See corresponding article on page 1219.

Probiotics in routine clinical care of moderately preterm infants

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Although outcomes of preterm infants have improved over time, neonatal morbidities remain common and contribute to adverse long-term neurodevelopmental outcomes (1). The vulnerability of preterm infants to many morbidities is thought to be, in part, related to abnormal development of the intestinal microbiome. Whereas the intestine of breastfed full-term infants is colonized by commensal bacteria including *Bifidobacterium* spp. that are specially adapted to the infant gut, the microbiome of hospitalized preterm infants is typically dominated by facultative anaerobes including *Staphylococcus*, *Enterococcus*, and the *Enterobacteriaceae*, such as *Klebsiella* and *Enterobacter* (2). These organisms are common causes of sepsis in preterm infants (3). Studies have shown that intestinal dysbiosis, characterized by low bacterial diversity and increased relative abundance of *Enterobacteriaceae,* can precede the development of necrotizing enterocolitis and postnatal growth failure in preterm infants (4, 5).

Probiotics are live microorganisms that confer health benefits to the host. Probiotics have been extensively studied as a therapy to prevent necrotizing enterocolitis and other adverse outcomes in preterm infants. Meta-analyses of randomized trials indicate that probiotics reduce the risk of necrotizing enterocolitis, late-onset sepsis, and mortality in preterm infants (6–8). In addition to data from clinical trials, a number of observational studies support the effectiveness of probiotics in clinical practice (9, 10). As such, probiotics are increasingly provided to infants in the neonatal intensive care unit (NICU) (10), yet questions remain regarding the optimal strains, dose, timing, and treatment population. With variation in treatment practices, product availability, and baseline incidence of neonatal morbidities across individual NICUs, single-center studies have potential to provide important data on treatment effects of specific probiotic preparations and implementation strategies in different clinical settings.

In this edition of the Journal, Bommer et al. (11) use an approach known as regression discontinuity (RD) design to evaluate the effectiveness of routine probiotic supplementation on infant outcomes in a neonatal care center. This quasi-experimental design is useful when the decision to provide a therapy is based on a threshold of a continuous variable. In this study, hospital guidelines recommended probiotic therapy for preterm infants with a birth gestational age (GA) threshold of <34 wk. In RD design, treatment effects are estimated by comparing subjects above and below the treatment threshold. A key assumption of this approach is that pretreatment characteristics and potential outcomes are continuous around the threshold. If this assumption is met, individuals falling just above and just below the threshold should be similar in observed and unobserved characteristics, and treatment assignment can be considered effectively random within a narrow window around the threshold.

The study outcomes were late-onset sepsis and *z*-scores for weight and length at hospital discharge. Data were collected from the electronic health records of infants born between 30 and 38 wk of gestation. Two different probiotic preparations were used, each of which contained >1 probiotic strain. The authors first conducted "intention-to-treat" analyses of infants above and below the <34-wk-GA threshold. However, because hospital guidelines for probiotic use were not mandatory, many (37.5%) infants with birth GA <34 wk did not receive probiotics, and some (3.1%) infants with GA ≥34 wk received probiotics. To address this partial compliance issue, the investigators conducted additional analyses in which the treatment threshold was used as an instrumental variable for actual treatment exposure. The threshold was used to predict the likelihood of receiving probiotics, and the likelihood of receiving treatment was then used to estimate the effect of the probiotics on the study outcomes.

The results showed no significant treatment effects of probiotics on any of the clinical outcomes. These findings were consistent in both the "intention-to-treat" analyses and when accounting for partial compliance with guidelines. As noted, a key assumption in RD design is that no potentially relevant variables, except treatment exposure, change discontinuously around the threshold. To meet this assumption, it is important that other treatments are not assigned by the same threshold. The investigators adjusted the analyses for diet to ensure results were not confounded by GA-specific nutritional practices. It was not specified whether any other GA-based guidelines were used, such as criteria for antenatal steroids or direct NICU admission, but the investigators performed multiple "placebo regressions" to ensure

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Abbreviations used: GA, gestational age; NICU, neonatal intensive care unit; RD, regression discontinuity.

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that the treatment threshold was not predictive of other infant characteristics or therapies.

An important factor in the interpretation of these results is that although RD design is useful to estimate local treatment effects around the threshold, these estimates might not be generalizable to observations further from the threshold. In this case, the absence of a significant treatment effect at the 34-wk-GA threshold does not disprove a significant effect in infants born at lower GAs, but rather suggests that extending probiotic use to include moderately preterm infants did not have a beneficial effect on sepsis or anthropometrics at discharge. Many probiotic trials have focused on very preterm (<32-wk-GA) infants (6, 7), who have higher rates of morbidity and mortality. The treatment threshold of <34 wk GA was likely selected to ensure all infants with potential to benefit from probiotics would receive treatment, but the absolute treatment benefit would be expected to diminish as infants neared the threshold given the low incidence of sepsis, growth failure, and necrotizing enterocolitis in this GA group. This low expected benefit likely contributed to the limited compliance with treatment guidelines near the threshold. Although trials and observational studies support the safety of probiotics in preterm infants (6, 7, 9, 10), cost and safety considerations should be balanced with the potential for benefit when selecting target infant populations for probiotic therapy.

The effect of probiotics on postnatal growth has not been studied to the same extent as necrotizing enterocolitis or sepsis. Some studies have reported a beneficial treatment effect, but findings have been inconsistent (7, 9). In this study, mean weight and length *z*-scores declined between birth and discharge in the overall cohort, but probiotic use was not associated with *z*-scores at discharge. The mean duration of hospitalization, and thus treatment, was relatively short among infants near the threshold, and part of the decline in *z*-scores in this time frame could reflect normal postnatal physiological adaptation. It is possible that effects on growth could be observed with longer treatment durations. Postnatal growth failure remains a major problem, especially among extremely preterm infants. Further study is needed to understand the metabolic effects of specific probiotics and their interaction with diet in an effort to identify strains with potential to improve nutrition and growth in preterm infants.

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