Diagnosis and management of infants with congenital cytomegalovirus infection

Soren Gantt MD PhD MPH FRCPC1, Ari Bitnun MD MSc FRCPC2, Christian Renaud MD MSc FRCPC3, Fatima Kakkar MD MPH FRCP5, Wendy Vaudry MDCM FRCP6

Abstract

Congenital cytomegalovirus infection (cCMV) is the most common congenital infection, occurring in approximately 0.5% of live births. Most infected newborns are asymptomatic, but up to 20% develop sensorineural hearing loss or other permanent neurologic sequelae. The presentation of newborns with symptomatic cCMV is highly variable, and the infection is usually not diagnosed in the absence of a screening program. Newborn CMV screening programs are estimated to be beneficial and cost-effective, and are increasingly being implemented. Diagnosis requires direct detection of virus in a sample obtained before 3 weeks of age, and is best performed by polymerase chain reaction (PCR) of saliva or urine, either of which is more sensitive than dried blood spot. Antiviral treatment of selected newborns with cCMV-related disease appears to improve hearing and neurocognitive outcomes. All infected infants should be evaluated promptly to determine appropriate therapy, and receive close audiologic and developmental follow-up.

Keywords: Congenital cytomegalovirus infection; Diagnosis; Treatment; Childhood hearing loss; Newborn screening.

Cytomegalovirus (CMV) is the most common congenital infection and the most common cause of acquired hearing loss in childhood. There have been a number of advancements in the testing and treatment of congenital (c)CMV infection in recent years, which are outlined here along with guidance on the current best practices regarding management of infants with cCMV.

Epidemiology and burden of disease

CMV is a herpesvirus that infects approximately half of adults in North America. Infection is lifelong, and is transmitted through contact with saliva, urine, breast milk, genital fluids or blood. In otherwise healthy people, CMV infection is typically asymptomatic or causes a non-specific, usually mild, febrile illness. However, when CMV is acquired congenitally, morbidity is common. cCMV occurs in roughly 1 per 150 live births, and is a major cause of sensorineural hearing loss (SNHL) and other neurologic deficits among children worldwide (1). It is estimated that 10–25% of all SNHL in children is due to cCMV. Although the risk of cCMV is approximately 30–40% among infants whose mothers acquire CMV during pregnancy, most infants with cCMV are born to women with evidence of pre-existing immunity (2).

Of the 10–15% of infants with cCMV who are symptomatic at birth, 40–60% will go on to have permanent sequelae including SNHL, visual deficits, and/or cognitive delay (1,2). Evidence of central nervous system (CNS) involvement at birth portends a worse outcome (3,4). Among infants with cCMV who do not have symptoms at birth, between 10% and 15% will develop SNHL or other permanent sequelae by the time they start school (1,2). Hearing loss from cCMV can be unilateral or bilateral, vary from mild to profound, be delayed in onset and can fluctuate, but when present is usually progressive. Overall, two-thirds of congenitally-infected children who develop permanent sequelae were asymptomatic at the time of birth.

Methods and indications for cCMV testing

Congenitally-infected infants persistently shed very high levels of CMV in the saliva and urine (median >12 months) (5–7), and these are therefore the optimal samples to test. CMV polymerase chain reaction (PCR) of saliva or urine using a validated assay is at least as accurate as urine culture, the historical standard, and is increasingly used for diagnosis and screening (8). Levels in blood are much lower than in saliva or urine, which contributes to inadequate sensitivity (30–80%) of testing dried blood spots collected at birth by PCR (8,9). Saliva is collected by oral (not throat) swab and is more convenient to obtain than urine. False-positive CMV PCR results are possible in breastfeeding infants tested by oral swab and confirmatory testing by urine PCR is required. The high sensitivity (97–100%) and specificity (99.9%) of saliva PCR testing as a screening method have been validated in a large population-based cohort study (8).

Definitive diagnosis of cCMV requires direct detection of the virus in infants before 3 weeks of age (10). The timing of sample collection is important...
because intrapartum and early postpartum infection is common and does not result in long-term sequelae. Thus, whenever cCMV is suspected, testing should be performed as soon after birth as possible. A negative CMV IgG serology effectively excludes congenital infection. Antibody testing is not otherwise useful for diagnosis of cCMV; the presence of CMV IgG does not differentiate between maternal or infant infection, and CMV IgM is not sufficiently sensitive or specific for congenital infection. Retrospective CMV testing of stored dried blood spots, if positive, may be helpful when the diagnosis of cCMV is considered beyond the newborn period, but a negative test does not exclude the diagnosis (9).

The diagnosis of cCMV is missed for the majority of symptomatic newborns when testing depends on clinical suspicion (11,12). Consequently, in the absence of an alternative explanation, any clinical finding consistent with cCMV infection (Table 1) should prompt cCMV testing as soon as possible after birth. Indications for cCMV testing include failing the newborn hearing screen (13). In most settings, confirmation of SNHL by auditory brainstem-evoked response (ABR) audiometry does not routinely take place until >3 weeks of age, which is too late to accurately diagnose cCMV and often beyond the period when antiviral therapy has proven benefits (see below). Therefore, testing for cCMV should take place upon hearing screen failure, prior to ABR audiometry.

Algorithms for targeted cCMV screening of high-risk newborns are increasingly being adopted. For example, reflexive cCMV testing of newborns that fail the hearing screen is now mandated in parts of the USA, including Utah and Connecticut (14,15), and similar approaches are being piloted in parts of Canada. Although targeted screening appears cost-effective and improves cCMV diagnosis (16,17), this strategy by design does not identify asymptomatic newborns without hearing loss at birth, and therefore misses the majority of children who will develop cCMV-related disease (18). In contrast, universal newborn cCMV screening using urine or saliva PCR would identify virtually all infected children. Universal screening has not yet been widely adopted, but appears to be both beneficial and cost-effective (17,18).

### Evaluation of newborns with cCMV infection

Any newborn with cCMV should be evaluated without delay in order to confirm the diagnosis and determine whether antiviral therapy is indicated. Parental counseling should be provided to explain the implications of a positive test. Neonates with confirmed cCMV should be promptly seen by paediatrics, audiology and ophthalmology and undergo laboratory testing and brain imaging (Table 2). Because the evidence supporting antiviral treatment for cCMV is largely limited to studies in which therapy is initiated in the first month of life, every effort should be made to complete the work-up within this period.

### Antiviral treatment for cCMV infection

Strong evidence from two NIH-sponsored randomized controlled trials supports antiviral treatment of symptomatic cCMV with neurologic involvement (19,20). In the earlier study, intravenous ganciclovir for 6 weeks, initiated within 1 month of birth, was shown to reduce progression of hearing loss at 6 months of age in children with baseline neurologic, ophthalmologic or hearing impairment (19). More recently, a randomized placebo-controlled trial of 6 weeks versus 6 months of ganciclovir given to newborns with symptomatic cCMV found that the longer treatment duration was associated with modestly better hearing at 12 and 24 months of age after adjusting for CNS involvement (20). Neurodevelopmental outcomes, including Bailey-III language composite and higher receptive communication scale scores at 24 months of age were also significantly improved in the longer treatment arm (21).

### Table 1. Indications for newborn cCMV testing

- Suspected or proven primary maternal CMV infection during pregnancy
- Fetal ultrasound findings consistent with in utero CMV infection
- Intrauterine growth retardation
- Hydrops fetalis
- Brain abnormalities, including calcifications or ventriculomegaly
- Hepatomegaly, splenomegaly or visceral calcifications
- Hyperechogenic bowel
- Placental enlargement
- Maternal HIV infection
- Placental CMV infection discovered on pathologic examination
- Symptoms of possible CMV disease in the newborn
  - Small for gestational age
  - Seizures, microcephaly, cortical atrophy, intracranial calcifications, ventriculomegaly, periventricular cysts, lenticulostrate vasculopathy, cerebellar hypoplasia, polymicrogyria, or lissencephaly
  - Lethargy, hypotonia, or poor feeding
- Thrombocytopenia
- Petechiae or purpura
- Jaundice at birth
- Conjugated hyperbilirubinemia or hepatitis
- Hepatomegaly or splenomegaly
- Pneumonitis
- Chorioretinitis, retinal scarring or optic atrophy
- Failed hearing screen or proven SNHL
- Primary immunodeficiency, including positive screen for SCID

### Table 2. Suggested evaluation of congenital cytomegalovirus infection

<table>
<thead>
<tr>
<th>Type of evaluation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Audiology</strong></td>
<td>Diagnostic ABR testing for all CMV positive newborns that failed the hearing screen should be performed as early as possible.*</td>
</tr>
<tr>
<td><strong>Paediatrics</strong></td>
<td>Paediatric evaluation, including a complete history and physical exam with anthropometrics</td>
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<tr>
<td><strong>Laboratory</strong></td>
<td>Urine CMV viral isolation or PCR to confirm diagnosis Complete blood count with differential Liver function tests BUN and serum creatinine Consider quantitative serum CMV PCR Consider CSF protein, cell count and CMV PCR</td>
</tr>
<tr>
<td><strong>Brain imaging</strong></td>
<td>Cranial ultrasound Consider CT or MRI†</td>
</tr>
<tr>
<td><strong>Ophthalmology</strong></td>
<td>Fundoscopic exam</td>
</tr>
<tr>
<td><strong>Otolaryngology</strong></td>
<td>Indicated for those infants with confirmed SNHL</td>
</tr>
<tr>
<td><strong>Parental counseling</strong></td>
<td>Families should be counseled about the natural history and standard precautions for prevention of CMV transmission to pregnant women or immunocompromised people.</td>
</tr>
</tbody>
</table>

*All evaluations should be completed as quickly as feasible so that antiviral therapy may be initiated at <1 month of age if cCMV-related disease is confirmed; †For infants that receive 6 months of ganciclovir treatment, laboratory monitoring is recommended weekly ×4 weeks, then every 2 weeks ×8 weeks, then every month ×3 months, with a complete blood count with differential, liver function tests, and BUN and serum creatinine (20). ††CMV levels in blood may have prognostic value (7,27); Some experts recommend lumbar puncture as part of the evaluation of cCMV central nervous system disease (28). **Brain imaging with CT or MRI should be considered for abnormal findings on neurologic exam or cranial ultrasound. Some experts recommend CT or MRI on all infected infants.**
higher in the longer treatment group after adjustment for CNS involvement, prematurity, and age of starting treatment.

Based on these data, the standard treatment for symptomatic cCMV is valganciclovir 16 mg/kg/dose twice daily for 6 months (10); at this time, there is no evidence for longer treatment. There is equipoise among experts regarding treatment of newborns with milder disease, for example isolated SNHL, mild thrombocytopenia or slight intrauterine growth retardation (21,22). However, newborns with clear symptoms of cCMV, especially CNS involvement, should be treated (10,21,22). Starting antiviral therapy at >30 days of life is of uncertain benefit although case series suggest efficacy (23,24), and controlled trials of late-onset disease are ongoing. Currently, there are no data to support antiviral therapy to prevent late-onset disease in infants with asymptomatic cCMV.

The major risk of ganciclovir is reversible neutropenia, but thrombocytopenia and hepatotoxicity are also reported (25). Neutropenia appears less common with valganciclovir, and treatment discontinuation is rarely needed (19,25). Laboratory monitoring of complete blood cell counts and renal and liver function in infants treated with valganciclovir is nevertheless required (20) (Table 2). The potential for adverse reproductive effects and carcinogenicity based on animal studies should be acknowledged, but these have not been observed in humans. Because of these complexities, treatment of cCMV should be discussed with a specialist in perinatal infectious diseases.

Follow-up care of cCMV-infected infants

All infants with cCMV should have close audiologic follow-up, to monitor for progression or development of SNHL for 6 years (26), or longer in consultation with an audiologist (15). Monitoring for developmental delay and learning disability is also important. Follow-up of infants for specific complications of cCMV should be individualized based on severity and other factors by the relevant specialty services (e.g., otolaryngology, ophthalmology, developmentally paediatrics). Infection control issues should be addressed with families of children with cCMV infection (10). These children do not require isolation if hospitalized or restrictions on childcare attendance. However, due to prolonged CMV shedding by infected children, hand hygiene is recommended and avoidance of contact with saliva and urine are advised for pregnant women or immunocompromised individuals.

Conclusions

cCMV is common and causes substantial morbidity. Prompt identification and treatment can improve hearing and cognitive outcomes. The diagnosis is made by CMV PCR or culture from saliva or urine collected prior to 3 weeks of age. Because clinical suspicion of infection is insensitive, targeted or universal newborn screening programs should be encouraged (29). All children with cCMV need close follow-up to monitor for hearing loss or other neurocognitive sequelae. Family practitioners, paediatricians and infectious disease specialists should be familiar with cCMV in order to facilitate the diagnosis and management of infected children.

References


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