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Are probiotics ready for prime time?

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Editor's note: *This is the second of a three-part series on prebiotics, probiotics and dietary supplements. Read the first article at http://bit.ly/347g6Nm.*

During the last 100 years, a variety of probiotic agents have been studied as single agents or combination therapies. A possible role for probiotics has been evaluated in several clinical settings, including amelioration of inflammatory bowel disease (IBD), *Clostridioides difficile* colitis and infantile colic, and reduction of risk of preterm birth, late onset neonatal sepsis and necrotizing enterocolitis.

Considerable differences exist in the bioavailability, biological activity, composition and doses of probiotics studied as well as length of time administered. Published studies of probiotics suggesting benefit and absence of harm have not been reproduced successfully using a rigorous clinical trial.

Inflammatory bowel disease

Most probiotic studies in patients with IBD, including Crohn's disease and ulcerative colitis, had small sample sizes, less than optimal controls and reported inconsistent results. In particular, probiotics have not been shown to induce or maintain remission in patients with Crohn's disease.

Genetic and environmental factors are recognized risk factors for IBD but do not fully explain the rates of disease, indicating that other environmental influences remain to be identified. Studies have not found a single pathogen associated with IBD, but studies have described an association between IBD and changes in the intestinal microbiome.

Preterm birth and vaginal seeding

One of the leading causes of morbidity and mortality in infants is preterm birth. Efforts are focusing on the role of the microbiome on preterm birth and maternal-infant death.

The microbiome study in pregnancy is an ongoing project supported by the National Institutes of Health to evaluate the influence of the vaginal microbiome on pregnancy, pregnancy-related complications and the impact on the infant microbiome.

Vaginal seeding involves the attempt to transfer the vaginal flora to the nose, mouth or skin of a newborn, particularly in the setting of delivery by cesarean section. The intention is to reduce the risk of asthma, atopic disorders and immune disorders in the newborn.

However, the safety and benefit of this practice are not known. Vaginal seeding is associated with a risk of infection of the newborn by pathogens such as herpes simplex virus and group B streptococcus. The American College of Obstetricians and Gynecologists states that this practice should not be performed outside of a research protocol approved by an institutional review board.

Infantile colic

Infantile colic is defined as periods of inconsolable crying that start around 2 weeks of age, peak at 6 weeks and generally resolve spontaneously by 3 months of age. The condition occurs in both bottle-fed and breastfed infants and consists of flexion of the legs, flatulence, abdominal distention and periodic, incessant crying in an apparently healthy infant. In some instances, the condition has been associated with intolerance to cow's milk protein or lactose.

Studies have reported differences in the intestinal microbiome of infants with colic when compared to infants without colic. This observation has led to the theory that providing probiotic bacteria might enhance gut function and reduce the symptoms associated with colic.

A 2019 Cochrane review of reports on this topic found no evidence that probiotics are more effective than placebo at preventing infantile colic, although daily crying time may have been reduced in infants receiving probiotics (Ong TG, et al. *Cochrane Database Syst Rev.* 2019;3(3):CD012473).

Which of the following statements are true?

a) Most dietary supplements have not been evaluated in pregnant women, lactating women or children.

b) Some dietary supplements may increase the risk of bleeding or affect response to anesthesia during surgery.

c) Gastric acid suppression medications are associated with an increased risk of *C. difficile* colitis in children and adults.

d) More than one-fifth of all estimated emergency department visits for adverse events related to diet supplements were caused by unsupervised ingestion by children.

Answer: All statements are true.

Antibiotics alter the microbiome of the gastrointestinal tract, at times resulting in *C. difficile* colitis or causing other types of antibiotic-associated diarrhea. The incidence of diarrhea in children who receive broad-spectrum antibiotics has been reported to exceed 10% and is thought to be caused by an overgrowth of enteropathogenic bacteria. The rationale for probiotic administration in this setting is to maintain or to re-establish a balanced microflora that resembles the pre-antibiotic bacterial population in the intestine.

A recent Cochrane review of 33 studies found a possible protective effect from probiotics in the prevention of antibiotic-associated diarrhea and in reducing diarrhea by less than one day (Guo Q, et al. *Cochrane Database Syst Rev.* 2019;4:CD004827). Noted shortcomings in the studies included:

- loss to follow-up of more than 20% overall,
- use of different probiotics (*Bacillus spp, Bifidobacterium spp, Clostridium butyricum, Lactobacilli spp, Lactococcus spp, Leuconostoc cremoris*, *Saccharomyces spp*, *Streptococcus spp)*,
- different definitions of diarrhea (some studies defined incidence and others defined duration),
- variation in dosing of probiotic (some studies used less than 1 billion colony forming units (CFU)/day and other studies used more than 1 billion CFU/day),
- variation in etiology of diarrhea (studies included patients with rotavirus, salmonella, shigella or *C. difficile*),
- use of different number of probiotics (some studies used a single probiotic and some used more than one probiotic) and
- different durations of probiotic administration.

In view of the inconsistency of study protocols and results, it appears premature to assume the benefits of probiotics outweigh the risks in any setting. While some clinical trials suggesting benefit are of high quality, other well-performed clinical trials report lack of benefit, indicating that incompletely understood factors are involved. Thus, an evidence-based recommendation for use of probiotics is not possible at this time.

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