# Preemptive Screening Strategies to Identify Postnatal CMV Diseases on the Neonatal Unit

*Seilesh Kadambari, MRCPCH,* Suzanne Luck, MRCPCH, MD,*† Paul T. Heath, FRCPCH,* and Mike Sharland, FRCPCH**

## BACKGROUND

Cytomegalovirus (CMV) is the most common congenital infection.[1] Congenital CMV (cCMV) is diagnosed if the virus is isolated in the first 3 weeks of life. It is challenging to differentiate between congenital and postnatal infection (pCMV) if the virus is detected after this time point. Retrospective diagnosis of cCMV requires the identification of the virus on the dried blood spot, a method which has been shown to be insensitive.[2] Additionally, there are no internationally accepted definitions for symptomatic pCMV.

More than 90% of seropositive mothers shed CMV into their breast milk; breast milk is therefore an important mode of transmission of CMV to newborn infants.[3]

The great majority of term newborns acquiring CMV infection postnatally remain asymptomatic and have no long-term consequences. This contrasts with cCMV infection and may be explained by the intensity and route of exposure: CMV viral loads in urine are lower in infants with pCMV compared with infants with cCMV.[4] Nonetheless, very premature (gestational age <32 weeks) or very low birth weight (VLBW, <1500 g) infants are susceptible to developing symptomatic illness after acquisition of CMV in the postnatal period. A recent prospective multicenter study in Atlanta of 539 VLBW infants revealed that the incidence of CMV acquisition at 12 weeks of age was 6.9% (95% confidence interval: 4.2%–9.2%).[5] Of these, 17% developed symptomatic disease or died.

Various clinical signs and syndromes have been described in infants with pCMV infection, including severe sepsis-like syndrome, pneumonia, hepatitis, renal impairment and thrombocytopenia.[6] Table 1 summarizes the clinical manifestations and investigations that should be considered in managing infants with pCMV.

A key issue is the potential for pCMV infection to cause adverse long-term outcomes. To date, studies investigating clinical sequelae have been small, single center and open to confounding because of study design. Although no impact on hearing has been reported in any study, a small case-controlled study showed that children at school age who had pCMV as a preterm (through breast milk acquisition) had poorer cognitive function and motor skills, although still within the normal range, compared with controls.[9] Another prospectively controlled study of 42 VLBW infants showed that infants with pCMV had significantly lower cognitive results using the Kaufman Assessment Battery for Children.[10] Other studies of postnatally infected preterm infants have shown that white matter changes including lenticulostriate vasculopathy are more common than in noninfected infants, although the significance of this for long-term outcomes remains unknown.[4,11]

These potential long-term effects, in addition to sometimes very severe acute illness, raise the question of whether antiviral therapy may have a role in pCMV infection.

There are no controlled studies, which have evaluated the efficacy or safety of antiviral or immunoglobulin-based treatment for symptomatic infants with pCMV, nor are there robust data to show improved short- or long-term outcomes. In particular, there are very limited safety and pharmacokinetic data on antiviral treatment in preterm infants; the group most likely to have severe disease.

As a consequence, the evidence on which to base treatment guidelines for the management of pCMV is sparse. Many clinicians therefore reserve treatment for babies with significant disease.[12]

There are therefore significant uncertainties, regarding the management of infants with pCMV disease, in part due to our limited understanding of the natural history of disease.

Accepted for publication July 6, 2016.
From the *Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George's University of London, London, United Kingdom; and †Kingston Hospital NHS Foundation Trust, Kingston Upon Thames, Surrey, United Kingdom.
The authors have no funding or conflicts of interest to disclose.
Address for correspondence: Seilesh Kadambari, MRCPCH, Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George's University of London, Cranmer Terrace, London SW17 ORE, United Kingdom. E-mail: skadamba@sgul.ac.uk.

ISSN: 0891-3668/16/3510-1148
DOI: 10.1097/INF.0000000000001303

The ESPID Reports and Reviews of *Pediatric Infectious Diseases* series topics, authors and contents are chosen and approved independently by the Editorial Board of ESPID.

**TABLE 1.** Summary of Risk Factors, Clinical Features and Investigations That Should be Considered When Managing an Infant With pCMV

| | |
|---|---|
| Risk factors | Gestational age <32 weeks, birth weight <1500 g, seropositive mothers breast feeding, early detection of virolactia, high virus burden in breast milk and long duration of virus detection in breast milk |
| Diagnosis | CMV-positive sample (saliva or urine sample to test for CMV DNA PCR) detected >21 days of life and CMV-negative sample collected <21 days of life |
| Clinical features | CMV sepsis-like syndrome (triad of apneas, bradycardias, grey/pallor), acute hepatitis, hepatosplenomegaly and CMV pneumonia, CMV enterocolitis, jaundice, cholestasis, petechiae and lymphadenopathy |
| Laboratory investigations | Full blood count (thrombocytopenia and neutropenia) and liver function test (elevated liver enzymes) |
| Neuroimaging | Serial CrUSS from diagnosis to hospital discharge to assess for cerebral abnormalities including lenticulostriate vasculopathy. Consideration of magnetic resonance imaging if abnormalities seen on CrUSS |
| Treatment | Consider treatment in severely symptomatic infants using ganciclovir/valganciclovir. Any decision to commence treatment should be made after discussion with local pediatric infectious diseases team |

Table 1 is derived from data from key publications.[3,7,8]
CrUSS indicates cranial ultrasound.

This review will therefore focus on possible strategies to minimize CMV transmission and disease in this vulnerable group by focusing on prevention and preemptive therapy.

## PREVENTION

It is possible to prevent transmission of CMV by treating breast milk through heat pasteurization or freeze-thawing. However, freeze-thawing does not fully prevent transmission, and heat pasteurization can negate some of the benefits of breast milk by decreasing its fat and lactose constituents.[13,14] The most recent conclusion from the American Academy of Pediatrics is that the benefits of giving fresh breast milk in CMV-positive mothers outweigh the risks.[7]

To our knowledge, only 1 placebo-controlled trial of CMV immunoglobulin has been published.[15] This study was conducted before CMV-negative blood transfusions were used as part of routine clinical care and showed that immunoglobulin reduced the likelihood of transmission compared with placebo (12.5% vs. 3.2%). The results of a prospective cohort study conducted in solid organ transplant (SOT) recipients to evaluate the neutralizing capacity of monoclonal antibodies in preventing viral transmission are awaited (NCT01753167). Promising results in this population could lead to similar trials to reduce transmission in maternal-fetal transfer.

## PREEMPTIVE SCREENING IN SOT RECIPIENTS

The adoption of CMV-specific antiviral therapy screening strategies has reduced the incidence of CMV disease among SOT recipients.[16] Preemptive screening involves administration of antiviral therapy in response to laboratory triggers, such as increasing viral load. Preemptive treatment is used as an alternative to antiviral prophylaxis for SOT recipients at high risk of CMV disease who are prospectively screened for CMV viremia. This strategy is based upon knowledge of the natural history of CMV viremia in adult SOT patients and recognition that a "threshold" can exist below which virus is tolerated without associated disease.

A meta-analysis by Strippoli et al[17] concluded that compared with placebo or standard care, preemptive treatment significantly reduced the risk of CMV disease, and comparative trials of preemptive therapy versus prophylaxis showed no significant differences in the risks of CMV disease. These studies are limited to adult SOT populations, and there are no data that define viral threshold limits in pCMV.

## IDENTIFYING PRESYMPTOMATIC PCMV INFECTION

A successful preemptive screening strategy would require a readily available, rapid, sensitive and easy to use surveillance test for CMV detection. Real-time polymerase chain reaction (PCR) on plasma or whole blood has been shown to be sensitive with turnaround times of 24 hours.[18] Point-of-care PCR assays are now also commercially available but have not yet entered clinical trials in neonates. Saliva swabs require no skills to obtain and are therefore a painless and highly accurate method of detecting the virus.[18]

## PREEMPTIVE SCREENING IN PRETERMS

Serial saliva samples could be obtained in preterm infants to test for CMV DNA using PCR to enable early identification of infection. Developing a strategy whereby saliva samples are taken at regular time intervals by health care staff on the neonatal unit in infants less than 32 weeks and sent to a regional laboratory for same day testing is conceivable. Batch testing of samples would further reduce costs. When CMV is detected, treatment could be started before symptoms develop.

Such a strategy could be coupled with prospective data collection in order to monitor outcomes and to model and define the relevance of different virologic parameters, using similar methodologies to those utilized in adult SOT populations.[19]

There are many questions that need to be addressed before considering a strategy of preemptive screening for pCMV. The clinical burden of pCMV disease is largely unknown, in part due to the limited long-term outcome data available. No studies have yet shown that antiviral treatment in infants with asymptomatic CMV infection is beneficial, and the side effects of therapy in this preterm population still need to be clearly defined.

Linking outcomes in this well-defined patient group to the existing neonatal datasets would, however, enable detailed data collection and allow comparison with non-CMV infected groups to start to address some of these questions.

## CONCLUSIONS

Postnatal acquisition of CMV can cause severe acute disease in preterm infants, but the longer-term consequences remain uncertain. The options available for prevention, such as pasteurization of breast milk, are limited, and their evidence base is inadequate. An approach, which has been successfully adopted in a different setting (adult organ transplantation), is preemptive screening of susceptible patients to detect presymptomatic infection and then treatment of those with a high risk of severe disease.

Recruiting subjects to a randomized controlled trial to evaluate the efficacy and safety of oral valganciclovir in postnatally acquired cases would take several years and need multiple recruiting sites because of the inherent difficulties of conducting antiviral treatment trials for rare diseases in the neonatal population. Disease registries, however, can efficiently collect high-quality safety and pharmacokinetic data in infants treated with antivirals, which in turn can be used to guide dosing and duration of treatment recommendations. Improving our understanding of the epidemiology of pCMV disease is also essential to inform evidence-based management.

## REFERENCES

1. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital

cytomegalovirus infection. *Rev Med Virol*. 2007;17:355–363.

2. 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;303:1375–1382.
3. Maschmann J, Hamprecht K, Dietz K, et al. Cytomegalovirus infection of extremely low-birth weight infants via breast milk. *Clin Infect Dis*. 2001;33:1998–2003.
4. Nijman J, van Loon AM, de Vries LS, et al. Urine viral load and correlation with disease severity in infants with congenital or postnatal cytomegalovirus infection. *J Clin Virol*. 2012;54:121–124.
5. Josephson CD, Caliendo AM, Easley KA, et al. Blood transfusion and breast milk transmission of cytomegalovirus in very low-birth-weight infants: a prospective cohort study. *JAMA Pediatr*. 2014;168:1054–1062.
6. Kurath S, Halwachs-Baumann G, Müller W, et al. Transmission of cytomegalovirus via breast milk to the prematurely born infant: a systematic review. *Clin Microbiol Infect*. 2010;16:1172–1178.
7. Lanzieri TM, Dollard SC, Josephson CD, et al. Breast milk-acquired cytomegalovirus infection and disease in VLBW and premature infants. *Pediatrics*. 2013;131:e1937–e1945.
8. Luck S, Sharland M. Postnatal cytomegalovirus: innocent bystander or hidden problem? *Arch Dis Child Fetal Neonatal Ed*. 2009;94:F58–F64.
9. Bevot A, Hamprecht K, Krägeloh-Mann I, et al. Long-term outcome in preterm children with human cytomegalovirus infection transmitted via breast milk. *Acta Paediatr*. 2012;101:e167–e172.
10. Goelz R, Meisner C, Bevot A, et al. Long-term cognitive and neurological outcome of preterm infants with postnatally acquired CMV infection through breast milk. *Arch Dis Child Fetal Neonatal Ed*. 2013;98:F430–F433.
11. Nijman J, Gunkel J, de Vries LS, et al. Reduced occipital fractional anisotropy on cerebral diffusion tensor imaging in preterm infants with postnatally acquired cytomegalovirus infection. *Neonatology*. 2013;104:143–150.
12. Gunkel J, Wolfs TF, de Vries LS, et al. Predictors of severity for postnatal cytomegalovirus infection in preterm infants and implications for treatment. *Expert Rev Anti Infect Ther*. 2014;12:1345–1355.
13. Hamprecht K, Maschmann J, Müller D, et al. Cytomegalovirus (CMV) inactivation in breast milk: reassessment of pasteurization and freeze-thawing. *Pediatr Res*. 2004;56:529–535.
14. Goelz R, Hihn E, Hamprecht K, et al. Effects of different CMV-heat-inactivation-methods on growth factors in human breast milk. *Pediatr Res*. 2009;65:458–461.
15. Snydman DR, Werner BG, Meissner HC, et al. Use of cytomegalovirus immunoglobulin in multiply transfused premature neonates. *Pediatr Infect Dis J*. 1995;14:34–40.
16. Fishman JA, Emery V, Freeman R, et al. Cytomegalovirus in transplantation—challenging the status quo. *Clin Transplant*. 2007;21:149–158.
17. Strippoli GF, Hodson EM, Jones CJ, et al. Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst Rev*. 2006;2:CD005133.
18. Boppana SB, Ross SA, Shimamura M, et al; National Institute on Deafness and Other Communication Disorders CHIMES Study. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. *N Engl J Med*. 2011;364:2111–2118.
19. Kotton CN, Kumar D, Caliendo AM, et al; Transplantation Society International CMV Consensus Group. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*. 2013;96:333–360.