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Preventing Postnatal Cytomegalovirus Infection in the Preterm Infant: Should It Be Done, Can It Be Done, and at What Cost?

In 2012, 56 252 very low birth weight (VLBW, <1500 g) infants were born in the US, accounting for 1.4% of all live births.[1] These infants encounter numerous morbidities, and 25%-30% experience long-term neurodevelopmental impairment (NDI).[2] Consequently, there has been an intense and elusive search for modifiable risk factors encountered in the neonatal intensive care unit (NICU) that impact long-term neurodevelopment. Whether preventing or minimizing exposure to these risk factors will prevent NDI, however, remains unclear. For example, large, randomized controlled trials demonstrate that efforts to minimize exposure to hyperbilirubinemia, hyperoxia, and hyperglycemia largely are ineffective in improving neurodevelopmental (ND) outcomes.[3-5] Thus, the search continues for preventive measures that will improve the outcomes of VLBW infants.

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Cytomegalovirus (CMV) is the most common congenital viral infection in high-resource countries, and infants with symptomatic infection are at high risk for NDI.[6] Whether postnatal CMV infection in the VLBW infant increases the risk of NDI, however, is unclear.[7] Although the use of CMV-seronegative, leukoreduced blood products essentially eliminates transfusion-associated infection, transmission to VLBW infants occurs via maternal breast milk and can result in an acute sepsis-like illness.[8] In addition, 2 epidemiologic facts indicate that we need to better understand the long-term ND effect of postnatal CMV infection in the VLBW: (1) In the US, CMV seroprevalence in women of childbearing age ranges from 30% to 90%, influenced by socioeconomic status and age[6]; and (2) the clinical use of maternal milk for VLBW is increasing because of its established health benefits for this infant population.[9] The intersection of high maternal CMV seroprevalence and an increasing CMV exposure risk through encouragement of maternal milk feeding has resulted in an inadequately informed practice that potentially puts thousands of infants at risk for NDI secondary to a potentially modifiable risk factor.

In this issue of *The Journal*, Brecht et al[10] report the results of neuropsychiatric testing in 3 groups of adolescents (11-16 years): former preterm (VLBW or <32 weeks of gestation) infants who acquired early postnatal CMV infection (n = 19), former non–CMV-infected VLBW infants (n = 23), and former term infants (n = 24). The authors demonstrate a significant negative effect of early postnatal CMV infection on overall cognitive abilities. These findings are especially worrisome, given the lack of demonstrable impact of postnatal CMV infection on NDI when assessed earlier in childhood.[11-14] Without these important data, we are at risk of making assumptions regarding the relative innocuous effect of postnatal CMV infection on preterm infants. The authors must be congratulated for providing us with this thoughtful and thorough long-term assessment after early CMV exposure. This study is critically important and potentially identifies postnatal CMV infection as a modifiable risk factor for NDI in preterm infants. Given that preterm infants may be at unique risk for NDI because of postnatal CMV infection, and that postnatal CMV exposure is increasing in the NICU setting after recognition of the considerable health benefits of breast milk feeding, we must ask the question: should more be done to minimize the risk of postnatal CMV acquisition for hospitalized preterm infants?

Before this question can be answered, the limitations of the current study must be acknowledged. The authors have appropriately identified that this is a small study. In addition,

CMV	Cytomegalovirus
ND	Neurodevelopmental
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit
VLBW	Very low birth weight

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although known independent risk factors for NDI, such as bronchopulmonary dysplasia, retinopathy of prematurity, and intracerebral hemorrhage were reported, they were not controlled for in the analysis in which the authors compared neuropsychologic test results.[15] Furthermore, other known independent risk factors for NDI, including receipt of caffeine or postnatal corticosteroids, duration of mechanical ventilation, sepsis, other congenital infections, necrotizing enterocolitis, and surgery, are not controlled for or reported here. Furthermore, an additional article in this issue of *The Journal* by Manley et al[16] makes it clear that social variables have a unique and demonstrable impact on the cognitive development experienced by VLBW infants between the ages of 2 and 5 years. Because CMV serologic status correlates with lower socioeconomic status, it may be that social risk factors that predict poor cognitive gain after discharge from the NICU have a disproportionately high prevalence in VLBW infants who acquire postnatal CMV, confounding the results reported here.

Additional questions remain unanswered regarding the relationship between postnatal CMV infection in the VLBW infant and long-term NDI. Does the infant's gestational or chronologic age at time of postnatal infection matter? The infants in the cohort described in the current study were born between 23 and 32 weeks of gestation and were infected at 36-190 days.[11] Can symptoms or severity of illness at time of infection predict NDI? Infants in this cohort had both symptomatic and asymptomatic infection.[11] A more thorough and controlled assessment of these potential confounding factors in a larger population is needed to answer these questions.

If we accept that postnatal acquisition of CMV results in NDI in VLBW infants, we have a unique opportunity to further improve their health and development by implementing safe and effective strategies to reduce the risk of CMV acquisition. Infants of mothers who are CMV-seronegative should be at no risk of CMV acquisition, barring acute CMV infection of the mother during lactation. Therefore, serologic testing of lactating mothers of preterm infants represents one option to identify at-risk infants.

Yet, the lack of well-defined maternal immunologic or virologic correlates that predict postnatal CMV transmission complicates identification of high-risk women-infant pairs. Although 90% of women who are CMV-seropositive shed virus in breast milk,[17] only ~20% of exposed infants will acquire postnatal CMV infection.[7,8] Therefore, routine maternal serologic testing and testing mother's milk for the presence of CMV are not efficient means of determining which infants are most at risk of infection. Although some studies have suggested that high virus load in milk predicts risk of transmission, the milk viral load is variable over time,[18] decreasing the effectiveness of spot testing. Moreover, the maternal cellular and humoral response measured in breast milk does not correlate well with symptomatic CMV disease in preterm infants.[19]

Finally, the corrected gestational age at which the infant is still at risk of NDI from CMV acquisition is unknown, preventing the establishment of an end point for testing to identify at-risk, hospitalized preterm infants. Therefore, although serologic and breast milk screening for CMV potentially could identify infants who stand to benefit from measures to reduce postnatal CMV acquisition, it is unclear whether this approach is time-efficient or cost-effective.

Processing the milk of mothers who are CMV-seropositive of VLBW infants to reduce or eliminate infectious virions is a potential strategy to reduce CMV acquisition while maintaining the health benefits of breast milk for those infants not at risk. However, we must be careful not to seek gains in ND outcomes via reduction in CMV acquisition at the expense of decreasing the benefits of exposure to maternal breast milk. Strong evidence exists that exposure to fresh mother's milk reduces the risk of morbidities associated with NDI, including necrotizing enterocolitis, late-onset sepsis, and retinopathy of prematurity.[20] There also is evidence that supports a long-lasting benefit of breast milk exposure, including a lower risk of metabolic syndrome, less insulin and leptin resistance, and improved ND outcomes.[20,21] Thus, avoiding CMV exposure for preterm infants by substituting maternal milk with formula is inappropriate. Routine freezing of mother's milk before the administration to the infant reduces—but does not eliminate—the risk of postnatal CMV acquisition.[22] In addition, the moderate reduction in CMV transmission may come at the expense of losing beneficial human milk components vulnerable to the freeze-thaw process.[23] Pasteurization eliminates infectious CMV virions in milk and prevents CMV transmission but destroys many of the protective factors thought to be responsible for the health benefits provided by mother's milk.[23]

Because currently we are without means to safely prevent postnatal CMV acquisition for VLBW infants without interrupting the benefits of breast milk feeding, the effectiveness of our therapies for CMV-infected infants must be considered. Long-term treatment with ganciclovir, or its oral derivative valganciclovir, has been shown to effectively improve both the hearing and developmental outcomes of full-term infants with congenital CMV infection.[24] Yet, whether this would have the same effect for VLBW who acquire postnatal CMV infection is unknown. Thus, long-term anti-viral treatment of preterm infants who acquire postnatal infection to ameliorate the potential NDI associated with CMV acquisition deserves study. Ongoing pharmacokinetic and pharmacodynamic studies of ganciclovir in preterm infants by the National Institutes of Health Collaborative Antiviral Study Group will provide much needed information on dosing and side effects of CMV treatment in this infant population.[25]

In summary, providing maternal milk to the preterm infant may have antagonistic effects, ie, protecting against a number of severe morbidities while increasing the risk of postnatal CMV infection. Importantly, the potential identification of a modifiable risk factor in the ND outcome of preterm infants provides a call to action that should not be ignored. Yet, are we stuck between the proverbial "rock and a hard place" in improving ND outcomes for preterm