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

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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

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 probiotics, prebiotics 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 of 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...
period (0–6 months), fewer infants received antibiotics in the symbiotic 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 anti-microbial consumption during the follow-up period (6–24 months).\(^7\) 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 (24) upper respiratory tract infections (URTI) were demonstrated (odds ratio = 0.56 [95% CI: 0.31–0.99]).\(^11\) 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).\(^1\) 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 symbiotic intervention group as compared with the control group.\(^13\) Mal donado 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 galactooligosaccharides 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 infants would have 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.\(^15\) 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 probiotics 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 prebiotic effects only. A recently conducted
study could not show any differences between the intervention group (oligofructose and inulin) and the control group. 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.

### 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. 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 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.

### UROGENITAL INFECTIONS

Data from RCTs have shown no decreased incidence of urinary tract infections (UTIs) in children who received probiotics. Also, synbiotic or prebiotic intervention did not result in a decreased incidence of UTIs. 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. 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. Probiotics are thought to favorably influence the disturbed vaginal microbiota, and different therapeutic regimes yield promising results. 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.

### SAFETY

Currently, there are no safety concerns for the use of probiotics and prebiotics in healthy infants and children. 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. Proper handling and administration of probiotics and prebiotics 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 transplant of probiotic use from alternative to more evidence-based medicine. 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. 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 solubile probiotic factors.

### REFERENCES


