Effect of probiotics in the prevention of infection in children

Učinek probiotikov pri preprečevanju okužb pri otrocih

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Izvleček

Številne dobro zasnovane randomizirane kontrolirane raziskave so potrdile ugodne učinke uporabe določenih sevov probiotikov pri določenih indikacijah. Indikacija, ki je za pediatre še posebej zanimiva, je preprečevanje okužb pri otrocih. Hospitalizirani otroci in otroci v vrtcih so tisti, ki so v razvitih deželah še posebej izpostavljeni okužbam. Cilj tega preglednega članka je zato povzeti podatke vseh trenutno razpoložljivih randomiziranih kontroliranih študij in meta-analiz o vlogi različnih sevov probiotikov pri preprečevanju okužb prebavil in dihal pri hospitaliziranih otrocih in otrocih v dnevnem varstvu.

Abstract

Several well-designed randomized controlled trials confirmed the beneficial effects of certain probiotic strains in specific clinical indications. One indication, which is of special interest for pediatricians, is the prevention of infections in children. Children who are especially prone to infections, in developed countries, are hospitalized children and children who attend day care centers. Therefore, the aim of this review was to summarize all currently available randomized controlled trails and meta-analysis on the role of different probiotic strains in the prevention of gastrointestinal and respiratory tract infection in hospitalized children and children attending day care centers.

Introduction

An increasing number of studies in the last three decades have been trying to identify the role of probiotics in the prevention and treatment of various diseases. Several well-designed randomized controlled trials confirmed their beneficial effect in specific clinical indications using specific probiotic strains. One indication, which is of special interest for pediatricians, is the prevention of infections. Children who are especially prone to infectious diseases are, in developed countries, hospitalized children and children who attend day care centers.

The mechanism that would allow probiotics to prevent infections is very complex and yet not fully elucidated, but it seems that their effect is strain- and dose-dependent. The proposed mechanisms include local response through the inhibition of pathogen effect on the intestinal mucosa by the secretion of antibacterial substances, lowering of pH, inhibition of pathogen adhesion and a systemic effect, which includes interaction with host immune response including immunomodulation of local immunity, and furthermore, exertion of innate and adaptive immunity.[1,2]

Taking all above mentioned into account, the aim of this review was to summarize all currently available randomized controlled trails and meta-analysis on the role of different probiotic strains in the prevention of gastrointestinal and respiratory tract infection in hospitalized children and children attending day care centers.

Prevention of nosocomial infections

Nosocomial infections or hospital-acquired infections by definition develop during a hospital stay, meaning that they are not present or incubating at hospital admission.[3] Usually, infections that occur more than 48 hours after admission are considered nosocomial. The incidence of nosocomial infections in children in developed countries is still high, ranging from 8 % to 30 % depending on time of the year and type of hospital ward.[4–6] Gastrointestinal and respiratory tract infections encounter for more than 1/3 of all infections at pediatric wards.[4–6] Nosocomial infections have several negative effects; they prolong hospital stay, worsen the treatment outcome, and, at the end significantly increase hospital expenses. Current measures for the prevention of infections in pediatric settings, such as vaccinations, good hand hygiene, and visitor screening, are often ineffective, highlighting the necessity for additional measures.[7]

The efficacy of probiotics in the prevention of nosocomial diarrhea in pediatric patients has been investigated in several studies (Table 1).[8–13] Three studies investigated *Lactobacillus rhamnosus GG* (LGG); Szajewska et al. performed a double-blind randomized controlled trial in 81 children and found that LGG reduces the risk of nosocomial diarrhea (6.67 % vs. 33.3 %; RR 0.2; CI 06–0.6) as well as the risk of rotavirus gastroenteritis (2.2 % vs. 16.7 %; RR 0.13; CI 0.02–0.8).[8] The second randomized controlled trial evaluating LGG in the prevention of nosocomial diarrhea did not confirm the preventive effect.[9] However, the largest study evaluating the efficacy of LGG involved 742 hospitalized children and showed a significantly reduced risk for gastrointestinal infections (5.1 % vs. 12.0 %; RR 0.4; CI 0.25–0.7), including diarrhea and vomiting episodes.[10] All those three studies were summarized in a meta-analysis which found overall preventive effect of LGG on nosocomial diarrhea.[14] Another study, performed in the same acute hospital setting as the previously mentioned LGG study[8] but testing another strain–*Lactobacillus (L.) reuteri,* failed to find a lowering effect on nososcomial diarrhea for this specific strain.[11] Two studies evaluated other probiotics in chronic hospital setting; Saavedra investigated the efficacy of *Bifidobacterium (B.) bifidum* and found positive effect (6.9 % vs. 31 %; RR 0.2; CI 0.06–0.8).[12] Following study that compared the same probiotic with placebo in 90 infants failed to confirm a reduction in the prevalence of diarrhea in the probiotic-treated group (28.3 % vs. 38.6 %; RR 0.7; CI 0.4–1.3).[13]

Based on the currently available evidence, probiotics, mostly LGG, seem to have a promising effect in the prevention of nosocomial diarrhea in acute hospital setting.

Data on respiratory tract infections at regular pediatric ward, are limited. There is only one study, which however included a high number of patients (n = 742 patients; 1–18 years old) and evaluated LGG.[10] This study found that use of LGG could prevent nososcomial upper respiratory tract infections (2.1 % vs. 5.5 %; RR 0.38; CI 0.18–0.85). Children who were at a greatest risk, accor-

Table 1: Effect of probiotics on the prevention of nosocomial gastrointestinal infections.

Author	N (age)	Probiotic (dose)	Effect
Szajewska (2000)[8]	81 (1–36 months)	*LGG* (6×10^9 CFU)	Reduced number of GI infections
Mastretta (2002)[9]	220 (1–18 months)	*LGG* (10^{10} CFU)	Insignificant
Saavedra (1994)[12]	55 (5–24 months)	*B. lactis* Bb12 10^{7-9} CFU/g	Reduced number of GI infections
Chouraqui (2004)[13]	90 (< 8 months)	*B. lactis* Bb12 (min. 10^8 CFU)	Insignificant
Hojsak (2010)[10]	742 (1–18 years)	*LGG* 10^9 CFU	Reduced number of GI infections
Wanke (2012)[11]	106 (1–48 months)	*L. reuteri* 10^8 CFU	Insignificant

CFU- colony forming units.

ding to that study, were children of younger age and prolonged hospitalization.

Prevention of infections acquired in day-care centers

Another group of children at a higher risk of acquiring acute infections are children who attend day-care centers. Their risk is 2–3 times higher than in children who stay at home.[15] Besides an increased number of infections, those children have more outpatient doctor and emergency room visits and increased use of prescribed antibiotics.[16] Daycare centers are ideal places for the transmission of infections often resulting in many missed days of both daycare and parental work.[17,18] Those illnesses have been estimated to cost almost two billion US Dollars per year in the United States and being an economic burden not only for child's family, but healthcare in general.[19]

There are altogether 6 well-designed randomized controlled trials evaluating a role of probiotics in the prevention of gastrointestinal and respiratory tract infection in children who attend day care centers (Table 2).[20–25]

Gastrointestinal infections

Two studies evaluated the effect of LGG strain (altogether 852 children aged 1–7 years) and both found no influence on gastrointestinal infections.[20,21] Other studies used different combinations of probiotics and yielded contradictory results. Saavedra's study (n = 118 children) showed that children treated with probiotics (*B. lactis* and

Table 2: Effect of probiotics on the prevention of respiratory and gastrointestinal infections in children who attend day care center.

Author	N (age)	Probiotic (dose)	Effect–respiratory infections	Effect–gastrointestinal infections
Hatakka (2001)[20]	571 (1–6 years)	*LGG* ($1–2 \times 10^8$ CFU/day)	Lower number of upper respiratory tract infections Lower number of prescribed antibiotics	Insignificant
Saavedra (2004)[22]	118 (3–24 months)	*B. lactis Bb-12* 10^7 CFU + *S. thermophilus* 10^6 CFU	Insignificant difference in the incidence of upper respiratory tract infection Lower number of prescribed antibiotics	Insignificant
Weizman (2005)[23]	210 (4–10 months)	*B. lactis Bb-12* or *L. reuteri* (min. 10^7 CFU)	Not significant difference in the incidence of upper respiratory tract infection *L. reuteri* group–lower number of prescribed antibiotics	Lower incidence of diarrhea
Lin (2009)[24]	1062 (preschool children)	*L. casei rhamnosus* (10^8 CFU), *L. rhamnosus T cell-1* (10^{10} CFU), multiple probiotic strains	Reduction in respiratory infection in the *L. casei rhamnosus* group Insignificant for other strains	Reduction in gastrointestinal infection combination of strains group
Hojsak (2010)[21]	281 (1–7 years)	*LGG* (10^9 CFU)	Lower number of upper respiratory tract infections No difference in prescribed antibiotics	Insignificant
Merenstein (2010)[28]	638 (3–6 years)	*L. casei* (+ *S. thermophilus* and *L. bulgaricus*) (> 10^7 CFU/g)	Lower number of upper and lower respiratory tract infections Lower number of prescribed antibiotics	Reduction of the gastrointestinal infections

CFU–colony forming units.

S. thermophilus) had a significantly lower number of episodes of colicky abdominal pain ($p < 0.001$), but with no influence on diarrheal stools and indicators of severity of gastrointestinal infections.[22] In the study by Weitzman et al. (n = 201) infants fed with a placebo formula had more diarrheal episodes than those supplemented with both investigated probiotics, *B. lactis* or *L. reuteri,* moreover, the episodes were of longer duration.[23] The study performed by Lin and colleagues (n = 1062) showed a significant reduction in gastrointestinal infection in the multiple probiotic group both during the short-term ($p = 0.007$) and the long-term ($p = 0.004$) intervention.[24] However, the use of a single probiotic strain (*Lactobacillus casei rhamnosus* and *L. rhamnosus* T cell-1) showed an insignificant ability to prevent diarrheal disease when compared to the placebo group ($p > 0.05$).[24] Randomized controlled trial performed in the USA (n = 638) found a lower incidence of gastrointestinal infection in children who received fermented probiotic drink (with *Lactobacillus (L.) casei* DN-114 001/CNCM I-1518 combined with two cultures commonly used in yogurt, *S. thermophilus* and *Lactobacillus (L.) bulgaricus*) ($p = 0.042$).[25]

In summary, while all probiotics tested were found to be completely safe, the evidence of their efficacy in preventing diarrheal episodes in infants and children attending day-care centers is only modest; a significant effect was found only for some strains and their combinations, and the clinical importance remains questionable.[26,27]

Respiratory tract infections

Contrary to gastrointestinal infections, all studies which included children older than one year of age who attended day care centers found positive effect of probiotics on lowering the incidence of upper respiratory tract infections.[10,20,21,24,28] Moreover, in 2011 Cochrane meta-analysis reviewed available literature and found altogether 10 trials which involved 3451 participants, not limited only to children.[29] The authors found that probiotics were better than placebo in decreasing the number of participants with acute upper respiratory tract infections (at least one episode: odds ratio (OR) 0.58; 95 % CI 0.36–0.92). Unfortunately, this meta-analysis did not analyze different age groups and different strains separately, and was not stratified according to the type of facility where probiotics were used.

It must be emphasized that positive effect in almost all reported studies was limited to upper respiratory infections. Unfortunately, for lower respiratory infection results are not promising; only one study[28] was able to yield positive effect. For other severe bacterial infections, such as acute otitis media, the data are also not promising. Although there are studies[20,21,30] mentioned in Table 2, which found lower frequency of otitis media in supplemented group, the difference was not significant.[31]

In summary, probiotic effect seems to be limited to viral infections of the upper respiratory tract and could not be expanded to invasive or severe bacterial infections. The question is whether probiotic use should be recommended routinely in all children who attend day care centers. Based on the above mentioned randomized controlled trials, probiotics are proven to be effective and their use can be recommended. However, until today there are no cost-effective analyses, except a regression analysis, which determined that children who would benefit the most from probiotic use are children of younger age and with recurrent respiratory infections.[10,21]

Conclusion and recommendations

- Probiotics have a promising effect in the prevention of nosocomial gastrointestinal and upper respiratory tract infections in acute hospital setting; the effect is strain specific – LGG being the most promising.
- They should be recommended especially to younger children in whom we expect prolonged hospitalization.
- Probiotics seem to have a promising effect in the prevention of infection in children in day care centers. Several strains

and their combination are proven to be effective.
- They should be recommended to younger children who attend day care center and in the season when most of the respiratory tract infections occur (late autumn and winter).
- Efficacy in preventing diarrheal episodes in children attending day-care centers is only modest and clinically questionable.

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