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Probiotics for preventing healthcare-associated diarrhea in children: A meta-analysis of randomized controlled trials

Probiotyki w zapobieganiu biegunce szpitalnej: metaanaliza badań z randomizacją

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ABSTRACT

Aim: To systematically update evidence on the efficacy of using probiotics for the prevention of healthcare-associated diarrhea in children. **Methods:** MEDLINE, EMBASE, The Cochrane Library, Health Source: Nursing/Academic Edition, two clinical trials and reference lists were searched in June 2013, for randomized controlled trials (RCTs) performed in children aged 1 month to 18 years that compared the effects of the administration of probiotics with placebo or no intervention. The primary outcome measure was the incidence of healthcare-associated diarrhea. **Results:** Six RCTs involving 1343 children met the inclusion criteria. Administration of *Lactobacillus rhamnosus* GG (LGG) compared with placebo reduced the risk of healthcare-associated diarrhea (2 RCTs, $n = 823$, RR 0.37; 95% CI 0.23–0.59), reduced the risk of rotavirus gastroenteritis (3 RCTs, $n = 1043$, RR 0.49, 95% CI 0.28–0.86), but did not reduce the risk of asymptomatic rotavirus infection (2 RCTs, $n = 301$, RR 1.39, 95% CI 0.74–2.62). Administration of *Bifidobacterium bifidum* & *Streptococcus thermophilus* compared with placebo reduced the risk of healthcare-associated diarrhea (1 RCT, $n = 55$, RR 0.22, 95% CI 0.05–0.96), rotavirus gastroenteritis (1 RCT, $n = 55$, RR 0.27, 95% CI 0.08–0.87), and rotavirus asymptomatic infection (1 RCT, $n = 55$, RR 0.27, 95% CI 0.08–0.87). Administration of two other probiotics (*i.e.*, *Lactobacillus reuteri* DSM 17938 and *Lactobacillus delbrueckii* H2B20) was ineffective. **Conclusion:** In hospitalized children, the administration of LGG, compared with placebo, reduced the incidence of healthcare-associated diarrhea, including rotavirus diarrhea. Evidence on the effects of other probiotics, whether positive or negative, is limited.

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Background

Healthcare-associated infections (HCAI) are defined as those occurring 48 h or more after admission to a hospital. They are a major problem for a patient's safety and are linked to a prolonged hospital stay, long-term disability, increased resistance of microorganisms to antimicrobials, massive additional financial burden, and excess deaths [1]. The risk of acquiring HCAI is international and varies between 5% and 15% [1]. In children, gastrointestinal infections, particularly of rotavirus origin, remain a leading cause of HCAI [1]. A recent meta-analysis showed that the risk of developing rotavirus healthcare-associated diarrhea was 2.9 per 100 hospitalizations, and the risk was higher during epidemic months (8.1:100 hospitalizations) [1].

Prevention of HCAI is a priority for settings and institutions committed to making healthcare safer. However, it is a challenge. Next to the isolation of sick patients, one of the cheapest interventions, although not fully satisfying, is improved hand hygiene according to the World Health Organizations' guidelines [2]. There are data suggesting a positive impact of mass vaccination against rotavirus on a reduction in nosocomial rotavirus gastroenteritis among pediatric patients [3]. Unfortunately, the high cost of these vaccines is an obstacle to their widespread use in many countries, thus maintaining interest in simple, effective, low-cost strategies for preventing HCAI.

Probiotics are live microorganisms thought to improve the microbial balance of the host, counteract disturbances in intestinal flora, and reduce the risk of colonization by pathogenic bacteria [4]. In children, there are convincing data to support the use of probiotics with documented efficacy for the treatment of acute gastroenteritis and the prevention of antibiotic-associated diarrhea [5, 6]. Previously, we documented that in hospitalized children, the administration of *Lactobacillus rhamnosus* GG (LGG), compared with placebo, reduced the overall incidence of healthcare-associated diarrhea, including rotavirus gastroenteritis [7].

The objective of this systematic review and meta-analysis, which adds to our previous report [8], was to systematically review data on the efficacy of use of various probiotics, alone or in combination, for the prevention of healthcare-associated diarrhea in children. Only data related to a specific probiotic strain or their combinations are reported. This is because it is known that not all probiotics are equal, and pooling data on different probiotics have been repeatedly questioned [8, 9].

Methods

The methods for this systematic review and meta-analysis were described in detail in our earlier review [8]. In brief, the guidelines from the Cochrane Collaboration for undertaking and reporting the results of a systematic review and meta-analysis and the PRISMA statement [10] were followed. Randomized controlled trials (RCTs) reporting incidence outcomes for healthcare-associated diarrhea were considered for inclusion. Participants had to be children aged 1 month to 18 years who were admitted to the hospital for any reason other than gastrointestinal infections. The interventions of interest compared use of probiotics (any strain or dose) *versus* placebo or no treatment for the prevention of healthcare-associated diarrhea. The primary outcome measure was the incidence of healthcare-associated diarrhea as defined by the investigators. The secondary outcome measures were the incidence of rotavirus gastroenteritis, the incidence of asymptomatic rotavirus infection, the duration of diarrhea, and the duration of hospitalization.

We searched MEDLINE, EMBASE, The Cochrane Library, including the Cochrane Central Register of Controlled Trials, Health Source: Nursing/Academic edition, and reference lists, with no language restrictions, through June 2013. The search strategy included the use of a validated filter for identifying RCTs, which was combined with a topic-specific strategy using the following PubMed MeSH terms: 1. (prevention OR prevent OR prevent* OR preventive therapy OR prophylaxis); 2. (diarrhea OR diarrhoe* OR diarhe* OR dysenter* OR gastro enteritis OR diarrhea OR diarrh* OR gastritis OR gastrit* OR gastroenteritis OR gastroenterocolitis OR vomit* OR intestinal infection* OR gastrointestinal infection* OR rotavirus); 3. (lactobacillus OR lactobacill* OR l acidophilus OR l casei OR l delbrueckii OR l helveticus OR l johnsonii OR l paracasei OR l plantarum OR l reuteri OR l rhamnosus OR l salivarius); 4. (Sacharomyces OR saccharomyce* OR s bulardii OR streptococcus OR streptococc* AND thermophilus OR enterococcus OR enterococc* AND faecium); 5. (Bifidobacterium OR bifidobacter* OR b animalis OR b bifidum OR b breve OR b infantis OR b lactis OR b longum); 6. 3 OR 4 OR 5; 7. 6 AND 1 AND 2. In addition, we searched two trial registries (ClinicalTrials.gov, www.clinicaltrials.gov, and EU Clinical Trials Register, www.clinicaltrialsregister.eu).

Using a standardized data extraction form, one author (MW) extracted the following data items: author, year of publication, language, study setting, methodological design, exclusion criteria for participants, patient characteristics (age, diagnosis), number of patients allocated to each group, types of interventions, and outcome measures. The data were entered into a computer program. The Cochrane Review Manager (RevMan) (version 5.2.6 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2013) was used for statistical analysis and to perform a meta-analysis of the RCTs.

The risk of bias was assessed as described in the Cochrane Handbook for Systematic Reviews of Interventions, and it included the assessment of the adequacy of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, and the extent of loss to follow-up (*i.e.*, incomplete outcome data). In all cases, an answer of 'yes' indicates a low risk of bias, and an answer of 'no' indicates a high risk of bias [11].

Heterogeneity was quantified by χ^2 and I^2. The quantity, I^2, describes the percentage of total variation across studies that is due to heterogeneity rather than to chance. Negative values of I^2 are made equal to zero so that I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. The