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The Role of Prebiotics and Probiotics in Prevention and Treatment of Childhood Infectious Diseases

Stefan Weichert, MD, Horst Schrotten, MD,* and Rüdiger Adam, MD*†*

Abstract: Infant formulae and food products marketed for children have been increasingly supplemented with probiotics and/or prebiotics. A vast number of studies have accounted for the transit of probiotic use from alternative to more evidence-based medicine. Data support the use of certain probiotics for the adjunct treatment of acute viral gastroenteritis, and for prevention of gastrointestinal diseases. Further roles of prebiotics and probiotics are seen in the prevention of overall infectious diseases and respiratory infections. Data from well-conducted randomized-controlled trials support the therapeutic role for probiotics toward necrotizing enterocolitis in preterm infants. However, it is difficult to translate heterogeneous-based study results, which are mainly due to varying genera, strains, doses, study settings and measured outcomes, into evidence-based recommendations. This article focuses on the evidence of clinical benefits of prebiotics, probiotics and synbiotics toward prevention and treatment of pediatric infectious diseases.

Key Words: probiotics, prebiotics, pediatric infectious diseases

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In the last decade, infant formulae and food products marketed for children have been increasingly supplemented with probiotics, prebiotics, or with the combination of both, synbiotics. Distribution and use of such products seem to be ahead of our basic understanding of how probiotics work and of what long-term impact they have on modulation of our gut microbiota. Also, interpretation and extrapolation of data is limited, mostly due to a high heterogeneity of clinical studies with regard to varying genera, strains, doses, study settings and measured outcomes. Nevertheless, with an increasing number of well-conducted clinical studies, the body of evidence for or against the use of probiotics and prebiotics is growing. This article will focus on the evidence of clinical benefits of prebiotics, probiotics and synbiotics toward prevention and treatment of pediatric infectious diseases.

DEFINITIONS AND RATIONAL FOR USE

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.¹ In contrast, prebiotics are nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon.² Synbiotics are the combination of probiotics and prebiotics. The rationale for the use of probiotics is mainly based on their ability to remodel microbial communities, and thereby promote growth and survival of commensal bacteria in favor over growth of pathogenic bacteria. Furthermore, they exert

immune-modulatory functions, influence and promote epithelial cell differentiation, proliferation and intestinal barrier function in vitro.³ Commercialized prebiotics have been developed to successfully mimic the prebiotic effects of human milk oligosaccharides found in human breast milk. They are used to selectively promote colonization, growth, survival and function of commensal bacteria and possibly modulate the immune system.⁴ Due to their structural differences to human milk oligosaccharides, they might lack the ability to promote further health benefits beyond their prebiotic function.⁵

PREVENTION OF OVERALL INFECTIOUS DISEASES

In a recent observational study (771 infants), the group receiving a follow-on formula supplemented with synbiotics had significantly less overall infectious diseases (ID) compared with the control group (31.0% versus 40.6%; $P < 0.05$), whereas if analyzed for specific ID, only frequency of gastrointestinal infections remained significantly different (3.5% versus 6.8%; $P = 0.03$).⁶ A randomized-controlled trial (RCT) demonstrated a 30% reduction in the total number of ID in the probiotic group compared with the control group (incidence rate ratio: 0.70; $P = 0.003$). There was no effect on overall febrile episodes between the intervention and the control group in this study.⁷ van Stuijvenberg et al specifically investigated the impact of prebiotics on fever episodes in the first year of life, but could not demonstrate a reduction in the intervention group.⁸ A recent trial demonstrated that during the intervention

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period (0–6 months), fewer infants received antibiotics in the synbiotic group compared with the placebo group (23% versus 28%; odds ratio: 0.74 [95% confidence interval [CI]: 0.55–1.00]; $P < 0.049$). In contrast, the authors observed no differences in antimicrobial consumption during the follow-up period (6–24 months).⁹ It remains to be seen if possibly beneficial effects of probiotics toward overall ID can be confirmed in further studies, or if these effects can be attributed to a reduction of specific ID.

RESPIRATORY INFECTIONS

An RCT (571 children; 1–6 years of age) showed no difference in the occurrence of otitis media (OM) between the intervention group using *Lactobacillus rhamnosus* GG (LGG) and the control group (72% versus 65%; odds ratio = 1.48 [95% CI: 0.87–2.52]) during 7 months of study period, but differences toward the lower incidence of recurrent (≥ 4) upper respiratory tract infections (URTI) were demonstrated (odds ratio = 0.56 [95% CI: 0.31–0.99]).¹⁰ Opposing results for the incidence of OM have been found in a trial of 72 infants (<2 months of age; follow-up until 12 months of age), who received either LGG and *Bifidobacterium lactis* or placebo. During the first 7 months of life, significantly less children in the intervention group experienced an episode of OM compared with the control group (22% versus 50%; relative risk [RR]: 0.44 [95% CI: 0.21–0.90]; $P = 0.014$). The probiotic group also had less recurrent respiratory infections in the first year of life (28% versus 55%; RR: 0.51 [95% CI: 0.27–0.95]; $P = 0.022$).¹¹ In a community-based RCT, the investigators could demonstrate reduced incidences of pneumonia by 24% (95% CI: 0–42%; $P = 0.05$), and of severe acute lower respiratory tract infection by 35% (95% CI: 0–58%; $P = 0.05$) in the synbiotic intervention group as compared with the control group.¹² Maldonado et al showed a 27% reduction in the incidence rate of URTI in children of the intervention group compared with the control group during the study period (incidence rate ratio: 0.729; $P = 0.026$), but could not show any differences toward the incidence rate of OM or lower respiratory tract infection.⁷ Data analyzed from 10 RCTs (including 8 RCTs involving children) from a recent Cochrane systematic review demonstrated that probiotics were better than placebo with regard to the incidence of URTI.¹³ Nevertheless, the heterogeneity of data and varying study quality limit evidence-based recommendations for the generalized use of probiotics to prevent respiratory infections.

Data on prebiotics in this respect are sparse. Infants who received formula supplemented with a mixture of galactooligosac-

charides and fructooligosaccharides for the first 6 months of life had a reduced risk for URTI (14/102 versus 30/104; RR: 0.5 [95% CI: 0.3–0.8]), and a reduced rate of recurrent respiratory tract infections (3% versus 10%; RR: 0.3 [95% CI: 0.09–0.99]), but similar incidences of OM compared with the non-supplemented formula-fed control group.¹⁴

PREVENTION OF ACUTE DIARRHEA

A recent systematic review of RCTs for probiotics in children showed only a modest benefit for preventing acute diarrhea in otherwise healthy children.¹⁵ Results from 3 pooled RCTs, in which the strain most often used was *B. lactis*, showed a significant reduction in the risk of gastrointestinal infections (3 RCT; $n = 302$; RR: 0.54 [95% CI: 0.36–0.81]).^{16–18} Therefore, the committee on nutrition of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition commented that there was some evidence from the pooled trials to support supplementation of infant formula with *B. lactis* (single or in combination) for reducing the risk of nonspecific gastrointestinal infections in children.¹⁵

A recent meta-analysis of 3 RCTs (>1000 infants), which investigated prevention of healthcare-associated diarrhea by adding fermented milk supplemented with LGG (or LGG in capsules or sachets), showed significantly lower rates of diarrhea and symptomatic rotavirus gastroenteritis in the intervention group compared with the control group (RR: 0.37 [95% CI: 0.23–0.59] and RR: 0.49 [95% CI: 0.28–0.86], respectively). To prevent 1 case of nosocomial diarrhea, 12 children would need to be treated with LGG (number needed to treat = 12). As this meta-analysis focused on LGG only, one should be cautious with extrapolation of these findings to other probiotics.¹⁹ In contrast, results from a recently conducted RCT using a different strain of a lactobacillus (*L. reuteri* DSM 17938) could not observe any differences toward prevention of nosocomial diarrhea.²⁰ Overall, there seems to be cumulative growing evidence that probiotics can prevent gastrointestinal nosocomial infections in otherwise healthy children, but less evidence for prevention of gastrointestinal infections in community settings and in day-care centers has been provided.²¹ Of note, in a recent review from the American Academy of Pediatrics, the authors rightly point to the fact that a rotavirus vaccine will most likely be more efficient in preventing acute infantile infectious diarrhea than the use of probiotics.²²

TREATMENT OF ACUTE DIARRHEA

The role of probiotics in the treatment of acute (viral) gastroenteritis in infants and

children has been investigated by a large number of clinical trials, which led to recommendations by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Infectious Diseases that selected probiotics with proven clinical efficacy and administered in appropriate dosages, according to the strain and the patient population, might be used as an adjunct to rehydration therapy for the management of acute (viral) gastroenteritis in children.²³ In a recently published Cochrane systematic review, including 56 studies with children, the authors conclude that probiotics have clear beneficial effects in shortening the duration of acute infectious diarrhea by a median of 24.76 hours (95% CI: 15.9–33.6 hours; 35 trials; >4500 participants) and in reducing mean stool frequency on day 2 (mean difference 0.8; 0.45–1.14; 20 trials; >2700 participants).²⁴ Results from an updated meta-analysis of RCTs investigating the impact of *Saccharomyces boulardii* on treatment of acute (viral) gastroenteritis in children also demonstrated a reduction in the duration of diarrhea by a median of 1.08 days (95% CI: –1.64 to –0.53); 5 RCTs; 944 participants) in the probiotic intervention group compared with the control group.²⁵

It is interesting to note that *S. boulardii* in combination with metronidazole was also found to decrease the duration of bloody diarrhea in children with amebiasis when compared with metronidazole alone (42.2±17.4 hours versus 72.0±28.5 hours; $P < 0.001$).²⁶ In this context, it was also recently demonstrated that human milk oligosaccharides, which serve as models for artificially synthesized prebiotics like galactooligosaccharides and fructooligosaccharides, reduced attachment and cytotoxicity of *Entamoeba histolytica* in a human cell culture model. Of note, in the same setting similar effects could be shown with galactooligosaccharides.²⁷

ANTIBIOTIC-ASSOCIATED DIARRHEA

In most published RCTs, probiotics were given in parallel to the started antibiotics (most often for treatment of acute respiratory infections). A meta-analysis of 6 RCT results demonstrated a reduced risk for developing antibiotic-associated diarrhea from 28.5% to 11.9% (RR: 0.44 [95% CI: 0.25–0.77]; $P = 0.006$; number needed to treat = 7).²⁸ A recently published Cochrane systematic review also demonstrated that high-dose prebiotics had a protective effect toward preventing antibiotic-associated diarrhea in children in comparison with placebo (prevalence 8% versus 22%; RR: 0.40 [95% CI: 0.29–0.55]; number needed to treat = 7).²⁹ As many studies investigated synbiotics, data are sparse for probiotic effects only. A recently conducted

study could not show any differences between the intervention group (oligofructose and inulin) and the control group.³⁰ Unlike in adults, therapeutic effects of probiotics in antibiotic-associated diarrhea or *Clostridium difficile*-associated diarrhea in children have not been investigated in RCTs.

HELICOBACTER PYLORI GASTRITIS

Although there is increasing evidence from RCTs, especially in adults, that probiotics in combination with triple therapy (2 antibiotics, 1 proton pump inhibitor) can eradicate *H. pylori* more effectively compared with triple therapy alone (eradication rate increased by around 10%), results from RCTs in children are inconclusive.^{31–33}

NECROTIZING ENTEROCOLITIS

We will not focus on necrotizing enterocolitis (NEC) in this concise review; however, infection is likely to play a role at some stage in the pathogenesis of NEC, albeit the exact interactions remain to be elucidated.³⁴ It is noteworthy that the actual debate about the pros and cons of the role of probiotics in NEC prevention demonstrates the difficulties in translating heterogeneous-based study results into evidence-based recommendations (and change of practice). In this regard, the gravity of the study results, namely reduced overall mortality and incidence of NEC by around 50% in the infants who received probiotics, have led authors to believe that it is unethical to withhold a life-saving therapy by conducting international, multicenter placebo-controlled trials. The question was raised of how much further evidence we would need, before we would start to change our practice.^{35–38}

SEPSIS

Although the results of single studies might suggest a beneficial or detrimental effect of giving probiotics to prevent culture-proven sepsis in infants, data from meta-analyses did not confirm this association.^{38–41} Mihatsch et al investigated whether probiotics could be of value in preventing nosocomial infections in a vulnerable risk group, very low birth weight infants (183 infants; <1500 g or <30 weeks of gestational age). When given *B. lactis*, neither differences in the incidence of nosocomial infections in very low birth weight infants nor adverse effects could be shown compared with the control group.⁴² A randomized trial, which investigated the role of probiotics in prevention of *Candida* colonization and late-onset sepsis, did not find any differences in invasive *Candida* infections between the intervention and the control groups.⁴³

UROGENITAL INFECTIONS

Data from RCTs have shown no decreased incidence of urinary tract infections (UTIs) in children who received probiotics.^{6,7,44} Also, synbiotic or prebiotic intervention did not result in a decreased incidence of UTIs.^{14,45} It is interesting to note that a prospective study demonstrated similar incidences for UTIs with probiotic and conventional antibiotic prophylaxis in children with persistent primary vesicoureteral reflux (18.3% [11/60] versus 21.6% [13/60]; $P = 0.962$). Also, renal scarring was not significantly different between the 2 groups.⁴⁶ Whether any “-biotic” medication is necessary for prevention of UTIs is subject for a different debate.

HIV INFECTION

Vertical transmission of HIV is increased 3-fold in HIV-positive women with bacterial vaginosis.⁴⁷ Probiotics are thought to favorably influence the disturbed vaginal microbiota, and different therapeutic regimes yield promising results.⁴⁸ Therefore, probiotics could have an indirect impact on childhood HIV infection. It is interesting to note that the natural prebiotics, human milk oligosaccharides, have shown to competitively interact with HIV for receptor binding sites in vitro.⁴⁹

SAFETY

Currently, there are no safety concerns for the use of prebiotics and probiotics in healthy infants and children.^{15,22} Critical risk assessment is required in immunocompromised children and in children with underlying diseases, in critically ill and in preterm infants. As probiotics are live organisms, there are potential risks of transferring antibiotic resistance to pathogenic bacteria, of gut translocation and subsequent development of systemic disease and sepsis, of developing D-lactic acidosis and of possibly adverse long-term effects on the gut microbiome.^{50–52} Proper handling and administration of prebiotics and probiotics as well as rigorous monitoring of potentially adverse effects will be essential for improving safety in children.

PERSPECTIVES

Since the days of Metchnikoff and his first proposal of the probiotic concept, a vast number of studies have accounted for the transit of probiotic use from alternative to more evidence-based medicine.⁵³ Despite a high heterogeneity of probiotics used in studies, cumulative evidence supports the important role of probiotics and prebiotics in sustaining and promoting human health. Study design and quality have to improve, as well as rigorous safety monitoring for potential infectious complications when adding live bacteria to

infant food. Also, quality control in the manufacturing process and unjustified health claims of probiotics and prebiotics remain important issues. Recently, the US Food and Drug Administration clearly classified probiotics as “drugs” when applied to “prevent, treat, or mitigate disease,” and within the European Union, health claims of functional foods and supplements are critically reviewed by the European Food Safety Authority.^{54,55} It remains to be seen how these regulatory developments will influence manufacturer engagement and scientific research. Metagenomics and whole genome approaches will sustainably influence our understanding of the interaction and co-evolution of beneficial microbes and the host. Basic research and clinical studies should not only focus on probiotics, but also on the role of nonviable agents, like prebiotics and soluble probiotic factors.^{56,57}

REFERENCES

1. Food and Agriculture Organization of the United Nations, World Health Organization. Report of a joint FAO/WHO expert consultation on evaluation of health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria [WHO web site]. October 4, 2001. Available at: http://www.who.int/foodsafety/publications/fs_management/en/probiotics. Accessed May 4, 2012.
2. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr*. 1995;125:1401–1412.
3. Preidis GA, Versalovic J. Targeting the human microbiome with antibiotics, probiotics, and prebiotics: gastroenterology enters the metagenomics era. *Gastroenterology*. 2009;136:2015–2031.
4. Roberfroid M, Gibson GR, Hoyles L, et al. Prebiotic effects: metabolic and health benefits. *Br J Nutr*. 2010;104(suppl 2):S1–63.
5. Bode L. Human milk oligosaccharides: prebiotics and beyond. *Nutr Rev*. 2009;67 (suppl 2):S183–S191.
6. Picaud JC, Chapalain V, Paineau D, et al. Incidence of infectious diseases in infants fed follow-on formula containing synbiotics: an observational study. *Acta Paediatr*. 2010;99:1695–1700.
7. Maldonado J, Cañabate F, Sempere L, et al. Human milk probiotic *Lactobacillus fermentum* CECT5716 reduces the incidence of gastrointestinal and upper respiratory tract infections in infants. *J Pediatr Gastroenterol Nutr*. 2012;54:55–61.
8. van Stuijvenberg M, Eisses AM, Grüber C, et al. Do prebiotics reduce the number of fever episodes in healthy children in their first year of life: a randomised controlled trial. *Br J Nutr*. 2011;106:1740–1748.
9. Kukkonen K, Savilahti E, Haahtela T, et al. Long-term safety and impact on infection rates of post-natal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. *Pediatrics*. 2008;122:8–12.
10. Hatakka K, Blomgren K, Pohjavuori S, et al. Treatment of acute otitis media with probiotics in otitis-prone children—a double-blind, placebo-controlled randomised study. *Clin Nutr*. 2007;26:314–321.
11. Rautava S, Salminen S, Isolauri E. Specific probiotics in reducing the risk of acute infections in infancy—a randomised, double-blind, placebo-controlled study. *Br J Nutr*. 2009;101:1722–1726.

12. Sazawal S, Dhingra U, Hiremath G, et al. Prebiotic and probiotic fortified milk in prevention of morbidities among children: community-based, randomized, double-blind, controlled trial. *PLoS ONE*. 2010;5:e12164.
13. Hao Q, Lu Z, Dong BR, et al. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev*. 2011;9:CD006895.
14. Arslanoglu S, Moro GE, Boehm G. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. *J Nutr*. 2007;137:2420–2424.
15. Braegger C, Chmielewska A, Decsi T, et al.; ESPGHAN Committee on Nutrition. Supplementation of infant formula with probiotics and/or prebiotics: a systematic review and comment by the ESPGHAN committee on nutrition. *J Pediatr Gastroenterol Nutr*. 2011;52:238–250.
16. Chouraqui JP, Grathwohl D, Labaune JM, et al. Assessment of the safety, tolerance, and protective effect against diarrhea of infant formulas containing mixtures of probiotics or probiotics and prebiotics in a randomized controlled trial. *Am J Clin Nutr*. 2008;87:1365–1373.
17. Corrêa NB, Péret Filho LA, Penna FJ, et al. A randomized formula controlled trial of Bifidobacterium lactis and Streptococcus thermophilus for prevention of antibiotic-associated diarrhea in infants. *J Clin Gastroenterol*. 2005;39:385–389.
18. Saavedra JM, Bauman NA, Oung I, et al. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. *Lancet*. 1994;344:1046–1049.
19. Szajewska H, Wanke M, Patro B. Meta-analysis: the effects of Lactobacillus rhamnosus GG supplementation for the prevention of health-care-associated diarrhoea in children. *Aliment Pharmacol Ther*. 2011;34:1079–1087.
20. Wanke M, Szajewska H. Lack of an Effect of Lactobacillus reuteri DSM 17938 in Preventing Nosocomial Diarrhea in Children: A Randomized, Double-Blind, Placebo-Controlled Trial [published online ahead of print February 3, 2012]. *J Pediatr*. doi: 10.1016/j.jpeds.2011.12.049.
21. Guandalini S. Probiotics for prevention and treatment of diarrhea. *J Clin Gastroenterol*. 2011;45(suppl):S149–S153.
22. Thomas DW, Greer FR; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. Probiotics and prebiotics in pediatrics. *Pediatrics*. 2010;126:1217–1231.
23. Guarino A, Albano F, Ashkenazi S, et al.; European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; European Society for Paediatric Infectious Diseases. 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. *J Pediatr Gastroenterol Nutr*. 2008;46(suppl 2):S81–122.
24. Allen SJ, Martinez EG, Gregorio GV, et al. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev*. 2010;11:CD003048.
25. Szajewska H, Skórka A. Saccharomyces boulardii for treating acute gastroenteritis in children: updated meta-analysis of randomized controlled trials. *Aliment Pharmacol Ther*. 2009;30:960–961.
26. Dinleyici EC, Eren M, Yargic ZA, et al. Clinical efficacy of Saccharomyces boulardii and metronidazole compared to metronidazole alone in children with acute bloody diarrhea caused by amebiasis: a prospective, randomized, open label study. *Am J Trop Med Hyg*. 2009;80:953–955.
27. Jantscher-Krenn E, Lauwaet T, Bliss LA, et al. Human milk oligosaccharides reduce Entamoeba histolytica attachment and cytotoxicity in vitro. *Br J Nutr*. 2012;1–8.
28. 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.
29. Johnston BC, Goldenberg JZ, Vandvik PO, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev*. 2011;11:CD004827.
30. Szajewska H, Weizman Z, Abu-Zekry M, et al.; The ESPGHAN Working Group on Probiotics and Prebiotics. Inulin and fructo-oligosaccharides for the prevention of antibiotic-associated diarrhea in children: report by the ESPGHAN working group on probiotics and prebiotics. *J Pediatr Gastroenterol Nutr*. 2012;54:828–829.
31. Sachdeva A, Nagpal J. Effect of fermented milk-based probiotic preparations on Helicobacter pylori eradication: a systematic review and meta-analysis of randomized-controlled trials. *Eur J Gastroenterol Hepatol*. 2009;21:45–53.
32. Sýkora J, Valečková K, Amlerová J, et al. Effects of a specially designed fermented milk product containing probiotic Lactobacillus casei DN-114 001 and the eradication of H. pylori in children: a prospective randomized double-blind study. *J Clin Gastroenterol*. 2005;39:692–698.
33. Szajewska H, Albrecht P, Topczewska-Cabanek A. Randomized, double-blind, placebo-controlled trial: effect of lactobacillus GG supplementation on Helicobacter pylori eradication rates and side effects during treatment in children. *J Pediatr Gastroenterol Nutr*. 2009;48:431–436.
34. Ullrich T, Tang YW, Correa H, et al. Absence of gastrointestinal pathogens in ileum tissue resected for necrotizing enterocolitis. *Pediatr Infect Dis J*. 2012;31:413–414.
35. Deshpande G, Rao S, Patole S, et al. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. *Pediatrics*. 2010;125:921–930.
36. Alfaleh K, Anabrees J, Bassler D, et al. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev*. 2011;3:CD005496.
37. Tarnow-Mordi WO, Wilkinson D, Trivedi A, et al. Probiotics reduce all-cause mortality and necrotizing enterocolitis: it is time to change practice. *Pediatrics*. 2010;125:1068–1070.
38. Mihatsch WA, Braegger CP, Decsi T, et al. Critical systematic review of the level of evidence for routine use of probiotics for reduction of mortality and prevention of necrotizing enterocolitis and sepsis in preterm infants. *Clin Nutr*. 2012;31:6–15.
39. Samanta M, Sarkar M, Ghosh P, et al. Prophylactic probiotics for prevention of necrotizing enterocolitis in very low birth weight newborns. *J Trop Pediatr*. 2009;55:128–131.
40. Lin HC, Hsu CH, Chen HL, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. *Pediatrics*. 2008;122:693–700.
41. Deshpande G, Rao S, Patole S. Probiotics for prevention of necrotizing enterocolitis in preterm neonates with very low birthweight: a systematic review of randomised controlled trials. *Lancet*. 2007;369:1614–1620.
42. Mihatsch WA, Vossbeck S, Eikmanns B, et al. Effect of Bifidobacterium lactis on the incidence of nosocomial infections in very-low-birth-weight infants: a randomized controlled trial. *Neonatology*. 2010;98:156–163.
43. Romeo MG, Romeo DM, Trovato L, et al. Role of probiotics in the prevention of the enteric colonization by Candida in preterm newborns: incidence of late-onset sepsis and neurological outcome. *J Perinatol*. 2011;31:63–69.
44. Ferrara P, Romaniello L, Vitelli O, et al. Cranberry juice for the prevention of recurrent urinary tract infections: a randomized controlled trial in children. *Scand J Urol Nephrol*. 2009;43:369–372.
45. Arslanoglu S, Moro GE, Schmitt J, et al. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *J Nutr*. 2008;138:1091–1095.
46. Lee SJ, Shim YH, Cho SJ, et al. Probiotics prophylaxis in children with persistent primary vesicoureteral reflux. *Pediatr Nephrol*. 2007;22:1315–1320.
47. Cu-Uvin S, Hogan JW, Caliendo AM, et al.; HIV Epidemiology Research Study. Association between bacterial vaginosis and expression of human immunodeficiency virus type 1 RNA in the female genital tract. *Clin Infect Dis*. 2001;33:894–896.
48. Senok AC, Verstraelen H, Temmerman M, et al. Probiotics for the treatment of bacterial vaginosis. *Cochrane Database Syst Rev*. 2009;4:CD006289.
49. Hong P, Ninonuevo MR, Lee B, et al. Human milk oligosaccharides reduce HIV-1-gp120 binding to dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN). *Br J Nutr*. 2009;101:482–486.
50. Morrow LE, Gogineni V, Malesker MA. Probiotic, prebiotic, and symbiotic use in critically ill patients. *Curr Opin Crit Care*. 2012;18:186–191.
51. Kunz AN, Noel JM, Fairchok MP. Two cases of Lactobacillus bacteremia during probiotic treatment of short gut syndrome. *J Pediatr Gastroenterol Nutr*. 2004;38:457–458.
52. Guenther K, Straube E, Pfister W, et al. Severe sepsis after probiotic treatment with Escherichia coli NISSLE 1917. *Pediatr Infect Dis J*. 2010;29:188–189.
53. Metchnikoff, E. The prolongation of life. Optimistic studies. *Essays Optimistes*. Paris. Translated and edited by P. Chalmers Mitchell. London: Heinemann, 1907.
54. Venugopalan V, Shriner KA, Wong-Beringer A. Regulatory oversight and safety of probiotic use. *Emerging Infect Dis*. 2010;16:1661–1665.
55. Rijkers GT, de Vos WM, Brummer RJ, et al. Health benefits and health claims of probiotics: bridging science and marketing. *Br J Nutr*. 2011;106:1291–1296.
56. Corr SC, Li Y, Riedel CU, et al. Bacteriocin production as a mechanism for the antiinfective activity of Lactobacillus salivarius UCC118. *Proc Natl Acad Sci USA*. 2007;104:7617–7621.
57. Yan F, Cao H, Cover TL, et al. Colon-specific delivery of a probiotic-derived soluble protein ameliorates intestinal inflammation in mice through an EGFR-dependent mechanism. *J Clin Invest*. 2011;121:2242–2253. The authors have no funding or conflicts of interest to disclose.