Screening Newborns for Congenital Cytomegalovirus Infection

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Screening Newborns for Congenital Cytomegalovirus Infection

To the Editor: Dr Boppana and colleagues[1] concluded that DBS real-time PCR assays are not suitable for screening newborns for congenital CMV infection due to their insufficient sensitivity. We believe that this is a premature conclusion, based on a number of considerations that were not sufficiently discussed in this article.

First, the sensitivity of DBS testing is highly variable, largely depending on the nucleic acid extraction methodology used,[2] so conclusions cannot be generalized. It appears that this problem can be reduced by using optimized techniques that differ from those applied in the study by Boppana et al.[1] In addition, performing independent triplicate testing to increase sensitivity has been advocated,[2] an approach not used in this study.

Second, it should be clear what the clinical relevance is of the cases that were missed. These cases will likely involve the samples with the lowest or even absent viral loads, and there is evidence that such cases are associated with lower risks of late-onset sequelae, including hearing loss.[3] Sensitivity should be judged by patients in whom hearing loss is eventually caused by CMV. The intended follow-up of the infants with congenital CMV infection in this study will reveal the clinical outcome, and these data should be awaited before discarding the screening test that was used.

Third, we are concerned about the possible inclusion of very common but generally harmless postnatal CMV infections. Oropharyngeal contamination during vaginal delivery might cause positive saliva samples soon after birth, as has been shown for herpes simplex virus.[4] Sampling in this study was mainly performed on the day of birth. Confirmation of the presumed congenital infections was carried out at a mean age of more than 6 weeks, although it is commonly accepted that only CMV infections diagnosed within the first 2 or 3 weeks can be considered proof of congenital CMV infection.[5] If postnatally infected neonates were indeed included, this would falsely suggest a lower sensitivity of DBS testing.

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1. Boppana SB, Ross SA, Novak Z, et al; National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) Study. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. *JAMA*. 2010;303(14):1375-1382.
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To the Editor: The study by Dr Boppana and colleagues[1] conducted newborn screening for congenital cytomegalovirus (CMV) infection and found dried blood spots (DBS) to have a testing sensitivity of 28% to 34%. We believe that the authors' conclusion that DBS PCR assays are not suitable for screening newborns for congenital CMV infection is premature.

The low sensitivity may have been due in part to the specific methods used. It may be that neither the M48 robotic system nor the column extraction method used is optimal for detection of low copy number viral DNA in DBS. Demonstration of poor sensitivity with a particular diagnostic test, or even several tests, does not preclude future development of a test with sufficient sensitivity.

Studies in Belgium[2] and Sweden[3] performed universal screening for CMV by urine culture and demonstrated DBS testing sensitivity of 80%, providing proof of concept that CMV is measurable in blood in most congenitally infected infants. These studies used manual DNA extraction methods not suitable for newborn screening, but methods may eventually be appropriate for universal CMV screening.

Use of a CMV screening test with only 70% to 80% sensitivity would represent a change compared with existing US newborn screening programs that use highly sensitive tests for various disorders. However, congenital CMV infection is different from other screenable disorders in that only 15% to 20% of infected infants develop sequelae.[4] Thus, the sensitivity that matters most is for detection of those children at highest risk for developing CMV-related sequelae. Accumulating evidence suggests that infants with the lowest viral loads, who may be missed by DBS screening, are at lower risk for developing sequelae.[5] Thus, a DBS-based test will likely have higher sensitivity for detecting CMV-related sequelae than for detecting CMV infection.

We believe that in the interest of moving forward with screening capability for congenital CMV, diagnostic methods using DBS should remain under investigation in addition to methods based on urine and saliva.

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In Reply: Dr de Vries and colleagues and Drs Dollard and Schleiss believe that it was premature to conclude that DBS PCR assays are not suitable for newborn CMV screening. We agree that currently available DNA extraction methods and PCR protocols result in considerable variation in DBS PCR assay performance. To address these issues, we compared 2 different extraction methods and PCR protocols for detecting CMV DNA in DBS. Although changing the extraction method and the PCR protocol did not enhance the DBS PCR performance, we cannot discount that these methods could have missed infants with very low viral loads. However, a recent study found that 6 of 24 (25%) infants with symptomatic congenital CMV infection with significant neurologic involvement were whole blood PCR-negative, suggesting that not all symptomatic congenitally infected neonates have detectable viremia.[1]

The availability of DBS samples for triplicate testing as proposed by de Vries et al may be limited, as well as impractical for a screening procedure. With triplicate testing, the study by de Vries et al could only obtain an optimal sensitivity of 50% for DBS with low CMV DNA loads.[2] Because it is not possible to accurately predict which of the infected children will have sequelae, a screening assay with sensitivity between 70% and 80% would likely miss children who will have adverse outcome, making it premature to consider implementing such a test. There is little evidence to suggest that methodological changes could increase the sensitivity of PCR assays to acceptable levels for newborn screening at this time. Although future improvements in DNA extraction methods and PCR assays could be envisioned, for now newborn CMV screening methods based on saliva should be explored.

Both letters raise the issue that infected infants negative by DBS PCR might be at lower risk for sequelae from congenital CMV infection. However, support for this idea is based on evaluation of small numbers of selected infants. The absence of prospective data correlating blood viral load and outcome makes it impossible to categorize infected newborns into risk groups by blood PCR results. Additionally, it has been documented that children with undetectable viral loads at birth can develop CMV-associated hearing loss.[3,4] Thus, the relationship between blood viral load and sequelae among infants with congenital CMV infection may not be straightforward.

De Vries et al also raise the possibility that some of the infants in our study may have had postnatally acquired CMV infection. Although this possibility cannot be definitively excluded in some of the infants, we believe that it is unlikely because only 6 of 18 (33%) infants who were confirmed to have congenital CMV infection before 3 weeks of life were DBS-positive, indicating that the sensitivity of our DBS testing was not lowered by postnatally acquired infections.

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Transition From Pediatric to Adult Care for Patients With Sickle Cell Disease

To the Editor: The cohort study by Dr Brousseau and colleagues[1] raised concerning issues regarding the care of patients with sickle cell disease when they turn 18 years old. The authors demonstrated high readmission and acute care utilization rates among hospitalized patients with sickle cell disease, particularly among those 18 to 30 years old. Thirty-day rates of return to any acute care were 27.4% in ages 10 to 17 years and 48.9% in ages 18 to 30 years, with lower rates in older groups. In addition to being a quality measure, early hospital readmission in patients with sickle cell disease has been correlated with increased mortality.[2]

Although, as pointed out by the authors, some of these trends can be explained by increasing burden of illness with age and the censoring of severe disease in older groups due to early mortality, the 18- to 30-year-old group also represents a unique population of patients transitioning from pediatric to adult care. As children age out of pediatric services, they are susceptible to many changes, including the loss of their primary medical home, access to ambulatory care, and health insurance.[3] Poor continuity due to incom-

