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Clinical Response

Probiotics in Infants

The Clinical Services Team has created this document to answer the clinical question related to current practice recommendations around the use of probiotics in infants.

Product

Probiotics are defined as live microorganisms that when applied to a human host in adequate amounts achieve an alteration of the microflora and result in a positive effect on health.[1] Often referred to as "good bacteria," common strains of these organisms include, but are not necessarily limited to members of the genera Lactobacillus and Bifidobacterium.[2] As reported by the National Institutes of Health (NIH), National Center for Complementary and Integrative Health (NCCIH), there is extensive research studying the efficacy of probiotic bacteria in the health and wellness of adults and children.[3] Specific disease conditions that have been studied include, but are not limited to gastrointestinal disorders like clostridium difficile infection, inflammatory and irritable bowel disease, dental disorders like periodontal disease and dental caries, allergic conditions like allergic rhinitis, asthma, and atopic dermatitis, and other various conditions like acne, hepatic encephalopathy, and urinary infections as examples. Specific to infants, conditions under study include infant colic, necrotizing enterocolitis (NEC), and sepsis.[3] As described by the NCCIH, while research is extensive and promising in some cases, the safety and overall effectiveness of probiotics largely remains inconclusive.[3] However, in the 2012 National Health Interview Survey (NHIS), probiotics and prebiotics were reported as the third most common dietary supplement taken by adults and are often found in infant formulas or recommended by pediatricians for breastfed babies.[3, 4] Of note, *probiotics* should not be confused with *prebiotics*, which are typically nondigestible oligosaccharides, either naturally occurring or additive which aid in the proliferation of certain strains of probiotic bacteria. Similarly, *probiotics* differ from *postbiotics* in that the latter is the byproduct of the metabolic process of probiotics.[5]

Clinical Practice Guidelines

Current evidence related to clinical practice guidelines is inconclusive, and in some cases contradictory. The following is provided as a sample of evidence supporting clinical practice.

- In 2021, the American Academy of Pediatrics (AAP) issued a clinical report on the use of probiotics in preterm infants. Citing the lack of FDA regulation and wide variation in practice, the report states that the universal use of probiotics is not supported by clinical evidence in this vulnerable population.[6]
- In 2020, the American Gastroenterological Association (AGA) issued clinical practice guidelines related to the use of probiotics in the management of gastrointestinal disorders. For preterm infants (<37 weeks gestational age), the AGA recommends specific combination probiotic strains (see reference) over no treatment for the prevention of NEC citing moderate/high evidence.[7]

Clinical Evidence

Clinical evidence for this topic is extensive and evidence related to the use of probiotics is specifically defined by the clinical question and population of study. There are multiple Cochrane Reviews in a search of *probiotics and*

infants and greater than one thousand meta-analyses, reviews and systematic reviews with probiotics as a major MeSH topic in the PubMed database. The following summaries are provided as a sample of the available literature.

- A Cochrane Review titled Probiotics to Prevent Infantile Colic by Ong et al. (2019) reviewed six randomized control trials (RCTs) (1,886 participants) to evaluate the use of prophylactic probiotics for colic in infants less than one month of age. The authors reported the evidence related to preventing infantile colic in probiotic vs. placebo is "low certainty" due to potential study bias and is largely inconclusive. However, the overall crying time appeared to be reduced in infants in the probiotic groups, with no difference in adverse events reported between groups. The authors did not recommend a change in practice as a result of their synthesis, suggesting additional evidence is needed.[8]
- A Cochrane Review titled Maternal Probiotic Supplementation for Prevention of Morbidity and Mortality in Preterm Infants by Grev et al. (2018) reviewed 12 RCTs (1,450 mothers, and 1,204 infants) to 1) evaluate the efficacy of maternal probiotic administration on preterm birth and preterm infant morbidity and mortality and 2) evaluate the efficacy of maternal probiotic administration vs. placebo, no intervention or neonatal probiotic administration on prevention of mortality and preterm infant morbidities. The authors reported that the quality of the evidence was low and therefore insufficient to draw conclusions related to the benefit of probiotic administration. More research is required.[9]
- A Cochrane Review titled Probiotics for the Prevention of Pediatric Antibiotic-Associated Diarrhea by Guo et al. (2019) reviewed 33 RCTs (6,352 participants) for children 0-18 years of age who received antibiotics, comparing probiotics to placebo, active alternative prophylaxis or no treatment. The authors reported the evidence was "moderate" in quality and suggested probiotics have a positive effect in the prevention of antibiotic-associated diarrhea. The authors note the potential for adverse events in immune-compromised children and recommend more research in the form of large trials to evaluate specific probiotic strains.[10]
- A meta-analysis by Chi et al. (2021) reviewed 45 RCTs (12,320 participants) to compare probiotic supplements for premature infants. Primary outcomes included morbidity and mortality of NEC. The authors determined specific combinations of bifidobacterium, lactobacillus, and prebiotic showed positive effects on mortality and NEC morbidity.[11]
- A systematic review by Simonson et al. (2021) reviewed 15 RCTs and five meta-analyses reporting an approximately 50% reduction in overall infant crying time as compared to placebo in breastfed infants. However, the evidence was inconclusive with respect to efficacy of probiotics to prevent infant colic.[12]

Summary/Considerations:

Additional safety considerations are noted throughout the literature. These include, but are not limited to the following information:

- According to the NCCIH, government regulation of probiotics is specifically determined by their intended use. If sold as a dietary supplement, FDA approval is not required.[3] Pharmaceutical grade probiotics are not currently available in the United States and as no premarket approval is required for their use in food or supplements, it is up to the manufacturer to meet safety requirements.[13, 14]
- The International Scientific Association for Probiotics and Prebiotics (ISAPP) describes the need for detailed attention and consideration prior to the use of probiotics. The ISAPP notes that certain high-risk

populations (immunodeficiency, short bowel syndrome, premature infants) may be at greater risk of adverse event.[13]

- The National Institutes of Health Office of Dietary Supplements additionally commented on the safety of probiotics, noting that reported opportunistic infections resulting from probiotic use are negligible when compared to the overall number of probiotics consumed globally. However, further studies on safety are needed to address specific gaps in the evidence.[15]

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