Revisiting the use of probiotics in premature infants for the prevention of NEC

— **Emily Heikamp, MD, PhD, MSc**

Necrotizing enterocolitis (NEC) is a major cause of morbidity and mortality among premature infants. One strategy for prevention of NEC is to administer probiotics to alter the balance of the gut microbiome in favor of non-pathogenic bacteria. A meta-analysis of 24 randomized controlled trials (RCTs) has concluded that probiotics reduce the incidence and mortality of severe NEC (*Cochrane Database Syst Rev* 2014;10:CD005496). However, none of these trials were conducted in the United States, and none have examined the safety and efficacy of *Lactobacillus rhamnosus* GG (LGG, Culturelle), the most commonly used probiotic in the US. Importantly, probiotic preparations may vary from product to product, and different species may have a different impact on the neonatal microbiome.

In this volume of *The Journal*, Kane et al report the results of a single US institution, retrospective observational cohort study (2008-2016) on the incidence of NEC among very low birth weight (VLBW) infants who received the probiotic LGG. Routine—but not universal—use of LGG in this study began in 2014, and the authors compared the incidence of NEC in the epochs before and after LGG. The study showed that use of LGG was not associated with a decreased risk of NEC.

There are several caveats to consider when interpreting the results of this study. First, the incidence of NEC was high (10-17%, compared with the national average of 4-7%). Second, it is unclear how physicians decided which infants should receive probiotics, but the results show that younger, smaller infants were more likely to receive LGG. It is difficult to assess how such indication bias may have influenced the results of a retrospective study. Finally, improved survival of premature infants in the post-LGG epoch may have introduced selection bias for patients at higher risk for developing NEC.

Although there have been numerous RCTs on the use of probiotics in VLBW infants, evidence is still lacking. Additional clinical trials are needed to evaluate both safety and efficacy of the most commonly used probiotic agents for prevention of NEC in VLBW infants in the United States.

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The incidental detection of alpha thalassemia

— **William S. Ferguson, MD**

All states mandate universal newborn hemoglobinopathy screening, the goal of which is to identify infants with sickle cell disease and provide an opportunity to initiate interventions, such as prophylactic antibiotics, prior to the development of life-threatening complications. The various technologies used to identify Hb S also identify other hemoglobinopathies, in particular the presence of Hb Barts, the homotetramer of gamma globin that results from quantitative defects in alpha globin chain production.

Normally there are 2 alpha globin genes on each chromosome 16, thus most individuals will have a total of 4 alpha globin genes. Single alpha globin gene deletions are common in sub-Saharan Africa and in many African Americans, but even in the homozygous state, which causes an approximately 50% decrease in alpha globin production, the result is only a mild thalassemia-trait phenotype (microcytosis and perhaps borderline anemia). In other populations—especially those from Southeast Asia—either one or both alpha globin genes may be deleted or defective, and in combination can result in three- or four-gene deletions with much more severe clinical consequences: individuals lacking 3 alpha globin genes will have moderate-to-severe hemolytic anemia (Hb H disease), and deletion of all 4 genes is fatal *in utero*. As alpha-thalassemia is likely to become even more prevalent in the US, pediatricians will increasingly see Hb Barts reported on their patients' newborn screens. The question of what to do next does not have an immediately obvious answer.

In this volume of *The Journal*, Fogel et al catalogue the recommendations from all 50 states regarding the incidental identification of Hb Barts on newborn screening. The diversity is quite striking: 19 states either do not report low levels of Hb Barts at all,