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Probiotics for the prevention of pediatric antibiotic-associated diarrhea

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Background

Antibiotics are frequently prescribed in children. They alter the microbial balance within the gastrointestinal tract, commonly resulting in antibiotic-associated diarrhea (AAD). Probiotics may prevent AAD via restoration of the gut microflora.

Objectives—The primary objectives were to assess the efficacy and safety of probiotics (any specified strain or dose) used for the prevention of AAD in children.

Search methods—MEDLINE, EMBASE, CENTRAL, CINAHL, AMED, and the Web of Science (inception to November 2014) were searched along with specialized registers including the Cochrane IBD/FBD review group, CISCOM (Centralized Information Service for Complementary Medicine), NHS Evidence, the International Bibliographic Information on Dietary Supplements as well as trial registries. Letters were sent to authors of included trials, nutraceutical and pharmaceutical companies, and experts in the field requesting additional information on ongoing or unpublished trials. Conference proceedings, dissertation abstracts, and reference lists from included and relevant articles were also searched.

Selection criteria—Randomized, parallel, controlled trials in children (0 to 18 years) receiving antibiotics, that compare probiotics to placebo, active alternative prophylaxis, or no treatment and measure the incidence of diarrhea secondary to antibiotic use were considered for inclusion.

Data collection and analysis—Study selection, data extraction as well as methodological quality assessment using the risk of bias instrument was conducted independently and in duplicate by two authors. Dichotomous data (incidence of diarrhea, adverse events) were combined using a

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Authors' conclusions: Moderate quality evidence suggests a protective effect of probiotics in preventing AAD. Our pooled estimate suggests a precise (RR 0.46; 95% CI 0.35 to 0.61) probiotic effect with a NNT of 10. Among the various probiotics evaluated, *Lactobacillus rhamnosus* or *Saccharomyces boulardii* at 5 to 40 billion colony forming units/day may be appropriate given the modest NNT and the likelihood that adverse events are very rare. It is premature to draw conclusions about the efficacy and safety of other probiotic agents for pediatric AAD. Although no serious adverse events were observed among otherwise healthy children, serious adverse events have been observed in severely debilitated or immuno-compromised children with underlying risk factors including central venous catheter use and disorders associated with bacterial/fungal translocation. Until further research has been conducted, probiotic use should be avoided in pediatric populations at risk for adverse events. Future trials would benefit from a standard and valid outcomes to measure AAD.

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pooled risk ratio (RR) or risk difference (RD), and continuous data (mean duration of diarrhea, mean daily stool frequency) as mean difference (MD), along with their corresponding 95% confidence interval (95% CI). For overall pooled results on the incidence of diarrhea, sensitivity analyses included available case versus extreme-plausible analyses and random- versus fixed-effect models. To explore possible explanations for heterogeneity, *a priori* subgroup analysis were conducted on probiotic strain, dose, definition of antibiotic-associated diarrhea, as well as risk of bias. We also conducted post hoc subgroup analyses by patient diagnosis, single versus multi-strain, industry sponsorship, and inpatient status. The overall quality of the evidence supporting the outcomes was evaluated using the GRADE criteria.

Main results—Twenty-three studies (3938 participants) met the inclusion criteria. Trials included treatment with either *Bacillus spp.*, *Bifidobacterium spp.*, *Clostridium butyricum*,*Lactobacilli spp.*, *Lactococcus spp.*, *Leuconostoc cremoris*, *Saccharomyces spp.*, *or Streptococcus spp.*, alone or in combination. Eleven studies used a single strain probiotic, four combined two probiotic strains, three combined three probiotic strains, one combined four probiotic strains, two combined seven probiotic strains, one included ten probiotic strains, and one study included two probiotic arms that used three and two strains respectively. The risk of bias was determined to be high or unclear in 13 studies and low in 10 studies. Available case (patients who did not complete the studies were not included in the analysis) results from 22/23 trials reporting on the incidence of diarrhea show a precise benefit from probiotics compared to active, placebo or no treatment control. The incidence of AAD in the probiotic group was 8% (163/1992) compared to 19% (364/1906) in the control group (RR 0.46, 95% CI 0.35 to 0.61; I2 = 55%, 3898 participants). A GRADE analysis indicated that the overall quality of the evidence for this outcome was moderate. This benefit remained statistically significant in an extreme plausible (60% of children loss to follow-up in probiotic group and 20% loss to follow-up in the control group had diarrhea) sensitivity analysis, where the incidence of AAD in the probiotic group was 14% (330/2294) compared to 19% (426/2235) in the control group (RR 0.69; 95% CI 0.54 to 0.89; I2 = 63%, 4529 participants). None of the 16 trials (n = 2455) that reported on adverse events documented any serious adverse events attributable to probiotics. Meta-analysis excluded all but an extremely small non-significant difference in adverse events between treatment and control (RD 0.00; 95% CI −0.01 to 0.01). The majority of adverse events were in placebo, standard care or no treatment group. Adverse events reported in the studies include rash, nausea, gas, flatulence, abdominal bloating, abdominal pain, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and low appetite.

Review commentary

Pediatric antibiotic-associated diarrhea (AAD) is defined as 3 or more loose stool events following antibiotic treatment, and presents after the use of antibiotic treatment in 11-40% of pediatric patients (Turck et al., 2003). The risk of AAD increases with an increasing duration of antibiotic treatment. Compared to adult AAD, pediatric AAD has a quicker onset after antibiotic exposure but a shorter duration, and is associated with fewer complications (surgery, Intensive Care Unit stay, fever etc.) (McFarland, Ozen, Dinleyici, & Goh, 2016). Current treatment recommendations for AAD from the American College of Gastroenterology are to discontinue antibiotics and, if *Clostridium difficile* infection is found in a patient ≥ 10 years old, to begin with metronidazole treatment and adjust care as

necessary (Surawicz et al., 2013). In children with *Clostridium difficile* infections aged 10 years old and younger, discontinuation of antibiotics and aggressive rehydration is recommended. In children, vancomycin use is reserved only for severe cases (Schutze, Willoughby, Committee on Infectious Diseases, & American Academy of Pediatrics, 2013).

Infancy and childhood are periods of dynamic growth and development throughout the body, not the least of which is development of the gastrointestinal microbiome(Koenig et al., 2011). Antibiotic use in children has been associated with an altered microbiome (Korpela, Salonen, Virta, Kekkonen, & de Vos, 2016) and increased risk of diseases like obesity (Mbakwa et al., 2016) and asthma (Wu et al., 2016). Thus, prevention of AAD by strengthening the microbiome using concomitant probiotics is a highly attractive option for children and infants undergoing antibiotic therapy. Probiotics are live microbial organisms, such as dairy fermenting bacteria, that are considered beneficial for health. They are commonly administered orally. Probiotics do not have a predefined regulatory pathway through the U.S. Food and Drug administration and often are routed through the dietary supplement pathway which has less rigorous requirements than the drug regulatory pathway. Nonetheless, pharmaceutical grade probiotics with high quality standards are available for prescription. A 2015 expert panel recommended the use of *Saccharomyces boulardii*, *Lactobacillus GG*, combination of *Lactobacillus casei* DN114 G01, *Lactobacillus bulgaricus*, *Streptococcus thermopolus* for AAD in general, and additionally *Lactobacillus reuteri* SD2112 for pediatric infections (i.e. necrotizing enterocolitis, inflammatory bowel disease, irritable bowel syndrome and *Clostridium difficile* diarrhea) with the highest level of evidence (grade A) (Floch et al., n.d.). Evidence is accumulating that probiotics should also be co-prescribed with antibiotics among healthy pediatric patients for the prevention of AAD.

This Cochrane review is the second update of a 2007 Cochrane review of randomized controlled trials on probiotics for the prevention of pediatric AAD (Brad C Johnston, Supina, Ospina, & Vohra, 2007; Bradley C Johnston, Goldenberg, Vandvik, Sun, & Guyatt, 2011). The 2011 update (Bradley C Johnston et al., 2011) found a significant relative risk of 0.52 with a 95% confidence interval of 0.38 to 0.72 for reduction of AAD with the use of probiotics. In this current update, Goldenberg, *et al.* identified 7 additional randomized control trials and over 500 more participants than the 2011 Cochrane review (Bradley C Johnston et al., 2011) giving the authors more power to discern significant effects. Data from 3,938 diverse pediatric participants (e.g., ages 1 month - 18 years old, from 15 different countries, recruited from diverse in-patient and out-patient settings, with 10 days to 12 weeks of follow-up) treated with antibiotics for variable durations (e.g., 3 to 30 days), and by various routes (e.g., oral versus intravenous), met the inclusion criteria.

The main finding from this review is that any probiotic use significantly reduces the occurrence of AAD with a relative risk of 0.46 and a 95% confidence interval of 0.35 to 0.61 when compared with an alternative active treatment (e.g., formula and diosmectite), placebo, or no treatment in the pediatric population. This result is consistent with the previous Cochrane reviews on this topic (Brad C Johnston et al., 2007; Bradley C Johnston et al., 2011) and findings in *Clostridium difficile*-specific AAD where both children and adults demonstrated a 64% reduction in risk of *Clostridium difficile*-specific AAD with probiotic

use (Alfaleh, Anabrees, Bassler, & Al-Kharfi, 2011). The preponderance of the evidence came from placebo controlled trials (n=15 studies and n=1575 participants) or trials with no active treatment control (n=5 studies and n=1550 participants). The authors suggest there is also some evidence of probiotics mitigating symptoms, such as the duration and frequency of bowel movements, but further research in this area is necessary to make conclusions. The efficacy of probiotic use on AAD and associated symptoms did not significantly differ by probiotic species, care setting, strain quantity, or study risk of bias (e.g., presence vs. absence of adequate blinding). However, meta-regression indicated that the impact of probiotics differed by probiotic dosage, with higher doses having a greater impact. Lactobacillus rhamnosus and Saccharomyces boulardii, at doses exceeding 5 billion CFU/day, were specifically identified as acceptable for treatment of healthy pediatric populations given the low risk of negative outcomes. These findings are in concordance with the panel recommendations mentioned earlier (Floch et al., n.d.). Lastly, improvements in preventing AAD were most pronounced in in-patient as opposed to out-patient settings. This could be evidence of differences in adherence or the quality of probiotics provided/recommended to out-patient vs. in-patient individuals.

All Cochrane reviews assess the quality of evidence for results as high, moderate, low or very low according to GRADE criteria (Guyatt et al., 2008). Evidence from randomized controlled trials begins as high quality, however the quality of evidence for the effect of probiotics upon the risk of AAD was downgraded from high to moderate because there was substantial unexplained variability between individual studies in the analysis. The interpretation of moderate quality evidence is that the authors are moderately confident that the true effect estimate is close to the observed estimate, but further research may result in an effect estimate that is substantially different. This is an improvement, as the previous review on this topic (Bradley C Johnston et al., 2011) concluded only low quality evidence supported the association due to sparse data. In addition to unexplained heterogeneity and high risk of bias in some studies, other limitations in the underlying research evidence are also present. Variable definitions of diarrhea with respect to the frequency, duration, and consistency of bowel movements significantly modified the reported benefit of probiotic treatment on risk of AAD. Also, while few side effects to treatment with probiotics have been observed among healthy pediatric patients, even among healthy newborns (Surawicz et al., 2013) the evidence from studies included in this review was sparse and did not cover all types of probiotics available. There is a need for definitions of diarrhea, related symptoms, and negative outcomes to be standardized (Clarke, 2007; Ioannidis et al., 2004; Bradley C Johnston, Shamseer, da Costa, Tsuyuki, & Vohra, 2010). These definitions would streamline investigations of the magnitude of the effect of probiotic use so that risk vs. benefit analyses can be conducted for children at high risk for negative outcomes. The lack of available literature suggests the need for additional study of probiotic use in children at risk for negative outcomes, such as those with disability or poor immunity, before clinical recommendations can be made for the entire pediatric population. Currently, clinicians should consider recommending only *Lactobacillus rhamnosus* and *Saccharomyces boulardii* in the healthy pediatric populations until further safety data can be collected on other microbes.

This review provides evidence that probiotics can mitigate the AAD-inducing effects of antibiotic use. These results have important regulatory, research, and clinical implications. To ensure vigilance against commercialization of potentially pathogenic or resistance-facilitating probiotics, two regulatory approaches have been recommended (Hoffmann et al., 2013; Sanders et al., n.d.). First, an Abbreviated Investigational New Drug Application for probiotics would ensure better quality while allowing researchers to forego some lengthy stages of traditional pharmaceutical regulation (Hoffmann et al., 2013). Secondly, following suit with Canada, the FDA could mitigate the preponderance of ill-supported assertions regarding the health benefits of probiotics by enforcing adherence to a pre-approved label layout and mandating that claims in excess of those outlined be substantiated with data (Hoffmann et al., 2013). This review's findings suggest that efficacy may be more closely tied to probiotic dosage, as opposed to the specific probiotic species and number of strains. However, more safety data is needed to determine both safe dosing and safe types of microbes for probiotics. The previously referenced recommendations of an Abbreviated Investigational New Drug application for probiotics would help fulfill this need by requiring more safety and efficacy data in order to move probiotics to market (Hoffmann et al., 2013).

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