Probiotics in antibiotic associated diarrhea in children

Preprečevanje driske zaradi zdravljenja z antibiotiki s probiotiki pri otrocih

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Abstract

The use of antibiotics that disturb the gastrointestinal microbiota is associated with diarrhea, which occurs in up to half of treated children. Symptoms are usually mild and children do not need hospitalization. Probiotics are live microorganisms, which restore intestinal microbiota during antibiotic therapy through different mechanisms such as stimulation of immunity, secretion of anti-inflammatory factors, and production of antimicrobial substances. The use of different strains of probiotics in antibiotic-associated diarrhea was evaluated in several studies in adults but less frequently in pediatric population. They also confirmed the value of probiotics in the prevention of antibiotic-associated diarrhea in children, particularly *Lactobacillus* strain *GG* and *Saccharomyces boulardii*. The use of probiotics in childhood is safe. A proper strain must be introduced at the beginning of antibiotic treatment in a sufficient concentration.

Izvleček

Antibiotiki ne vplivajo samo na škodljive mikroorganizme v črevesju, temveč tudi na normalno črevesno floro. To omogoča razrast odpornim vrstam, ki povzročijo drisko pri do polovici zdravljenih otrok z antibiotiki. Klinična slika je v večini primerov blaga in otroci zaradi prebavnih simptomov ne potrebujejo zdravljenja v bolnišnici. Probiotiki so živi mikroorganizmi, ki lahko na več različnih načinov obnovijo porušeno ravnovesje v mikrobioti črevesja. O učinkovitosti probiotikov pri preprečevanju driske, povzročene z antibiotiki, je bilo objavljenih veliko raziskav pri odraslih bolnikih, manj pa pri otrocih. Zaključki večine raziskav so, da je probiotik koristen pri preprečevanju drisk zaradi zdravljenja z antibiotiki in da je uporaba probiotikov varna. Učinkovitost pri preprečevanju driske je odvisna od probiotičnega seva in od odmerka probiotika. Probiotični pripravek je potrebno prejemati hkrati z antibiotičnim zdravljenjem. Najbolj raziskana probiotična seva pri preprečevanju drisk zaradi prejemanja antibiotikov pri otrocih sta *Lactobacillus GG* in *Saccharomyces boulardii*.

Introduction

Antibiotic-associated diarrhea (AAD) occurs in association with the administration of antibiotics and it is characterized by a change in the normal stool frequency to at least 3 loose or watery stools daily for 3 days. An onset of diarrhea may occur at any time during antibiotic therapy to 8 weeks after the antibiotic has been discontinued.[1]

Antibiotics belong among frequently prescribed drugs and its use is still increasing. The antibiotics disturb the normal gastrointestinal microbiota and cause a range of clinical symptoms, most frequently diarrhea. The incidence of AAD in general population treated with antibiotics varies between 5 % and 62 %.[2] The incidence is quite similar among children and ranges from 11 % to 62 %.[3] The frequency of AAD is higher in younger children and with the use of certain antibiotics such as aminopenicillins, cephalosporins and clindamycin. The human gut is colonized by a diverse community of microorganisms that exist in a complex symbiosis with their host. Antibiotics cause

diarrhea by disrupting a complex balance of diverse microorganisms–normal microbiota in the gastrointestinal tract. The administration of antibiotics suppresses members of the indigenous microbiota, allowing expansion of different microorganisms such as *Clostidium difficile* infection (*C. difficile*). In addition, erythromycin and clavulanate, for example, promote diarrhea by prokinetic activity. Finally, suppression of anaerobic bacteria results in reduced metabolism of carbohydrates, including an osmotic diarrhea. In the majority of cases AADs are mild and hospitalization is rarely required. AAD is usually a more serious medical condition when caused by *C.difficile*. *C.difficile* is an anaerobic, gram-positive bacillus that colonizes the intestinal tract after alteration of the normal gastrointestinal flora, usually by antibiotic therapy. Besides alteration of the flora, reduced colonic ion secretion and depressed motor function of the muscularis mucosae, are additional factors that encourage the overgrowth of *C. difficile*. Pathogenic strains produce enterotoxin A and cytotoxin B. The toxins directly affect the colonic cells by altering cellular actin filaments.[4] It causes a range of diseases, from mild diarrhea to pseudomembranous colitis and death. Patients at risk for *C. difficile* are older patients, and those with multiple comorbidities, inflammatory bowel disease, immunosupression, liver disease, long proton pump therapy, longer hospitalization, the use of broad spectrum antibiotics and prolonged antibiotic treatment.

According to FAO/WHO definition, probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. In humans, the most commonly used probiotics are microorganisms belonging to genus *Bififobacterium, Lactobacillus, Saccharomyces* and *Bacillus.*[5] They are used as single species or mixture of different species. The beneficial effects of probiotics seem to be strain-specific and dose-dependent. The clinical studies of probiotics in man are rapidly increasing. There are certain diseases, such as acute diarrhea and inflammatory bowel disease, where the beneficial effect of probiotic use has been already confirmed.[6] AAD is also a field in which particular interest in using probiotics is on the increase and where a positive effect of the use of certain strains has already been confirmed.

There are several mechanisms of action of probiotics in the prevention of AAD. Probiotics assist in reestablishing the disrupted intestinal microbiota by secreting mucins, producing bacteriocins, increasing production of immunoglobulin A, IL-10 and transforming growth factor beta, and influencing the differentiation of T helper cells into Th1 or Th2 cells.[7]

There were numerous trials published in adults as well as in children where the efficacy of probiotics for the prevention of AAD was confirmed. At least two meta-analyses have been published in adult population. In the D'Souza meta-analysis four trials used *Saccharomyces boulardii* (*S. boulardii*), four used *Lactobacilli* and one used a strain of *enterococcus*.[8] The odds ratio in favor of active treatment over placebo was 0.39 (0.25–0.62, $p < 0.001$) for yeasts and 0.34 (0.19–0.61, $p < 0.01$) for *Lactobacilli*. Meta-analysis by Cremonini et al. included seven trials.[9] A total number of 881 patients were included. Again *Lactobacilli* and *S. boulardii* were used in the studies. The combined relative risk was 0.39 (0.27–0.57, $p < 0.05$) and the results suggested a strong beneficial effect of probiotic administration on AAD in adults . Six double-blind placebo-controlled studies in children were included in a meta-analysis of probiotics preventing AAD published in 2006.[10] The probiotics reduced the risk of AAD from 28.5 % to 11.9 %. A Cochrane database review of the data on probiotics in preventing AAD in children was published two years ago.[11] Sixteen studies were reviewed and included 3432 children. Probiotics were generally well tolerated and the review showed that probiotics were effective in preventing AAD. In addition, in the recent recommendations it was concluded that the evidence for probiotic efficacy for AAD is very strong (level A).[12] It must be stressed out that probiotic efficacy for AAD is strain--specific.

In the majority of trials with AAD, *Lactobacilli* (*Lactobacillus GG* (*LGG*), *Lactobacillus reuteri* ATCC 55730 , *L. casei* DN-114001)

or *S. boulardii* are used either alone or in combination with other microorganisms. Therefore, these strains also have the strongest evidence for probiotic use in preventing pediatric AAD.

Lactobacillus

LGG was most frequently studied among *Lactobacilli*. This probiotic strain was first described by Gorbach et al..[13] They isolated it from human stool and demonstrated its probiotic activity. This probiotic can survive in acidic environment of the stomach and also in the small intestine, if it is exposed to bile acids. *LGG* has shown beneficial effect on intestinal immunity. It increases the local level of IgG and interferon. In addition, it produces substances that inhibit growth of different types of bacteria.

Vanderhoof et al. included 202 children between 6 months and 10 years of age in a double-blind placebo-controlled randomized trial of probiotics. In a study, *LGG* $1–2 \times 10^{10}$ CFUs per day was administered for 10 days. During the 10-day antibiotic therapy, 26 % of placebo treated children had diarrhea as defined by 2 or more liquid stools per day. AAD was reduced to 8 %, when children were concomitantly treated with *LGG*. The conclusion of the study was that co-administration of *LGG* statistically significant reduces the incidence of AAD.[14]

In another double-blind placebo-controlled randomized trial of *LGG*, Arvola et al. included 119 children aged from 2 weeks to 13 years. All of them received antibiotic therapy due to the respiratory infection. The patients were randomized to receive placebo or 2×10^{10} CFUs of *LGG* during antibiotic therapy. The incidence of diarrhea was 16 % in the placebo group and 5 % in the probiotic group. The conclusion was that the *LGG* is a safe and useful adjunctive therapy to prevent AAD.[15]

The effectiveness of *L. rhamnosus* (strains E/N, Oxy and Pen) in the prevention of AAD in children was evaluated in a study from Poland. Two hundred forty children with common infections were included in a double-blind placebo-controlled randomized trial in which 120 children were treated with 2×10^{10} CFUs of probiotics twice a day throughout the antibiotic therapy. The principal finding was that probiotics, compared to placebo as an adjunct to antibiotic therapy, reduce the risk of diarrhea in children effectively. In 11 patients, one less will develop diarrhea if concomitant therapy with *L. rhamnosus* is applied.[16]

The prevention of AAD with *L. acidophilus* and *Bifidobacterium infantis* in infants and children was studied by Jirapinyo et al..[17] The results of the study showed that the group receiving probiotics had fewer diarrheal episodes (37.5 %) than the control group (80 %), although the numbers were too small for statistical analysis. The authors concluded that probiotic administration to patients receiving high doses of broad-spectrum antibiotics may prevent the occurrence of AAD.

The efficacy and safety of mixed probiotics *L. acidophilus* and *L. bulgaricus* was compared with placebo for the prevention of amoxicillin-induced diarrhea in children. Mixed probiotics (3 billion CFUs) or placebo were administered once a day for the duration of antibiotic therapy. The *Lactobacillus* preparation did not appear to consistently prevent diarrhea in this patient population.[18]

Saccharomyces boulardii

S. boulardii is yeast isolated from the skin of lychee grown in Indochina. *S. boulardii* survives gastric acid and bile and can be detected alive throughout the entire digestive system. As is the case with all yeasts, *S. boulardii* is resistant to antibiotics.

There are several possible therapeutic mechanisms of yeasts. A strong direct antagonist effect has been demonstrated by *S. boulardii* against a number of pathogens. Two main mechanisms against enteric pathogens are recognized: the production of factors that compete with bacterial toxins, and the modulation of the host cell signaling pathways implicated in the proinflammatory response during bacterial infection.[19] *S. boulardii* also stimulates growth and differentiation of intestinal cells in response to trophic factors such as insulin and IgF-1 by

activating certain kinases.[20] It stimulates the production of glycoproteins on brush border of microvilli such as hydrolases, secretory IgA, transporters and the receptor for polymeric immunoglobulins.[21] *S. boulardii* diminishes inflammation by decreasing the production of proinflammatory cytokine IL-8, by secreting anti-inflammatory factor that inhibits NF-kapaB-dependent signaling pathway in the presence of *C. difficile* toxin.[22]

There are at least three trials determining the role of *S. boulardii* for the prevention of AADin the pediatric population. In a double-blind placebo-controlled randomized trial, Kotowska et al. included 269 children with ear or respiratory infection in the probiotic study. Half of them were treated with standard antibiotic therapy plus 250 mg of *S. boulardii* and the other half received placebo orally instead of probiotic twice a day for the duration of antibiotic treatment. The conclusions were that *S. boulardii* therapy is safe and that probiotics statistically significantly reduce the risk of AAD (17.3 % vs. 3.4 %; RR 0.2; 95 CI 0.07–0.5).[23] The aim of the double-blind placebo-controlled randomized study from Turkey was to determine the efficacy of *S. boulardii* in AAD with commonly used antibiotics such as sulbactam- ampicillin and azithromycin. A total of 653 children between 1–15 years of age were included in the study. AAD was observed in 42 of 222 children (18.9 %) receiving only antibiotic therapy and in 14 of 244 patients (5.7 %) who received double therapy including probiotics (RR 0.3; 95 % CI 0.2 to 0.5).[24] The third trial evaluated the role of *S. boulardii* in *C. difficile* AAD. Buts et al. conducted an open-label trial. It was a small study with 19 enrolled children suffering from *C. difficile* infection. *S. boulardii* was given orally over 15 days, 250 mg 2–4 times per day, according to age. The authors suggested that *S. boulardii* may be effective in *C. difficile* diarrhea.[25]

Safety

The safety of therapy with various probiotics is not a concern in otherwise healthy individuals. A small number of case reports have been published describing bacteremia or fungemia. In all those cases the patients had serious co-morbidities.[26] A systematic review of case reports demonstrating probiotics' safety revealed that preterm neonates, severely debilitated and immune-compromised children are at higher risk for important side effects due to probiotic therapy. All of these children recovered after probiotics were discontinued, central catheter was removed, and antifungal or antibacterial drug was administered.[27]

The other concern is transfer of genetic material between probiotics and other microorganisms. Bacterial probiotics might be able to transfer their resistance genes to pathogenic bacteria, if they are located on plasmid DNA, while yeasts have no capability of doing so and this is especially important in AAD.[28]

The use of probiotics in patients with severe pancreatitis has been noted to increase mortality due to bowel ischemia.[29]

Conclusion

The prevalence of AAD in children is high and similar as in adults. In the prevention of AAD in children probiotics show a beneficial effect, which was also concluded by The American Academy of Pediatrics in 2010.[30] *LGG* and *S. boulardii* have been the most common probiotics used in AAD in children.

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