

Use of Probiotics in Pediatric Patients: A Review of the American Gastroenterological Association 2020 Guidelines

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In August 2020, the American Gastroenterological Association (AGA) published clinical practice guidelines for the role of probiotics in the management of gastrointestinal disorders.¹ The document is not specific to pediatric practice per se, but recommendations are included for specific populations that include children and neonates.

While the role of probiotics in clinical practice continues to evolve, the number of available products and potential indications has exploded over the last 20 years or so. The Food and Agriculture Organization of the United Nations and the World Health Organization define probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."² Many of our patients may use probiotics and are familiar with the term, but evidence has been confusing at times.

The AGA outlined 8 recommendations, the strength of the recommendation, and the quality of evidence. Seven of these recommendations speak specifically to

the management of children. Of those, 4 have conditional recommendations, which means for the patient that most would want to use the recommended course, but many would not. For the clinician, it means that the decision is based on clinical judgement, values, and preferences. Patients and clinicians may need more time to work toward a plan.¹

Recommendations in Children

The first of the 4 conditional recommendations is for children taking antibiotics. The AGA recommends using a regimen containing the following bacteria over using no probiotics or other probiotics for preventing *Clostridioides difficile* infection:

- *Saccharomyces boulardii*
- 2-strain combination of *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* BC80R
- 3-strain combination of *L acidophilus*, *Lactobacillus delbrueckii* subsp *bulgaricus*, and *Bifidobacterium bifidum*

- 4-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B bifidum*, and *Streptococcus salivarius* subsp *thermophilus*

This recommendation is conditional with low-quality evidence. A technical review of 39 studies showed that while probiotics had reduced the overall risk of *C difficile* infection vs placebo, this benefit had been driven by patients at highest risk for *C difficile* infection. Therefore, patients who value minimizing financial cost or potential harm, such as those who are immunocompromised or those at low risk for *C difficile* infection, may choose not to use any probiotics.

The second conditional recommendation is for children with pouchitis. Pouchitis is a frequent complication after total proctocolectomy and ileal pouch-anal anastomoses for the treatment of ulcerative colitis. A technical review of 7 studies points to the following 8-strain combination of bacteria over no probiotics or other probiotics:

- *Lactobacillus paracasei* subsp *paracasei*
- *Lactobacillus planetarum*
- *L acidophilus*
- *L delbrueckii* subsp *bulgaricus*
- *Bifidobacterium longum* subsp *longum*
- *Bifidobacterium breve*
- *B longum* subsp *infantis*
- *S salivarius* subsp *thermophilus*

The overall quality of evidence is very low for this recommendation, mainly because of small sample sizes in all available studies.

The third conditional recommendation is one familiar to most community pedi-

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atricians. The AGA suggests against the use of probiotics in children with acute gastroenteritis in the United States and Canada. Many pediatricians may recall studies supporting the use of probiotics in children with acute gastroenteritis, but those studies were performed outside the United States and Canada.³ A technical review of 89 studies showed that some strains had improved diarrhea duration in children. However, 2 recent multicenter, randomized, double-blind, placebo-controlled trials studied *Lactobacillus rhamnosus* ATCC 53103 and a combination of *L rhamnosus* R0011 and *Lactobacillus helveticus* R0052 for 5 days. Results from both studies had showed no benefit in the occurrence of moderate to severe gastroenteritis. Two additional studies confirm these findings.^{1,3}

The fourth conditional recommendation is for use of probiotics in preterm, low birth-weight infants for preventing necrotizing enterocolitis (NEC). NEC is a condition in preterm infants in which intestinal microbial dysbiosis precedes the onset. The following combinations are suggested over using no probiotics or other probiotics:

- *Lactobacillus spp* and *Bifidobacterium spp*
- *Bifidobacterium animalis* subsp *lactis*
- *Lactobacillus reuteri*
- *L rhamnosus*

A technical review of 63 studies showed a reduction in all-cause mortality compared with placebo. The quality of evidence was moderate to high.

Numerous studies describe relative abundances of proteobacteria and decreased relative abundances of firmicutes and bacteroidetes prior to NEC onset.⁴ Preemptive optimization of the microbiome in such patients using probiotics is one strategy that has been studied many times. A systematic review of the literature had showed an overall preventive effect on NEC in preterm infants.⁵ Unfortunately, these studies are limited by heterogeneity of study protocols and treatment regimens.

A particular caution in this vulnerable population is the risk of infection. Current US preparations are manufactured as dietary supplements rather than as medications marketed for treatment. As such, probiotics are not subjected to the rigor of the US Food and Drug Administration's process for approval. However, in a meta-analysis that included more than 10,000 infants, the researchers observed with moderate certainty that probiotics reduce mortality and late-onset invasive infection.⁶ According to a survey of 500 US neonatal intensive care units, 14% prescribed probiotics for very-low birth weight neonates (70 out of 500).⁷

Discussion

In summary, the future is promising for the use of probiotics in pediatric patients. With respect to NEC, this intervention has a significant impact on reduction in death, length of hospital stay, and feeding intolerance.^{5,8,9} The recommendation is conditional for selecting infants for probiotic use because of substantial knowledge gaps (eg, regimen) and lack of a high-quality product with known purity and viability of organisms. The most recent American Academy of Pediatrics clinical report suggests that practitioners who use probiotics in select preterm infants use a formalized informed consent process, develop guidelines, and conduct surveillance.¹⁰

As we continue to explore microbiota and their implications for clinical practice and general health, probiotics continue to offer hope. Even with conditional recommendations, current evidence is optimistic. Limitations of the studies reviewed for these recommendations include small study samples, risk of bias, heterogeneity in patient populations and probiotic strains studied, lack of harms reporting, and variation in dosage of treatment.¹¹ An additional limitation is lack of product manufacturing details and access to products.

Upon review of my local big box store's food and supplement sections, I have found a plethora of products. Unfortu-

nately, the terminology is loose at best. Adding some bacteria to a food product or supplement does not make it a probiotic, as by definition it must be an adequate amount and confer benefit. How do we know if it is an adequate amount? Units of dosing for probiotics should be in colony-forming units, which indicate the number of viable cells. How do we know if it is effective? Our best bet is to use the strains specified in the AGA's guidelines for the indication. Some commonly available products include:

- VSL#3 junior (*B breve*, *B longum*, *Bifidobacterium infantis*, *L acidophilus*, *L planetarium*, *L paracasei*, *L bulgaricus*, and *Streptococcus thermophilus*)
- Align Kids (*B coagulans Lacto-Spore*)
- Culturelle Kids (*L rhamnosus* GG, *B animalis* subsp *lactis*)
- Similac Probiotic Tri-Blend (*Bifidobacterium lactis*, *B infantis*, *S thermophilus*)
- Biogaia (*Limosilactobacillus reuteri*)
- Gerber Soothe (*L reuteri*)
- Flora baby (*B breve*, *L rhamnosus*, *B bifidum*, *B infantis*, *B longum*)
- Florastor (*S boulardii*)
- Up and Up Children's Chewable Probiotic Supplement (*L rhamnosus* GG, *L acidophilus*)
- Garden of Life Baby (*B infantis* Bi-26, *B bifidum* Bb-06, *B longum* Bl-05, *B lactis* BL-04, *L rhamnosus* G6, *L acidophilus* La-14, *L reuteri* IE1)
- Evivo (*B infantis*)

Conclusion

The AGA conditionally recommends the use of 4 specific strains or combinations of probiotics for select children taking antibiotics who are at risk for *C difficile* infection, as use may reduce the overall risk. Use of a specific 8-strain product is conditionally recommended in pediatric patients with pouchitis. The AGA recommends against the use of probiotics in children with acute gastro-

enteritis. Lastly, the AGA conditionally recommends the use of 4 specific strains or combination products for select premature infants at risk for NEC.

High-yield future work includes securing pharmaceutical-grade products to reduce errors in cross-colonization, viability, purity, and dosing. The AGA plans to consider an update to these guidelines in 3 to 5 years.

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