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The Hidden Treasure of Neonatal Screening: Identifying New Risk Factors and Possible Mechanisms of Necrotizing Enterocolitis Through Big Data

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Necrotizing enterocolitis (NEC) remains a challenge for very low birthweight infants.[1] Care for premature infants has improved significantly, especially for respiratory problems, but new approaches are required to improve survival of premature infants in light of NEC's increasing contribution to their morbidity and mortality.[1,2] Almost one-half of survivors of NEC have visual, psychomotor, and cognitive handicaps, greatly in excess of those associated with other preterm morbidities.[3] Furthermore, survivors of NEC experience higher rates of functional impairment throughout childhood, and of bloodstream infections secondary to short gut syndrome.[4]

The pathogenesis of NEC remains poorly understood, hindering the development of preventive strategies. Multiple studies have looked at clinical, demographic, and host variables to identify risk factors for NEC.[5–7] Preventive strategies, such as probiotics, holding feeds during transfusions, truncating antibiotic use during the first week, and providing exclusive human milk feedings have not eradicated the disease, and in some cases their efficacy has been refuted by randomized control trials.[8–12] For example, in a recent UK study, Costeloe et al[13] reported no effect of probiotics in a very large cohort, and a meta-analysis by Samuel et al[14] found no additional value of probiotics for infants who received breast milk. We clearly need better-defined mechanistic interventions to prevent NEC.

In this volume of *The Journal*, Sylvester et al[15] repurposed a large collection of newborn screening data in preterm infants (in California, for 2005–2008) to determine the potential of acylcarnitine levels for predicting NEC. The rationale was based on the known disturbances in nutrient metabolism and gut microbial dysbiosis present in preterm infants. Specifically, could there be a metabolic phenotype resulting in a maladaptive response to diet and/or microbial byproducts (ie, organic and short chain fatty acids) that predisposes to NEC and can be identified early during metabolic screening? Acylcarnitine levels and multiple

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See related article, p 80

demographic and clinical variables were combined in a backward stepwise regression model to improve prediction of at risk infants. The final model included a acylcarnitine:acylcarnitine ratio of 5:1, as well as gestational age by birth weight and the use of total parenteral nutrition. The model was validated with a second dataset from California for 2009. Although the prediction increased only modestly for the highest-risk preterm population in their cohort (<32 weeks gestational age), including acylcarnitine levels improved risk prediction in the infants born at 32–36 weeks gestational age to 90% in the validation dataset.

These findings are intriguing, pointing to a metabolic immaturity that cannot be attributed simply to preterm birth. The authors took care to correct for gestational age and day of screening, which affect the profiles.[16] Of note, methylbutyrylcarnitine (C5) and other acylcarnitines have significantly different metabolic screening results in infants born at the shortest gestational ages (23–26 weeks),[16] which could explain the reduced impact of acylcarnitine levels on model prediction in extremely preterm infants.

Perturbations in fatty acid metabolism are highly important in infants, whose diet consists mainly of fats as an energy source. Byproducts of gut microbial communities also contribute to enteric lipid load. Acylcarnitine level could be a proxy for metabolic prematurity, which increases the risk of abnormal responses to metabolic challenges, such as feeding. The authors speculated that a link exists between abnormal systemic fatty acid oxidation and increased mucosal damage owing to increased acidity (accumulation of organic acids in the gut).[17–19] We agree that this is a possible mechanism for NEC, but also consider cell membrane perturbations, as well as microbial community imbalance as a result of fatty acids in the gut. For example, although short-chain fatty acids are generally considered beneficial for the host,[20] Kaiko et al[21] recently demonstrated that butyrate (C4) inhibits intestinal stem cell proliferation. Branched amino acid catabolism is another source of short-chain acylcarnitines (C3 and C5), and its perturbation should not be dismissed as a possible factor in NEC development. An accumulation of short-chain fatty acids in the gut due to metabolic imbalance could accelerate NEC development by inhibiting enterocyte proliferation, increasing gut permeability, and promoting tissue injury. Along these lines, the changes in acylcarnitine concentrations that Sylvester et al associated with NEC appear to be fatty acid chain length-specific, with increases in short-chain acylcarnitines and decreases in long-chain acylcarnitines conferring the risk. These results are counterintuitive but intriguing, given that long-chain acylcarnitines are often considered deleterious, by virtue of their ability to integrate in membranes and act as detergents, and their capacity to reduce carnitine palmitoyltransferase activity.[22] The various physiological roles and effects of acylcarnitines should be considered when investigating the possible implications of acylcarnitines in the development of NEC.

We wish to call attention to a major strength of this article. Specifically, putative risk-associated changes in acylcarnitine levels were detected shortly after birth, providing a long intervention window. Because of the low incidence of NEC, especially in moderate or late preterm infants, exceptionally large pre-event patient datasets are needed to identify statistically robust NEC-associated signals. Nonetheless, Sylvester et al now demonstrate the utility of large datasets of clinical or screening information in providing new avenues for

preventive strategies in NEC. This opens the possibility of developing a personalized approach, allowing for more accurate risk stratification in advance of NEC onset.

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Glossary

NEC Necrotizing enterocolitis

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