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Probiotyki w zapobieganiu działaniom niepożądanym antybiotykoterapii u dzieci

Streszczenie rozprawy na stopień doktora nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki medyczne

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Abstract

Probiotics for preventing harms during antibiotic therapy in children

Antibiotics are one of the most used and overused drugs in the pediatric population. Their influence on the gut microbiome may lead to both acute and chronic adverse effects. Probiotics are usually used to reduce the risk of antibiotic-associated diarrhea (AAD). However, the effectiveness of most of them is not scientifically proven. To acquire unequivocal evidence, it is vital to conduct randomized controlled trials assessing clearly defined, clinically relevant outcomes.

In the first study, a multispecies probiotic consisting of 8 bacterial strains (*Bifidobacterium bifidum* W23, *B. lactis* W51, *Lactobacillus acidophilus* W37, *L. acidophilus* W55, *Lacticaseibacillus paracasei* W20, *Lactiplantibacillus plantarum* W62, *Lacticaseibacillus rhamnosus* W71 and *Ligilactobacillus salivarius* W24) was assessed for its effectiveness in reducing the risk of AAD in children. A randomized, quadruple blind, placebo-controlled trial involving 350 children aged 3 months – 18 years (median age: 28 months) receiving broad-spectrum systemic antibiotics was conducted according to the previously published protocol (Łukasik et al. BMJ Open. 2018; 8[5]:1-7). Within 24 h following initiation of antibiotic therapy, the participants were randomized to receive either the multispecies probiotic (at a daily dose of 10^{10} colony-forming units) or a placebo for the duration of antibiotic treatment and for 7 days after. The primary outcome was AAD, defined as 3 or more loose or watery stools per day in a 24-hour period, caused either by *Clostridioides difficile* or of otherwise unexplained etiology. In the intention-to-treat analysis, children from the probiotic group (n=158) compared to the placebo group (n=155) had a similar AAD risk (relative risk [RR] 0.81, 95% confidence interval [CI] 0.49 to 1.33) when assessed according to the most stringent definition, based on the exclusion of rotaviruses, noroviruses, adenoviruses, *Salmonella spp.*, *Campylobacter spp.*, and *Yersinia spp*. However, children in the probiotic group had a lower risk of diarrhea regardless of the etiology (RR 0.65; 95% CI 0.44 to 0.94). No differences were observed between the groups for most of the secondary outcomes. The risk of adverse events was similar in both groups (Łukasik et al. JAMA Pediatrics. 2022; accepted).

The second study, a scoping systematic review, documented outcomes reported in studies on probiotic use during antibiotic therapy in children. Among 37 included studies, as many as 16 different diarrhea definitions were identified. Diagnostic criteria were not clearly defined in 12 out of 33 studies assessing AAD as an outcome. Tests for common diarrheal

pathogens were performed to confirm the AAD diagnosis only in 7 studies. Diarrhea duration was assessed in 9, and severity only in 4 studies. Only 2 studies assessed quality of life-related outcomes (Łukasik et al. PLoS One. 2020; 15[5]:e0228824).

In conclusion, the administration of the studied multispecies probiotic may be considered for diarrhea prevention during antibiotic treatment in children. The results of the scoping review show considerable outcome heterogeneity and a scarcity of patient-relevant outcomes reported in the studies on probiotic use during antibiotic therapy in children. The summarised results of the two studies demonstrate that the AAD outcome definition has a significant impact on clinical trial results and their interpretation.