To give or not to give probiotics to preterm infants

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Should probiotics be routinely used in preterm infants? This is one of the most common questions asked with regard to probiotics. In this issue of the Journal, Athalye-Jape et al. (1) present the results of a meta-analysis (search date: April 2014) that assessed the effects of probiotic supplementation on enteral feeding in preterm (gestational age <37 wk) or low-birth-weight (<2500 g) infants. Compared with the control group, preterm neonates in the probiotic group had a reduced time until full enteral feeding (19 randomized controlled trials, n = 4527; mean difference: −1.54 d; 95% CI −2.75, −0.32 d).

The findings are not new. Previously, a Cochrane review also reported a reduced time until full enteral feedings (2). However, the current meta-analysis is based on a larger number of studies. Although the time to reach full enteral feeding is important in neonatal intensive care units, necrotizing enterocolitis (NEC), sepsis, and death are more important issues. A number of earlier meta-analyses consistently showed that there are significant benefits of probiotic supplementation (as a group) in reducing the risk of NEC and all-cause mortality, but not of sepsis, in preterm neonates.

But can we trust the results of meta-analyses on probiotics? The Cochrane Handbook recommends that data be pooled only if the data summarized are homogeneous [i.e., the participants, intervention, comparison, and outcomes must be similar (homogeneous) or at least comparable]. With regard to probiotics (intervention), the current standpoint is that the health effects of probiotics seem to be strain specific. If so, pooling data from different genera, species, strains, and dosages of probiotics obtained in different settings and populations is highly questionable, and no change in practice should be made.

Recently, this standpoint was challenged. The International Scientific Association for Probiotics and Prebiotics (ISAPP) posed the question of whether there are core benefits that can be attributed to the general category of probiotics (3). The ISAPP experts proposed 3 possible main mechanisms of action of probiotics (widespread, frequent, and rare). In brief, widespread mechanisms are thought to be common among probiotic genera. Examples of these mechanisms include colonization resistance, acid and short-chain fatty acid production, regulation of intestinal transit, normalization of perturbed microbiota, increased turnover of enterocytes, and competitive exclusion of pathogens. Frequent mechanisms, considered to be common among probiotic strains, include vitamin synthesis, direct antagonism, gut barrier reinforcement, bile salt metabolism, enzyme activity, and neutralization of carcinogens. Finally, rare, strain-specific effects include immunologic effects, the production of specific bioactives, endocrinologic effects, and neurologic effects. It is likely that several mechanisms operate simultaneously; however, it is considered unlikely that a given individual probiotic might exert all mechanisms. The ISAPP also concluded that evidence is accumulating across probiotic strains. If so, some generalizations can be made beyond strain-specific effects.

This ISAPP concept may be substantiated. Indeed, a number of meta-analyses demonstrated that certain health effects may be attributed to many, if not all, probiotics. Examples of such meta-analyses in which most trials showed a positive effect include the effects of probiotic administration on the risk of NEC (2), acute gastroenteritis (4), or antibiotic-associated diarrhea (5). Also, in the meta-analysis by Athalye-Jape et al. (1), an improvement in the time to achieve full feedings was found irrespective of whether bifidobacterium or non–bifidobacterium strains, or whether single or multiple strains, were used.

However, this approach is not without danger. For example, in the meta-analysis by Athalye-Jape et al. (1), heterogeneity between the trials was very high (I² = 93%), which leaves one to question whether the benefit is a true class effect. Rather, it suggests that differences between individual probiotic strains are of importance. This has been shown as well by the largest study to date, which showed no effect of a probiotic combination on mortality rates (6).

In research, such disagreements are common. Eventually, they are resolved by collecting more data or they are replaced by more sophisticated, or entirely new, hypotheses. However, clinicians do not want to wait. They want clear answers to guide their clinical practice. Hence the question: Should probiotics be routinely used in preterm infants?

Currently, there is no agreement with regard to this question. The recommendations from the scientific organizations (7–9), although focusing mainly on the prevention of NEC, are in agreement that the presently available data do not permit recommending the routine use of probiotics in preterm infants. However, a number of worldwide known experts have called for a change in practice.  

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Perhaps the most interesting is one statement expressed by 2 authors that differed in their opinions in 2010 (10, 11). However, 4 y later, one of them changed his previous view that more evidence is needed. This allowed both of them to write a joint commentary, the title of which speaks for itself: “Probiotic Supplementation in Preterm Infants: It Is Time to Change Practice” (12).

Even if one agrees with this position, there are some practicalities with regard to the use of probiotics. One of us (HS) resides in a setting in which there are tens of different probiotic products available. Is there really enough evidence to say that one may use any probiotic product available? We doubt it. Moreover, many clinicians have concerns with regard to the reliability of some of the products currently on the market. On the other hand, one of us (JBvG) comes from a country where probiotics are not licensed to be prescribed to preterm infants, and one needs to seek permission to import a specific product. How does one proceed in such circumstances? Some hints were provided by Deshpande et al. (13), but worldwide, not everyone is in such a favorable situation that they can import a probiotic with documented efficacy into the country.

Back to the question asked earlier: Should probiotics be routinely used in preterm infants? In settings in which the incidence of NEC is high, one may consider the use of probiotics—single or in combination. However, care should be given to choose those that are the best studied, with the highest effect size, and the best safety profile. Still, more trials are needed. Many readers may find this disappointing.

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