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EDITORIAL

# Necrotizing enterocolitis: is it time for zero tolerance?

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One of the hardest jobs of a neonatologist is discussing with anxious parents the potential impact that premature birth may have upon the life of their son or daughter. Although we have the ability to use 'calculators' to determine the likelihood of death or neurodevelopmental impairment based on gestational age, sex and other risk factors,[1] we must remember that parents do not view these numbers in a vacuum. Once we take their newborn to the intensive care unit, it does not get any easier. Their child seems miles away, tucked in an incubator and attached to pumps and a ventilator, while we attempt to discuss terms such as respiratory distress syndrome, patent ductus arteriosus, sepsis and, probably the most daunting, intraventricular hemorrhage.

It is well-known that severe ($\geqslant$Grade 3) intraventricular hemorrhage worsens neurodevelopmental outcomes in the youngest premature infants.[2,3] Severe intraventricular hemorrhage and the subsequent neurodevelopmental impairment may be linked to several contributing factors, including post-hemorrhagic hydrocephalus (some cases requiring placement of ventricular shunts), suppression of neuronal cell proliferation and white matter injury. A recent study showed that infants with intraventricular hemorrhage (not necessarily severe) unaccompanied by white matter damage had only a slight risk of neurodevelopmental impairment at 2 years of age.[4] Even with this information at hand, it is difficult to counsel parents on prognosis. Just like predicting the risk of neurodevelopmental impairment during pre-delivery, head ultrasound reports only provide part of the whole picture. When counseling, we must take into account other diagnoses and co-morbidities, such as acid–base balance, oxygenation, blood pressure homeostasis and, of course, the infant's gestational age.

In this month's issue of *Journal of Perinatology*, Goldstein *et al.*[5] provide new insights into the associations between gestational age, intraventricular hemorrhage and neurodevelopmental outcome.[5] Looking retrospectively at prospectively collected data from the National Institute of Child Health and Human Development Neonatal Research Network, Goldstein *et al.* wanted to determine if death or neurodevelopmental impairment after severe intraventricular hemorrhage was more likely to occur at younger (23–25 weeks') or older (26–28 weeks') gestational ages. In addition, they sought to quantify the impact of gestational age on neurodevelopmental outcome when controlled for severity of hemorrhage. Analysis of nearly 5500 infants found that gestational age increased the risk of death, but the risk of neurodevelopmental impairment was highest in the youngest infants with no hemorrhage or Grade 3 hemorrhage (not Grade 4). In addition, they found that necrotizing enterocolitis (NEC) and late-onset infections increased the odds of death after 30 days for infants with severe hemorrhage.

Most surprising, however, was their analysis of individual components of neurodevelopmental impairment (cerebral palsy, Mental Developmental Index $<70$ and Psychomotor Developmental Index $<70$). The authors tested demographic, perinatal and neonatal factors to determine how they might independently affect neurodevelopmental impairment. Of all the variables they tested, the only factors that were associated with all three components of impairment were postnatal steroids (in infants with Grade 3 hemorrhage), ventricular shunt placement and NEC requiring surgery (in infants with Grade 4 hemorrhage).

The association of postnatal steroids, especially dexamethasone, with poor long-term outcomes has been well documented, and we have come far in trying to limit their use.[6] In addition, placement of a ventriculoperitoneal shunt for post-hemorrhagic hydrocephalus signifies great risk for future cognitive and motor development.[7] Yet, in the nearly three and a half decades since Bell's landmark paper describing the clinical staging of NEC, we have made little more than a dent in the effect that NEC has on our patient population.[8] Infants with NEC continue to have a significant risk for neurodevelopmental impairment and the incidence of NEC has remained steady in the Vermont Oxford Network (6.6% in 1990 versus 6.4% in 2010).[9] The paper by Goldstein *et al.* in this issue is an additional reminder of the significant neurodevelopmental burden on surgical NEC survivors.[10–12] NEC has also been shown to increase the risk of attention problems, visual perception, motor function and intelligence in school-age children in at least two separate studies from Europe.[13,14] The contributing factors to this long-term neurodevelopmental impairment in the survivors of surgical NEC remain to be elucidated. However, there is increasing evidence of sustained elevation of pro-inflammatory factors and downstream risk of neurodevelopmental impairment. O'Shea and colleagues recently demonstrated that elevated levels of several different pro-inflammatory proteins at 7 and 14 days of age were associated with mental and motor development impairment at 2 years of age.[15] NEC originates from an excessive innate immune response and it is thought that persistence of this inflammatory state (as occurs in cases of surgical NEC) may perturb brain development.[16]

Our challenge going forward could not be clearer. NEC is a principal cause of morbidity and mortality in the neonatal intensive care unit (NICU); study after study has shown that it is a formidable driver of neurodevelopmental impairment. Unfortunately, we have made little or no progress in reducing either the incidence or the severity of this illness in our NICUs over the last three decades.[9] There are many opinions about how best to attack NEC; however, surely the answer is not how we treat it, but in its prevention. Experts have suggested that we could cut the incidence of NEC in half if neonatologists would just do four things: (1) practice as a group (instead of individuals), (2) promote breast-milk feeding and start it as trophic feeds early in life, (3) have a standardized feeding advance that is gestational age-based and (4) minimize the feeding intolerance episodes with liberal use of glycerin.[17] My own personal bias also favors minimizing 'rule-out sepsis' antibiotic duration to zero if the patient was delivered for maternal indications, or to 48 h if it is a 'soft call' because prolonged antibiotic exposure is also a risk factor for NEC.[18] These are quality measures that every NICU could put in place tomorrow.

There are NICUs with extremely low NEC rates, bordering on none. Such NICUs consist mostly of inborn infants and thus have complete control of their patient population. What they show us is that NEC is similar to central line infections. It is possible to dramatically reduce NEC incidence if you can control enough variables and, like central line infections (and blindness from retinopathy of prematurity), the goal must be zero tolerance–not beating the national average.

NEC in our NICUs continues to occur at an alarming rate and, unfortunately, this disease continues to affect our patients for the

long term. We will never conquer NEC until we strive to significantly reduce its presence in our NICUs through quality improvement measures, adherence to protocols and checklists, and strict surveillance for feeding difficulties. Until that time, we are also not going to be able to look parents in the eyes and tell them that their premature child has avoided all the major risks of neurodevelopmental impairment, because until pre-term infants are corrected to term, they are still at risk for NEC.

## CONFLICT OF INTEREST

The author declares no conflict of interest.

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