Probiotics for antibiotic-associated diarrhea in children

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Abstract

Question I recently had a parent ask me if their child should be taking probiotics to reduce the impending diarrhea while using antibiotic treatment for an ear infection. Are probiotics effective and safe in preventing antibiotic-associated diarrhea, and, if so, what strain and dose are recommended?

Answer The 2 types of probiotics recommended to prevent pediatric antibiotic-associated diarrhea are *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. Although an optimal dose has yet to be established, higher doses in the range of 5 to 40 billion colony-forming units per day were reported to be the most efficacious in trials. The safety profile of probiotics is excellent in healthy children; however, rare serious adverse events have been documented in severely debilitated or immunocompromised children.

Antibiotics account for a quarter of all prescriptions for children and are a common source of adverse events including antibiotic-associated diarrhea (AAD).[1] *Antibiotic-associated diarrhea* is defined as 3 or more loose stools within a 24-hour period after antibiotic administration, which might occur within hours or up to 8 weeks following commencement of antibiotic use.[2]

Elements associated with AAD include the age of the child and the antibiotic agent used, among other factors, with an estimated incidence of 5% to 30% in children according to a review of 10 studies with 1438 children from 6 different countries.[3] Cephalosporins, clindamycin, and broad-spectrum penicillins have been associated with a higher risk of AAD.[4]

Current standard of care treatment for AAD includes discontinuing or changing the inciting antibiotic,[3] providing rehydration,[5] or administering oral metronidazole or vancomycin if *Clostridium difficile* is the suspected culprit.[6]

Probiotics for prevention of AAD

Probiotics are defined by the World Health Organization as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[7] The mechanisms of action of different probiotics include providing a physical barrier from pathogens, promoting goblet cell mucus secretion, maintaining the integrity of intestinal epithelial tight junctions, producing antimicrobial factors, and stimulating the immune system.[8]

A study from almost 30 years ago involving 60 children between the ages of 5 months and 6 years was the first to investigate the relationship between probiotics and AAD in this population.[9] Children requiring treatment with amoxicillin were randomized to receive either 500 million colony-forming units (CFUs) of Lactinex (a combination of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*) or placebo (lactose) 4 times daily for 10 days, with similar rates of children still experiencing diarrhea (≥ 1 loose stools per day; 66% vs 69.5%, respectively; $P = .563$).[9]

Sixteen years later, a meta-analysis (N = 766) examined the use of probiotics in reducing the incidence of pediatric AAD across 6 randomized controlled trials (RCTs), reporting a lower risk for those receiving probiotics (12% and 29% in probiotics and placebo groups, respectively, relative risk [RR] of 0.44, 95% CI 0.25 to 0.77).[10] Particularly, *Lactobacillus rhamnosus* GG (RR = 0.3, 95% CI 0.15 to 0.6; n = 307), *Saccharomyces boulardii* (RR = 0.2, 95% CI 0.07 to 0.6; n = 246) and a combination of *Bifidobacterium lactis* and *Streptococcus thermophilus* (RR = 0.5, 95% CI 0.3 to 0.95; n = 157) were reported to be efficacious in preventing pediatric AAD.[10] However, it is difficult to generalize these conclusions owing to the small sample size in each of the trials.

A recent Cochrane review analyzed 33 studies with 6352 children up to 18 years of age who received antibiotic therapy for 3 to 30 days.[11] The probiotics were coadministered with the antibiotic regimen for infections such as in the respiratory tract, impetigo, and *Helicobacter pylori*.[11] The reported incidence of AAD after follow-up (5 days to 12 weeks) was 8% in those receiving probiotics compared with 19% among those receiving placebo (RR = 0.45, 95% CI 0.36 to 0.56; number needed to benefit of 9, 95% CI 7 to 13), suggesting an important role of probiotics in preventing AAD in children.[11]

Choosing probiotics

While the number of probiotic options can be daunting, 2 probiotics in particular have emerged at the forefront for preventing pediatric AAD.[12,13] In a 2015 meta-analysis of 5 RCTs with 445 children, *L rhamnosus* GG was associated with an AAD incidence of 9.6% in the probiotic group and 23% in the placebo group (RR = 0.48, 95% CI 0.26 to 0.89).[12] Another meta-analysis from the same

group reported that with the use of the yeast *S boulardii*, AAD incidence was 8.8% and 20.9% (probiotic and placebo groups, respectively) among 1653 children across 6 RCTs (RR = 0.43, 95% CI 0.3 to 0.6).[13]

Other probiotics including *Lactobacillus reuteri, L rhamnosus* (strains E/N, Oxy, and Pen), combination *Clostridium butyricum* and *Bifidobacterium*, combination *B lactis* and *S thermophilus*, and yogurt (containing active cultures of *S thermophilus* and *Lactobacillus delbrueckii*) have demonstrated efficacy in reducing pediatric AAD incidence in some trials; however, these therapeutic options need further study.[14] Of note, neither *Lactobacillus plantarum* (AAD in 2.8% of probiotic group compared with 4.1% in placebo group [N = 438], *P* = .4)[15] nor kefir beverage (containing lactic acid bacteria such as *Lactobacillus kefiri, Lactobacillus kefiranofaciens, L acidophilus*, and *L plantarum*, as well as yeasts such as *Kluyveromyces marxianus, Saccharomyces unisporus, Saccharomyces cerevisiae,* and *Saccharomyces exiguus*) (RR = 0.82, 95% CI 0.54 to 1.43)[16] were efficacious in their respective studies.

Upon reviewing 21 RCTs involving 3255 children, the Working Group on Probiotics of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published its 2016 guidelines recommending *L rhamnosus* GG and *S boulardii* as the 2 probiotics with sufficient evidence for AAD prevention.[17] However, *S boulardii* is recommended over *L rhamnosus* GG when *C difficile*–associated diarrhea is isolated.[17] These recommendations were made only if 2 or more RCTs were available for the specific strain of probiotic.[17]

Optimal dose

The optimal dose of probiotics remains largely unknown, as evidenced by the range of doses used in pediatric clinical trials from 100 million to 1.8 trillion CFUs per day.[18] *Lactobacillus rhamnosus* GG has greater evidence for a dose-dependent response in children.[12,13] In a meta-analysis including 445 children up to age 17 from 3 countries (Poland, Finland, and the United States) who received coadministration of *L rhamnosus* GG with antibiotics, the highest dose of *L rhamnosus* GG (10 to 20 billion CFUs per day) achieved a 71% reduction in AAD incidence compared with a dose of 3 billion CFUs per day, which only achieved a 34% reduction in incidence.[12] In contrast, a meta-analysis with 1653 children reported that among 6 trials with a daily dose of *S boulardii* ranging from 50 mg to 1000 mg (1 billion to 20 billion CFUs per day), efficacy in preventing AAD did not demonstrate a clear dose-dependent relationship.[13] The most recent 2016 ESPGHAN guidelines do not affirm specific recommendations for doses of *L rhamnosus* GG and *S boulardii*.[17] The ESPGHAN guidelines suggest that 10 to 20 billion CFUs per day of *L rhamnosus* GG or 250 to 500 mg (5 to 10 billion CFUs per day) of *S boulardii* can be used to match the doses used in some RCTs.[17] This general range of doses was supported by a 2019 Cochrane review that noted that in the 33 included trials, high-dose probiotics (5 to 40 billion CFUs per day) were more effective than low-dose probiotics (RR = 0.37, 95% CI 0.30 to 0.46, *P* = .06; number needed to benefit of 6, 95% CI 5 to 9).[11]

Safety

Among 24 studies, rates of mild to moderate adverse events (eg, rash, nausea, gas, flatulence, abdominal bloating, constipation) were low, with an incidence of 4% (86 of 2229) in the probiotic groups compared with 6% (121 of 2186) in the control groups.[11] No serious adverse events were reported in either group.[11] However, serious adverse events were reported in a large systematic review of 20 case reports and 52 randomized and non-randomized trials involving 4131 patients (children and adults) who received probiotics through enteral or parenteral nutrition.[19] In the case reports, some of which reported on more than 1 patient, 32 cases of serious adverse events (ie, fungemia, bacteremia) were documented.[19] Eleven of these cases were either preterm neonates, severely debilitated children, or immunocompromised children, and involved risk factors such as central venous catheters and disorders associated with increased bacterial translocation.[19] All 11 recovered from the infection after discontinuing the probiotic, removing the central venous catheter, or administrating an antibiotic or antifungal.[19] While probiotics appear to be safe in healthy children, use in severely debilitated or immunocompromised children requires caution owing to the potential for reversible but serious adverse events as documented in several case reports.

Conclusion

Lactobacillus rhamnosus GG and *S boulardii* are 2 probiotics that are effective in preventing pediatric AAD when coadministered with antibiotics. While an optimal dose remains unknown, a range of 5 to 40 billion CFUs per day appears to be the most efficacious. There is insufficient evidence to recommend other strains of probiotics at this time. Probiotics appear to be safe in children, with minimal side effects; however, serious adverse events have been documented in case reports of severely debilitated or immunocompromised children.

Competing interests
None declared

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