PROBIOTICS USE IN PEDIATRIC PATIENTS: GENERAL PRINCIPLES

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INTRODUCTION

- 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

American Gastroenterological Association

GUIDELINE RECOMMENDATIONS

AMERICAN GASTROENTEROLOGICAL ASSOCIATION 2020 GUIDELINES

FOUR CONDITIONAL RECOMMENDATIONS IS FOR CHILDREN TAKING ANTIBIOTICS

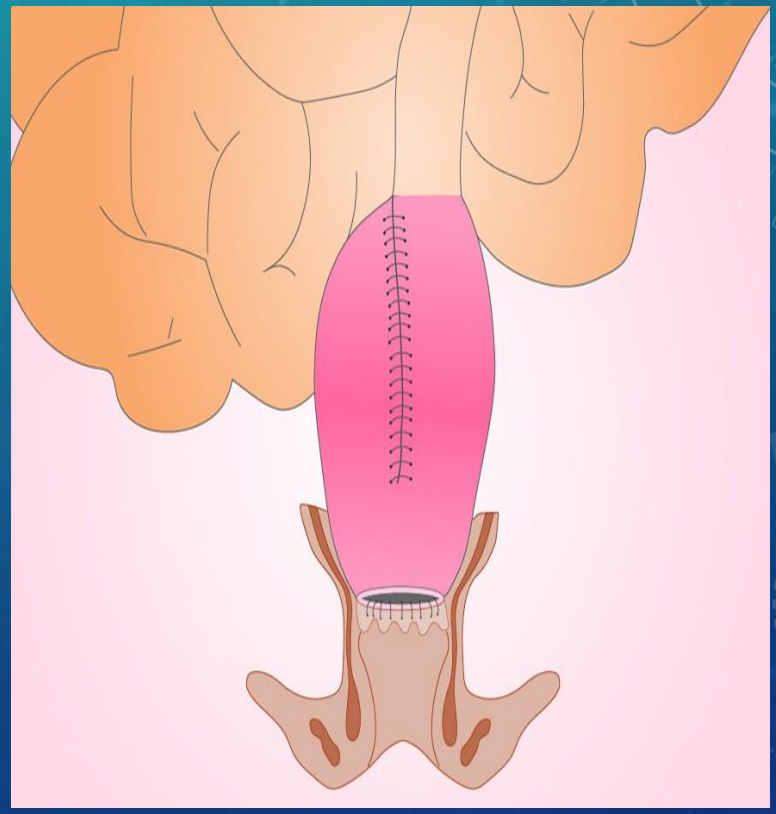
- The first conditional recommendations is for children taking antibiotics. The AGA recommends using a regimen containing the following bacteria over using no probiotics or other probiotics for preventing Clostridioides difficile infection:
  - Saccharomyces boulardii
  - 2-strain combination of Lactobacillus 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

FOUR CONDITIONAL RECOMMENDATIONS IS FOR CHILDREN TAKING ANTIBIOTICS (CONT.)

- 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.

FOUR CONDITIONAL RECOMMENDATIONS IS FOR CHILDREN TAKING ANTIBIOTICS (CONT.)

- The second conditional recommendation is for children with pouchitis. Pouchitis is a frequent complication after total proctocolectomy and ileal pouchanal 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.
- The overall quality of evidence is very low for this recommendation, mainly because of small sample sizes in all available studies.



FOUR CONDITIONAL RECOMMENDATIONS IS FOR CHILDREN TAKING ANTIBIOTICS (CONT.)

- 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

FOUR CONDITIONAL RECOMMENDATIONS IS FOR CHILDREN TAKING ANTIBIOTICS (CONT.)

- The third conditional recommendation is one familiar to most community pediatricians. 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.
- 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.

FOUR CONDITIONAL RECOMMENDATIONS IS FOR CHILDREN TAKING ANTIBIOTICS (CONT.)

- 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

FOUR CONDITIONAL RECOMMENDATIONS IS FOR CHILDREN TAKING ANTIBIOTICS (CONT.)

- A technical review of 63 studies showed a reduction in all-cause mortality compared with placebo. The quality of evidence was moderate to high.
- 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.
- According to a survey of 500 US neonatal intensive care units, 14% prescribed probiotics for very-low birth weight neonates (70 out of 500)
- APA does not recommend

OTHER RECOMMENDATIONS

- In patients with C difficile infection, we recommend the use of probiotics only in the context of a clinical trial.
  - The technical review identified 5 placebo-controlled randomized controlled trials (RCTs) evaluating probiotics as adjunct treatment with antibiotics, testing 4 different probiotic formulations. The patient populations across studies differed, including patients with an initial C difficile infection, recurrent infection, or both. Probiotics or placebo was administered together with metronidazole or vancomycin at low dose or high doses. Due to these variations in the study design, as well as in clinical outcomes, data were deemed too heterogeneous to be pooled in the analysis. All 5 published studies contained uncertain or high risk of bias regarding blinding of outcome assessment and selective reporting.

OTHER RECOMMENDATIONS (CONT.)

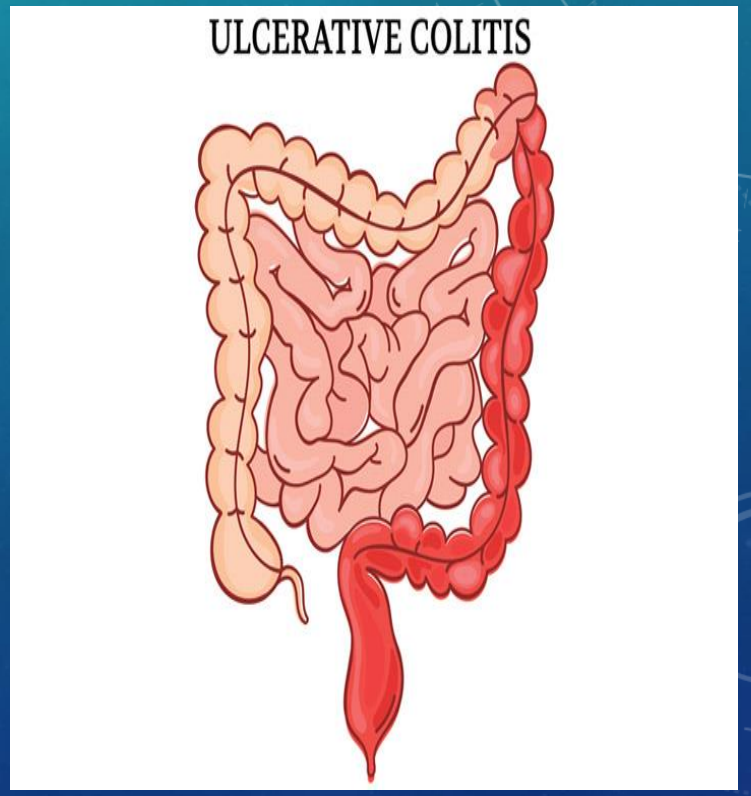
- While currently available data suggest that some probiotics might be beneficial in treatment of C difficile, further studies with standardized study design and larger number of patients are needed to define those probiotics, as well as to identify which patient populations may benefit from this intervention.

OTHER RECOMMENDATIONS (CONT.)

- In adults and children with Crohn's disease, we recommend the use of probiotics only in the context of a clinical trial.
  - The overall quality of the evidence was rated as low for induction of remission and maintenance of remission. Given the overall small study samples, as well as heterogeneity in patient populations, probiotic strains studied, and study design, it is unclear whether there is potential for specific probiotic strains to be beneficial for either induction or maintenance of remission in Crohn's disease. Further studies are needed to define specific populations of patients with Crohn's disease who might benefit from probiotics, as well as the most effective probiotic strains.

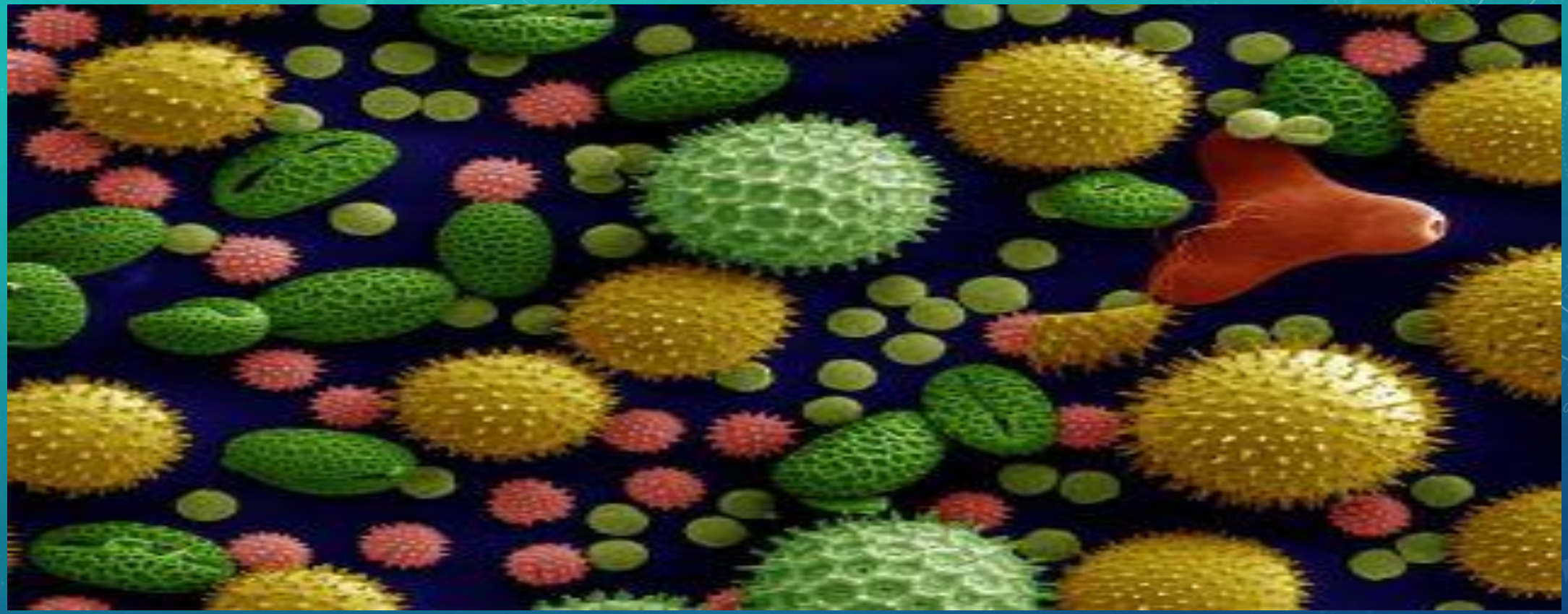
OTHER RECOMMENDATIONS (CONT.)

- In adults and children with ulcerative colitis, we recommend the use of probiotics only in the context of a clinical trial.
  - Available evidence is limited by small sample sizes, differences in patient populations, variability in study design, and heterogeneity in the probiotic formulations used. The most extensively tested formulation was the 8-strain combination of L paracasei subsp paracasei, L plantarum, L acidophilus, L delbrueckii subsp bulgaricus, B longum subsp longum, B breve, B longum subsp infantis, and S salivarius subsp thermophilus for induction of remission, although even here the available studies were limited by potential for bias and pooled results did not show evidence of benefit. Further research is needed



OTHER RECOMMENDATIONS (CONT.)

- In symptomatic children and adults with irritable bowel syndrome, we recommend the use of probiotics only in the context of a clinical trial
  - In the remainder of the studies, the majority of the single RCTs using different probiotic and probiotic combinations of variable duration reported some benefit, but the sample sizes were all relatively small and had significant differences in study subjects and designs.
  - The overall quality of evidence was very low. There was also significant concern for publication bias, as the Technical Review team found numerous registered protocols that yielded no peerreviewed publications or results that were publicly available. Although there has been significant interest and potential for the use of probiotics in IBS, further studies are needed to clarify this important question



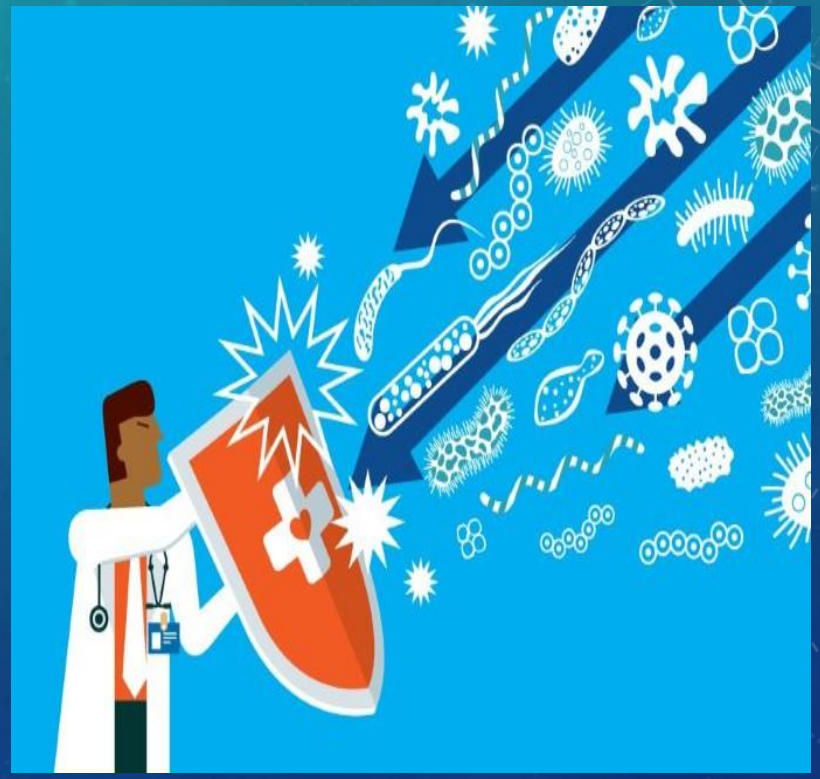
PROBIOTICS IN ALLERGIC DISEASE

PREVENTION

- There is evidence from animal models and in vitro studies that gut microbiota modulate immune programming and can prevent the allergic phenotype. However, there is still an incomplete understanding of the optimal patterns of colonization for promoting immune tolerance and the possible impact of prebiotics and probiotics in this process.
- Meta-analyses suggest a benefit of probiotics in reducing the development of eczema, but not any other allergic outcomes, in at-risk infants (defined as presence of a biologic parent or sibling with asthma, allergic rhinitis, eczema, or food allergy). However, the effect is moderate, and the only probiotic strain with reproducible data is Lactobacillus rhamnosus GG (LGG). In addition, the great heterogeneity of the studies makes it difficult to advise on specifics regarding therapy (eg, strains, dose, timing, and duration). Prebiotics and synbiotics, which are anticipated to have a more global effect on the gut microbiota, have shown some promise, but further studies are needed

PREVENTION

- We suggest not giving probiotics during pregnancy, lactation, and infancy for the prevention of eczema (Grade 2C). However, we do not discourage this approach if parents/caregivers express strong interest and there is a family history of atopic disease, given the low risk of adverse events and modest potential for benefit. Parents/caregivers who choose this approach should first discuss it with the appropriate clinician (eg, obstetrician, pediatrician, other primary care provider).



TREATMENT

- There is no definitive evidence that prebiotics, probiotics, or synbiotics have efficacy in the treatment of any allergic conditions. Several meta-analyses suggest no benefit of probiotics in the treatment of eczema or asthma. Two meta-analyses reported a beneficial effect of probiotics in the treatment of allergic rhinitis, and studies evaluating prebiotics and synbiotics in the treatment of allergic disease show some promise. However, further studies are needed before any definitive conclusions can be drawn.

WARNINGS/PRECAUTIONS/ INTERACTIONS

WARNINGS/PRECAUTIONS

- **Disease-related:**
  - Immunocompromised patients: Use dietary supplements containing live bacteria or yeast with caution in immunocompromised patients. A fatal case of GI mucormycosis caused by the mold Rhizopus oryzae has been previously reported in a premature infant administered a dietary supplement containing 3 species of live bacteria.

WARNINGS/PRECAUTIONS (CONT.)

- **Dosage form specific issues:**
  - Interchangeability: Significant differences may exist from one preparation compared to another with respect to biologic activity and composition.
  - Lactose: Some products may contain lactose; use with caution in patients with lactose intolerance.

WARNINGS/PRECAUTIONS (CONT.)

- **Other warnings/precautions:**
  - Dietary supplement: Probiotics are classified as dietary supplements; therefore, there are no safety reviews or approved therapeutic indications by the FDA. There is no conclusive evidence to support widespread use in the treatment of diarrhea.

WARNINGS/PRECAUTIONS (CONT.)

- **Warnings: Additional Pediatric Considerations**
  - Dietary supplements containing live bacteria or yeast may be associated with a risk of invasive fungal disease in the immunocompromised. A premature neonate developed a fatal case of GI mucormycosis caused by Rhizopus oryzae; this mold was found in an unopened bottle of ABC Dophilus powder that was used to treat the infant
  - Case reports of Lactobacillus sepsis have also been reported in at least 5 pediatric patients (ages 18 days to 17 years) treated with Lactobacillus Rhamnosus GG

WARNINGS/PRECAUTIONS (CONT.)

- **Warnings: Additional Pediatric Considerations**
  - The AAP recommends avoiding use of probiotics in pediatric patients who are seriously or chronically ill, including ill preterm neonates and patients with indwelling medical devices or IV catheters.
  - Other trials evaluating the addition of probiotic formulations (various live bacteria/yeast have been reported) to infant formula have reported no adverse effects when used in healthy infants. Use with caution; Lactobacillus-containing products are considered a dietary supplement and therefore less regulated by the FDA in terms of production, safety and efficacy, and definitive data reporting in these areas are lacking

INTERACTIONS

- Theoretically antibiotics could affect the probiotics effects, specially clindamycin and beta lactams
- It is better if this complements are avoided in patients using immunosuppressant drugs such as corticosteroids

GOOD LUCK AND GOODBYE