

VIEWPOINT

Improved Neonatal Outcomes With Probiotics

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Evidence is a spectrum. The US Food and Drug Administration (FDA) Guidance for Industry¹ states that “[w]ith regard to quantity, it has been FDA’s position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.” However, in practice, care is often changed if standard of care is limited, if the underlying disease is severe, or if the new treatment is comparatively safe. In October 2012, a commentary in *JAMA* stated that “[u]nlike treatments used in other fields of medicine, most medications administered to preterm infants lack convincing data to support their safety and efficacy with more than 90% not approved...for the prescribed indication. No new medications have substantially improved outcome for preterm infants since the introduction of antenatal corticosteroids and surfactant 15 to 20 years ago.”^{2(p1493)} There are many potential reasons for this, including a lack of financial incentives, the expense of clinical trials, the difficulty in conducting trials in neonatal intensive care units, and FDA regulations. This need not be the case, as more than 5 well-conducted clinical trials have shown that probiotics can greatly improve the mortality and morbidity of preterm infants. We call for a paradigm shift in US neonatal intensive care units with an impact potential similar to that seen with the universal uptake of respiratory surfactant.

Prematurity, prolonged hospitalization, immunodeficiency, broad-spectrum antimicrobials, and delayed enteral feeding are challenging ways to begin life. Yet this is the environment for approximately 475 000 premature infants born annually in the United States who are at considerable risk of necrotizing enterocolitis (NEC), a devastating disorder. The projected economic burden of NEC has been reported to be as high as 1 billion dollars per year in the United States, without accounting for the long-term care of impaired survivors and death.³

Although our understanding of the physiological mechanisms of NEC and its risk factors remains incomplete, a common trigger appears to be perturbation in the intestinal microbiota. Probiotic supplementation provides beneficial microorganisms to a microbiologically perturbed gut. Dissenters claim that the heterogeneity of product, dose, and indication in probiotic intervention studies makes it difficult to compare individual study results. However, a Cochrane review by Alfaleh et al⁴ published in 2011 identified 16 eligible trials of 2842 preterm infants (<37 weeks’ gestational age or with a birth weight of <2500 g). Although there was variability in subject demographics, in probiotic products used, and in dosing, the review concluded that enteral probiotic supplementation significantly reduced the incidence of NEC (relative risk, 0.35 [95% CI, 0.24-0.52]) and mortality (relative risk, 0.40 [95% CI, 0.27-0.60]). Notably, there was no evidence of sepsis associated with probiotic products in the trials. As readers are aware, Coch-

rane reviews are very conservative with the wording of their conclusions and data interpretation; however, Alfaleh et al⁴ state that their “updated review of available evidence supports a change in practice.” It is difficult to find such a definitive conclusion statement in other contemporaneous Cochrane reviews.

Owing to the increased use of probiotics in pediatric practice, representatives from the American Academy of Pediatrics conducted a review of probiotic applications, published in 2010, which concluded that “there is some evidence that probiotics prevent necrotizing enterocolitis in very low birth weight infants (birth weight between 1000 and 1500 grams), but more studies are needed.”^{5(p1217)} The questions remain: how much more evidence is needed, and of what quality? This cautious way of thinking on the part of the American Academy of Pediatrics has contributed to the failure to improve outcomes for preterm infants over the last 15 to 20 years. The authors of the American Academy of Pediatrics review⁵ did not discuss the regulatory roadblocks that have halted clinical trials with probiotics in the United States or the fact that currently no studies are being conducted. A review of the clinical trials registry, ClinicalTrials.gov, in January 2013 yielded 16 registered trials with the terms *probiotic* and *necrotizing enterocolitis*; none are being conducted in the United States.

The FDA Center for Biologic Evaluation and Research is committed to policies that effectively prohibit probiotic efficacy trials in the United States, even though such trials are commonplace in other countries. Although probiotic products are sold at every supermarket and are present on hospital formularies, the FDA demands that probiotic research that makes a health claim obtain an investigational new drug application. Because dosing and safety data from one strain may differ from another strain, each strain or multistrain product requires a separate investigational new drug application. Limited funds and protracted time lines make this approach untenable both for manufacturers and for researchers. The absurdity of this approach for probiotics is underscored when compared with the recent apparent acceptance of a completely novel approach to managing *Clostridium difficile* infection, fecal transplantation, a process by which undefined mixtures of colonic microbes are administered to the patient. Fecal transplantation now has a *Current Procedural Terminology* code and is widely accepted as a means of altering the colonic microbiome. However, well-defined probiotics, generally recognized as safe for use in foods and infant formulas, are precluded from use in phase 3 or phase 4 clinical trials. In neonatal intensive care units, antibiotics are readily used on our youngest patients and on our most at-risk patients without FDA approval.

The safety of any intervention must be closely considered, and its use monitored, especially with regard to

medically fragile neonates. Sporadic cases associating the administration of a probiotic with the isolation of a molecularly matched organism from a sterile site in premature neonates have been reported. Invasive infections have also been associated with the consumption of human milk. Anaphylaxis, drug reactions, and immune-mediated complex syndromes have been associated with antimicrobials. Yet we still advocate that premature neonates receive human milk and antimicrobials. Every intervention has its risks. Of greater risk is the unmonitored, unguided use of probiotics in neonates without appropriate follow-up and documentation.

As the debate in the United States regarding routine probiotic supplementation continues, other countries are satisfied with the current evidence and use probiotics routinely. In Australia, a probiotic product is offered to premature neonates receiving care in academically affiliated hospitals with a catchment area of 350 000 persons.⁶ The Therapeutic Goods Administration of Australia (equivalent to the US FDA) provided permission to use probiotics under strict regulatory guidance, with informed consent and opt-out options.

Weighing the potential benefits and risks to the individual child, as well as to the neonatal community, most countries conclude that the evidence for the use of probiotics in the prevention of NEC is strong, but they follow their recommendations with a call for larger, well-designed, randomized placebo-controlled trials. Although we concur with the need for rigorous, well-designed studies, the complex issues associated with conducting the ideal study have halted progress in the United States, and unless the FDA revises its policies, these studies will not be conducted in a US setting for the next 20 to 30 years. We propose that the administration of probiotics to prevent NEC be studied in a comparative effectiveness design, similar to the forward-thinking approach of our Australian colleagues. In this way, the benefits of probiotics will be received by at-risk neonates, and the requirements for strict monitoring will be fulfilled. This strategy will combine an evidence-based approach and a rational approach to improve neonatal outcomes. The other option is to continue with the standard of care, in which no new products are provided; we believe that this last option is ethically unacceptable.

ARTICLE INFORMATION

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