B. bifidum (LMG-P 17500), 5×10^{8} CFU, twice daily; or Enterococcus faecium (SF 68), 7.5×10^{7} CFU, twice daily	Supplement, Added to water	↓ duration of diarrhea for LGG and probiotic mix groups
Gaon D et al.[46]	89 hospitalized infants with acute diarrhea	Average age 1 year	L. casei and L. acidophilus (CERELA), 1×10^{10} to 1×10^{12} CFU/g, twice daily	Supplemented formula	↓ duration of diarrhea
Guarino A et al.[47]	100 children with mild diarrhea	1 ½ years	L. casei strain GG, 3×10^{9} CFU, twice daily	Supplemented milk	↓ duration of diarrhea ↓ rotavirus shedding
Lee MC et al.[48]	100 infants and children with acute diarrhea	6 to 60 months	L. acidophilus and B. infantis, 6×10^{9} CFU, daily	Capsules	↓ duration of diarrhea in both rotavirus positive and negative diarrhea

Reference	Patients	Age	Probiotics use/dosage	Source	Benefit in patients receiving probiotics
Mao M et al.[49]	142 children with severe acute diarrhea,	1 year	B. lactis (Bb-12), 1×10^{9} CFU/g; and S. thermophilus, 5×10^{8} CFU/g	Supplemented formula	↓ rotavirus shedding
Rosenfeldt V et al.[50]	69 hospitalized children with acute diarrhea	average age 1 ½ years	L. rhamnosus 19070–2,1.7×10^{10} CFU, twice daily; and L. reuteri DSM 12246, 0.5×10^{10} CFU, twice daily	Powder supplement, reconstituted	↓ duration of hospital stay In children treated within 60 hours of diarrheal onset: ↓ duration of diarrhea ↓ rotavirus excretion
Rosenfeldt V et al.[51]	43 children attending daycare with acute diarrhea,	average age 2 years	L. rhamnosus 19070–2,1×10^{10} CFU, twice daily; and L. reuteri DSM 12246, 1×10^{10} CFU, twice daily	Powder supplement, reconstituted	↓ duration of diarrhea ↓ number of children with resolution of diarrhea within 5 days of supplementaton
Shornikova AV et al.[52]	40 children hospitalized with acute diarrhea (75 % rotavirus)	6–36 months	L. reuteri *SD2112* 1×10^{10}–10^{11} CFU,	Powder supplement, reconstituted	↓ number of children having watery diarrhoea on the 2nd day ↓ number of children with vomiting ↓ duration of diarrhea

ing, *Lactobacillus casei* DN-114 001 (*L casei imunitass*) (1.0×10^{8} colony forming units/ml), *S thermophilus* (1.0×10^{8} cfu/ml), and *L bulgaricus* (1.0×10^{7} cfu/ml), compared to a non-supplemented milkshake. The participants administered the drinks within 2 days from the introduction of antibiotics until 1 week after the end of the treatment. The final analysis after the follow-up included 57 patients in the probiotic and 56 in the placebo group. The results showed a significant reduction in the incidence of antibiotic-associated diarrhea (P = .007) and *C. difficile*-associated diarrhea (P = .001) in the probiotic group.[30]

A systematic review in adults, published in 2005, did not justify the use of probiotics for either the prevention or the treatment of *C. difficile* with probiotics[31]. Although there have been some promising studies in children with CDAD using the probiotic yeast *Saccharomyces boulardii*[32,33], further clinical trials are needed to prove the efficacy of the use of probiotics in the prevention of CDAD. The 2011 updated recommendations for probiotic use of 10 experts participating at the third Yale Workshop concluded that Lactobacillus-containing probiotic mixtures and *S. boulardii* may be effective in the prevention of C. difficile-associated diarrhea in high-risk antibiotic recipients, but this finding was based on small, individual studies[8]. Further larger, well-controlled studies are needed to confirm preliminary positive findings and to better delineate the efficacy of probiotics in CDI prevention.

In summary, there is some evidence that *Lactobacillus GG* and *Saccharomyces boulardii* may be helpful in preventing Cl. difficile infection, but more studies are needed before their use can be recommended routinely.

5. Treatment of acute diarrhea

One of the major benefits that probiotics demonstrated was in the treatment of mild-to-moderate acute viral diarrhea.[34,35] In a double-blind, placebo-controlled study, Isolauri showed the efficacy of *L. casei rhamnous GG (LGG)* in the treatment of acute diarrhea in patients that needed hospitalization.[36] In 2010, Allen et al.[37] in a publis-

hed Cochrane review extracted data from 63 RCTs, with more than 8000 participants and evaluated the efficacy of probiotics in the treatment of acute infectious diarrhea in patients of all ages. Most of the studies (56) were conducted in infants and young children. Some of the trials (17) studied a mixture of 2 to 8 probiotics, while the other 46 trials tested a single probiotic. Among the probiotics, the most commonly tested were *Lactobacillus GG* (13RCTs) and *S. boulardii* (10 RCTs). *LGG* was reported to be effective in the treatment of acute gastroenteritis[37] as the data extracted from the updated Cochrane review showed a reduction in the duration of diarrhea in 11 RCTs (n = 2072; MD:–26.69; 95 % CI:–40.5 to – 12.88), with an average difference of 24 hours, as well as a reduction in the number of stools on day 2, in 6 RCTs (n = 1335; MD:–0.76; 95 % CI:–1.32 to – 0.2).[37] Another meta-analysis reported that the use of LGG was associated with moderate clinical benefits in the treatment of acute diarrhea in children, particularly in those with rotavirus infection.[38] Similarly, Guandalini et al. showed in a RCT conducted in 287 patients that *LGG* was not effective in diarrheas of bacterial origin.[39] A meta-analysis conducted by Szajewska H et al.[40] reported that *S. boulardii* reduced the duration of diarrhea for 1 day on average, and the risk of diarrhea lasting more than 4 days (RR: 0.37; 95 % CI: 0.21–0.65; NNT 3, 95 % CI: 2–3).[40] Furthermore, Szajewska H et al. published a meta-analysis of controlled trials showing that *L. reuteri ATCC 55730* was effective in reducing diarrheal episodes in the first 3 days of illness.[41] A different strain of *L. reuteri*, called *L. reuteri DSM 17938,* replaced *ATCC 55730* which presented antibiotic resistance. A recent study performed in Italy included 74 children, aged 6–36 months, hospitalized because of acute diarrhea ; the study evaluated the efficacy of the probiotic *L. reuteri DSM 17938* in the treatment of acute diarrhea infections.[42] The results showed a reduction in the duration of diarrhea in the group that received probiotics compared to the group receiving placebo, as well as a reduction in the risk of diarrhea on days 2 and 3 and in the relapse rate of diarrhea (15 % vs. 42 %, respectively; $p < 0.03$).[42] There have been several studies showing the efficacy of several species of probiotics in the treatment of acute diarrhea (Table 2). Finally, a study conducted in India showed that *VSL#3,* which is a mixture of 7 different strains of probiotics, was also effective compared to placebo in the treatment of acute rotavirus-diarrhea.[43]

The ESPGHAN/ESPID evidence-based guidelines for the management of acute gastroenteritis in children in Europe[6] reported that the beneficial effects of probiotics in acute diarrhea in children were moderate, strain-dependent, dose-dependent (greater for doses > 10^{10}–10^{11} colony-forming units), significant for watery diarrhea and viral gastroenteritis but not significant for invasive bacterial diarrhea. Furthermore, the effect was more evident when treatment with probiotics was initiated early in the course of disease, and in children in developed countries.[6] *LGG* and *S. boulardii* were reported to be beneficial in meta-analyses devoted to single probiotics.[6] The authors recommended *LGG* and *S. boulardii* as an adjunct to rehydration therapy in children with acute gastroenteritis.[6] Safety issues with probiotics were related to bacterial translocation and sepsis and to the risk of antibiotic resistance.

The 2011 updated recommendations for probiotic use by 10 experts participating at the third Yale Workshop concluded that *Saccharomyces boulardii, LGG* and *Lactobacillus reuteri SD2112* were efficacious in treating infectious diarrhea.[8]

In summary, there is significant evidence that *LGG* and *S. boulardii* and modest evidence that *Lactobacillus reuteri SD2112* are beneficial as an adjunct to rehydration therapy in children with acute gastroenteritis.

Conclusion

The available evidence suggests that certain probiotic species and strains are safe when used in healthy children and effective in preventing and treating infectious diarrhea. Further studies are required to assess the efficacy of selected probiotics in preventing childhood Cl. difficile-associated diarrhea and traveller's diarrhea.

Competing interests

The authors declare the following potential conflict of interest:

1. A. Papadopoulou: Speakers Honorarium from Danone and Ferring. Research grant from Biogaia.
2. M Maragkoudaki: Research grant from Biogaia.

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