Perinatal Cytomegalovirus Infection

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Abstract

Purpose of review There have been recent advances in the field of congenital CMV infection (cCMV) related to antiviral treatment of pregnant women and infants, the implementation of newborn CMV screening programs, and the frequency and diagnosis of complications among infected children. In addition, postnatal CMV infection (pCMV) is increasingly recognized as a potential cause of long-term sequelae in addition to acute complications among preterm infants, raising important questions related to treatment, and prevention.

Recent findings High-dose valacyclovir appears to be safe and effective for the prevention of cCMV among women with first-trimester primary CMV infection. New studies reveal high rates of vestibular dysfunction and neuropsychiatric manifestations among children with cCMV. Some studies report associations between pCMV and long-term consequences, including neurodevelopmental delay and bronchopulmonary dysplasia, among very low birth weight infants, in addition to high risk of sepsis and death acutely, which has motivated efforts to eliminate the virus from breast milk by different methods.

Summary More long-term complications of cCMV are increasingly recognized among children previously thought to be asymptomatic. Although a preventive CMV vaccine may be achievable, strategies to reduce the burden of cCMV disease include maternal education about risk-reduction behaviors, antiviral treatment of pregnant women with primary infection, and newborn screening to allow timely, appropriate care. Similarly, although it remains unclear if pCMV causes long-term problems, there is growing interest in identifying and preventing disease from CMV infections among preterm infants.
Introduction
This review specifically addresses CMV infection of the fetus and newborn. CMV continues to be the most common congenital infection worldwide and is a major cause of sensorineural hearing loss (SNHL) and other neurodevelopmental problems in childhood. There has been considerable progress in understanding the epidemiology and pathogenesis of cCMV, though the true extent of disease among “asymptomatic” cases is still being defined. Despite the fact that a vaccine to prevent CMV infection is still at least several years away, the combination of increased recognition of the importance of risk-reduction education among pregnant women, newborn CMV screening, and other interventions hold promise to help reduce the massive public health burden of cCMV in the shorter term. In contrast, pCMV is relatively less well studied. Now appreciated as a common cause of sepsis among preterm infants, major knowledge gaps regarding the long-term sequelae of pCMV, as well as optimal prevention and treatment strategies, limit the ability to formulate evidence-based evaluation and management recommendations.

Congenital cytomegalovirus infection

Maternal seroprevalence and risk of fetal infection
The prevalence of cCMV varies depending on the overall CMV seroprevalence in the population, and the socioeconomic and cultural status of the mother, with values between 0.2 and 2% worldwide [1]. In Europe and North America, the seroprevalence among women of childbearing age is 50–60%, while in most of Asia, Africa, and Latin America estimates are 90–100% [1, 2]. The rate of maternal primary infection (MPI) during pregnancy is ~1.8% in high-income countries [3], with an associated risk of fetal transmission of 30–40% [4]. The risk of fetal infection depends on the timing of MPI, being 21% if periconceptional, 36% in the first, 40% in the second, and 66% in the third trimester [5]. In populations with high CMV seroprevalence (≥90%), almost all fetal infections are related to maternal non-primary infection (MNPI), which can be due either to reinfection or reactivation of chronic infection [6]. However, even in countries with lower maternal seroprevalence, most cCMV are due to MNPI [7•, 8–10]. Increasingly, the severity of cCMV from MPI and MNPI is recognized to be similar; both can cause severe fetal compromise and long-term sequelae, mainly when they occur during the first trimester of pregnancy [11, 12•].

Diagnosis of cCMV
cCMV is diagnosed by direct identification of the virus in a sample collected within 3 weeks of birth. As viral culture is rarely used anymore, PCR to detect CMV DNA is the standard. This includes amniotic fluid obtained prenatally, or any sample from the newborn, preferably saliva or urine. Viral loads tend to be lower or absent in blood [13, 14] as compared to saliva and urine, in which infected infants consistently shed CMV at high levels [15, 16]. As such, dried blood spots (DBS) collected at birth can be useful for confirming a diagnosis.
of cCMV beyond 3 weeks of age, but do not reliably exclude infection. Infection diagnosed later than 3 weeks of age could reflect intrapartum or early postpartum acquisition, and is therefore not definitive, even in the setting of symptoms suggestive of cCMV. Saliva swabs are convenient to obtain but are subject to false positive PCR results—typically at copy numbers \( < 10^3/\text{mL} \)—due to residual virus in milk among breastfed infants [17, 18••]. As such, oral swabs should be collected at least 30 min after breastfeeding, and positive results should be confirmed by urine testing [19, 20]. Negative CMV serology in the mother and/or infant can be used to rule out infection but is not otherwise useful for diagnosing cCMV.

**Presentation and complications of cCMV**

Most cCMV are asymptomatic or subclinical at birth [7•]. According to a meta-analysis of studies in which cCMV was identified by universal newborn screening, approximately 12% of infants were symptomatic at birth, of whom 3 to 4% died, and 50% developed at least one long-term neurodevelopmental complication [21]. Across studies, however, the definition of symptomatic varies, and while some presentations are severe, most findings at birth (Table 1.) are subtle or non-specific, such that even most symptomatic newborns go undiagnosed in the absence of screening [22, 23••].

Permanent sequelae of cCMV are mostly associated with fetal infection during the first trimester of pregnancy and among children with symptoms at birth [23••, 24, 25]; in these cases, >20% of the infected newborns, will develop neurological sequelae ranging from isolated SNHL to severe intellectual disability [24]. Sensorineural hearing loss (SNHL) is the most recognized complication of cCMV overall, occurring in approximately 10–15% of cases, 20–60% in symptomatic infected newborn, and 6–20% in asymptomatic infected newborn [26, 27•]. SNHL may be unilateral or bilateral, be present at birth or develop anytime until 5–6 years of age, and wax and wane over time [28•, 29]. Furthermore, vestibular disorders are also increasingly recognized to be highly prevalent, even in children with no other discernable manifestations of cCMV [30••, 31]. Like hearing loss, vestibular loss from cCMV is highly variable and has been reported in over 45% of cases [30••, 31, 32]. In addition, behavioral problems such as attention-deficit hyperactivity and autism spectrum disorders have been suggested, but not proven, to occur more often among children with cCMV [33–35].

**Evaluation of newborns with cCMV**

Because high-quality evidence supporting the benefits of antiviral therapy is limited to symptomatic infants when it is initiated within the first month of life (see below), the following evaluations should be expedited to determine if treatment is indicated.
Physical examination

All infected infants should be examined by a physician for the presence of associated findings (see Table 1). The head circumference should be measured, and a thorough neurological examination should be performed on all newborns with cCMV.

Laboratory testing

Testing of infected newborns should include a complete blood count and differential, and liver and renal function testing, to assess complications of infection and to provide a baseline should antiviral treatment and toxicity monitoring be indicated. Some experts recommend blood viral load testing, though there is limited data on its use as a prognostic indicator or to guide response to antiviral therapy [37, 38]. Similarly, CMV DNA testing in CSF is not routine at all centers and is of unclear clinical significance [39, 40].

### Table 1. Clinical findings and indications for cCMV testing

| Maternal serology                      |
|----------------------------------------|
| Evidence of maternal CMV seroconversion|

| Maternal immunodeficiency              |
|----------------------------------------|
| HIV infection or immunosuppressive therapy|

| Symptoms and signs                     |
|----------------------------------------|
| Petechiae, purpura, or thrombocytopenia|
| Hepatosplenomegaly or hepatitis        |
| Jaundice                               |
| Microcephaly                           |
| Symmetric intrauterine growth retardation|
| Seizures or abnormal neurologic exam   |

| Audiological                           |
|----------------------------------------|
| Failed neonatal hearing screen         |
| Sensorineural hearing loss             |

| Prematurity                            |
|----------------------------------------|
| To assist the possible diagnosis of postnatal infection among high-risk infants|

| Laboratory parameters                  |
|----------------------------------------|
| Transaminitis                          |
| Conjugated hyperbilirubinemia          |
| Thrombocytopenia                       |

| Neuroimaging abnormalities             |
|----------------------------------------|
| Including periventricular calcifications or cysts, ventriculomegaly, white matter abnormalities, lenticulostriate vasculopathy |

| Ophthalmologic examination             |
|----------------------------------------|
| Chorioretinitis                        |

*Adapted from the European Consensus Guidelines [36••]*
Hearing evaluation

All infected infants should undergo audiologic testing [41]. Routine hearing screening of healthy newborns is performed with automated otoacoustic emissions (OAE) and/or brainstem evoked response audiometry (also called an automated or screening auditory brainstem response) [42]. However, most experts recommend that a diagnostic auditory brainstem response (ABR) be performed on newborns with cCMV, even if the hearing screen is normal [43].

Brain imaging

Neuroimaging should be performed on all newborns with cCMV. While the choice of imaging remains a subject of debate, at minimum, every infected newborn should receive a cranial ultrasound. Ultrasound is safe, relatively easy to perform, and highly sensitive for detecting central nervous system involvement, including germinolytic cysts, periventricular calcifications, and ventriculomegaly [44]. Infants with abnormal ultrasound findings should also undergo magnetic resonance imaging. The inability of ultrasound to identify white matter, posterior fossa, and cortical abnormalities has led to the earlier and more systematic use of magnetic resonance (MR) imaging [40, 45]. However, it is unclear if MR should be performed in newborns with normal neurological exams and reassuring ultrasound findings, since more severe lesions uncovered by MR (e.g., neuronal migration abnormalities) are typically not described in such cases [45, 46]. Furthermore, more subtle findings, such as non-specific white matter changes, identified by MR in isolation are currently of unclear clinical significance.

Ophthalmological evaluation

A fundoscopic examination should be performed by an ophthalmologist to assess the possibility of chorioretinitis, retinal hemorrhage or scarring, or optic atrophy [47, 48].

cCMV treatment considerations

Treatment of selected newborns with symptomatic cCMV is indicated with valganciclovir (16 mg/kg/dose PO every 12 h), for a duration of 6 months [36••, 49••]. This is based on clinical trial data that first showed that symptomatic newborns randomized to ganciclovir (6 mg/kg/dose IV every 12 h) for 6 weeks had significantly better hearing at 6 months compared to untreated controls [50]. Subsequently, newborns with symptomatic cCMV were randomized to oral valganciclovir for 6 months or for 6 weeks followed by placebo improvement in total hearing and neurodevelopment (cognitive, language, and motor) at 24 months of age in the 6-month group [51••]. The incidence of neutropenia was similar between the 6-month and 6-week valganciclovir groups, suggesting that neutropenia in newborns treated with the latter may
be at least in part attributable to the viral infection [51••]. Ganciclovir should be used in critically-ill patients, or when oral administration is not possible. In addition to bone marrow suppression, valganciclovir, and ganciclovir are rare possible causes of nephro- and hepatotoxicity; these drugs also carry theoretical risks of carcinogenicity and gonadotoxicity based on animal studies, but that have not been documented in humans.

Although all guidelines [36••, 49••, 52, 53] recommend antiviral treatment for neonates with moderate or severe cCMV, initiated as early as possible, the indications for treatment of mildly symptomatic infections are controversial and differ across guidelines. The recommendation to treat newborns with isolated SNHL, for example, varies by guideline and practitioner. We suggest that such infants should be evaluated case-by-case by a clinician experienced in cCMV, and the risks and benefits of valganciclovir should be discussed with the family. Asymptomatic newborns or children with late-onset hearing loss should not routinely be treated outside of a clinical trial due to a lack of evidence for benefit in these groups.

**Follow-up of children with cCMV**

*Monitoring during antiviral therapy*

For infants receiving valganciclovir, laboratory monitoring with a complete blood count and differential, liver transaminases, and creatinine is suggested at least every 2 weeks during the first month, then monthly until the end of therapy [14, 51••]. If neutropenia is severe (<500 cells/µL), treatment should be suspended [14]. In patients with severe neutropenia, and/or if continued antiviral treatment is required, hematopoietic growth factor (GSCF) treatment may be considered [14, 54]. Monitoring of the CMV viral load in blood is of unclear utility, though sustained viral suppression through 6 months of therapy has been correlated with better hearing outcomes [51••].

*Hearing*

Close audiologic follow-up is critical for all children with cCMV, to identify late-onset hearing loss among those with normal hearing at birth, and to monitor for progression in those with SNHL. The current recommended frequency of audiologic monitoring for a child with cCMV and normal hearing at birth is every 3–6 months for the first year, then every 6–12 months until age 3, and annually thereafter through age 6 years [43, 49••]. It appears that surveillance in these children can typically be performed using OAE in the absence of middle-ear effusion [43]. More frequent evaluations with ABR and/or behavioral audiometry are indicated in children with SNHL [55]. Prompt provision of appropriate support (hearing aids, cochlear implants, speech therapy, etc.) is essential to optimize language and educational outcomes [56]
Vestibular function

Vestibular evaluation in young children is complex, and there are currently no guidelines regarding how it should be performed in children with cCMV. Based on the high prevalence of dysfunction [31], vestibular assessment of all children affected by cCMV would be ideal [57]. After 3 months, when there is head support, vestibular evoked myogenic potentials may be performed. As the child grows, the vestibular function can be evaluated with other studies, such as the rotary chair or video head impulse tests [32, 57]. However, these evaluations require an experienced examiner and the cooperation of the child.

Vision

Chorioretinitis and other ophthalmologic abnormalities are commonly detected at birth in symptomatic cCMV infection, especially those with other central nervous system involvement, and may result in long-term visual impairment [58]. Follow-up should be dictated by the ophthalmologist for these children depending on their disease, but may not be indicated among those without abnormalities at birth [13, 49••].

Neurodevelopment

Neurodevelopmental evaluation by a pediatrician at least annually is recommended, with subspecialty referrals (e.g., developmental pediatrics, neurology, occupational therapy) as appropriate [33, 34].

Newborn cCMV screening

Programs to systematically perform CMV testing at birth on newborns with risk factors for, or findings consistent with, cCMV have become common [59–61]. This approach, which is technically case-finding but is usually referred to as “targeted CMV screening” has been adopted in many parts of N. America and Europe. Indeed, CMV testing of newborns that fail the hearing screen or have other findings suggestive of cCMV (Table 1.) should be considered the minimum standard of care. However, this targeted approach misses the majority of children without cCMV-related hearing loss, including nearly half of those that develop hearing loss in early infancy [62]. As such, the incorporation of CMV into universal screening programs is increasingly being considered and adopted [63, 64]. The main advantage of universal screening for cCMV is to identify all children at risk of developing late-onset SNHL, and thus allow hearing surveillance and early intervention [64]. In short, universal newborn CMV screening is required for ensuring efficient evaluation of infected newborns, consideration of treatment, and appropriate follow-up care. Given the enormous public health burden and disability costs [65], newborn CMV screening appears to be cost-effective as well as medically beneficial [66–68]. Challenges to the implementation of universal
newborn CMV screening programs include the poor sensitivity of DBS CMV PCR [69] and the fact that urine or saliva samples are currently not routinely collected at birth.

**Prevention of cCMV**

Education about behavioral measures to prevent CMV primary infection or reinfection during pregnancy, in particular around contact with saliva and urine of young children, is the mainstay of cCMV prevention at this time [70]. No vaccine against CMV is currently available for clinical use. However, several promising CMV vaccine candidates aimed at preventing cCMV are in clinical trials [71]. The use of CMV hyperimmune globulin is not recommended outside a clinical trial due to lack of proven efficacy to prevent vertical transmission or disease [72, 73]. Early evidence indicates that antenatal treatment with high-dose valacyclovir may be effective in MPI. A double-blind, randomized, placebo-controlled study evaluated oral valacyclovir (8 g/day) in pregnant women with evidence of primary infection acquired during the periconceptional period or in the first trimester of pregnancy. Fetal infection occurred significantly less often (11%) in the treatment group compared to the placebo group (29%) [74••]. Recently, another group published similar results [75•] from an observational cohort in which high-dose valacyclovir for treatment of first-trimester MPI was associated with a significantly lower rate of fetal infection (29% vs. 12%, \( p = 0.029 \)).

**Postnatal cytomegalovirus infection**

**Prevalence and presentation of pCMV**

Postnatal CMV infection (pCMV) is rarely clinically significant among immunologically-normal term infants. However, among preterm, particularly very low birth weight (VLBW; <1500 g), infants, pCMV is an important cause of acute morbidity, which can result in multi-organ disease and death [76]. pCMV disease in preterm infants typically presents in the second or third month of life, coinciding with the abundance of viral shedding in breast milk [76]. Risk factors for infant symptomatic infection include VLBW, gestational age <32 weeks, and level of DNA lactia [77••]. Three systematic reviews [78–80] published regarding CMV transmission via untreated or fresh breast milk found a rate of transmission to infants between 19 and 25%.

Symptoms of sepsis, including pneumonitis, hepatitis, and neutropenia/thrombocytopenia, occur in roughly 15% of VLBW infants with pCMV (Table 2). Necrotizing enterocolitis (NEC) has also been associated with pCMV in preterm infants [81], and a small proportion of NEC cases appear to be due to direct viral damage to the intestine [82]. Attributing clinical disease to pCMV infection can be challenging; however, since infection is
frequently asymptomatic and preterm infants typically have multiple possible causes of clinical deterioration [76].

Transmission

Breast milk

Nearly all lactating women who are seropositive for CMV will shed virus in breast milk at some point, though this tends to be intermittent [77••, 83]. DNA lactia and risk of transmission are highest at 4–8 weeks of lactation, and declines in the subsequent weeks [84].

Mucosal secretions

CMV-seropositive women can also shed virus in genital secretions [85]. Early pCMV infection, occurring within the first 4–6 weeks of life, may therefore also be acquired during passage through the birth canal [85]. Accordingly, prolonged rupture of membranes has been associated with an increased risk of early pCMV [86•].

Transfusions

As a result of routine leukofiltration, blood products are now a rare cause of pCMV [86•, 87].

| Table 2. Clinical presentation of pCMV in preterm infants |
|----------------------------------------------------------|
| Clinical manifestations | Comments |
|-------------------------|----------|
| Sepsis-like symptoms    | pCMV should be suspected with clinical deterioration of unclear etiology, particularly if no improvement is observed with antibiotic treatment |
| Hepatitis               | Jaundice, hepatomegaly and cholestasis (hyperbiliarubinaemia 66% and transaminitis 23%) |
| Marrow-suppression      | Thrombocytopenia, neutropenia, lymphopenia |
| Intestinal              | NEC, strictures, volvulus, and colitis |
| Pneumonitis             | Due to direct viral tissue damage and/or indirect inflammatory response |
| Retinopathy             | Increased risk of severe retinopathy of prematurity |
| Meningitis/encephalitis | Rare |
Long-term complications of pCMV

**Hearing-loss**

Most studies suggest that pCMV infection does not increase rates of long-term hearing loss in preterm infants [76, 88]. There are, however, case reports of bilateral SNHL and retrocochlear auditory neuropathy among preterm infants with pCMV [89, 90]. In addition, a large retrospective cohort study found that preterm infants with pCMV infection had an 80% increased relative risk of failing a hearing test [91].

**Neurodevelopmental outcome**

There are conflicting reports with respect to motor or cognitive outcomes between preterm infants with pCMV compared with uninfected controls. One prospective study [92] that followed VLBW infants with and without pCMV reported no differences in neurodevelopmental outcomes between 2 and 4.5 years; however, worse neurodevelopmental outcomes were observed among children with pCMV in this same cohort with longer follow-up [93]. Other prospective studies indicate functional MR or neurodevelopmental abnormalities among children with pCMV infection born pretermly compared with uninfected controls [94–96]. Further studies are required to verify whether there are any long-term neurodevelopmental effects of pCMV and differentiate these from the consequences of extreme prematurity.

**Bronchopulmonary dysplasia**

pCMV may be a risk factor for bronchopulmonary dysplasia (BPD), according to some studies, but not others [97•]. Given the pneumonitis and systemic inflammation associated with pCMV among preterm infants, a link to more severe BPD is plausible.

**Diagnosis**

CMV DNA PCR is present at high copy numbers in urine and saliva in pCMV but is also frequently detected in respiratory secretions (nasopharyngeal aspirate or bronchoalveolar lavage), blood, and cerebrospinal fluid [97•]. The diagnosis of the pCMV is confirmed by detection of virus in an infant without cCMV, i.e., with a negative saliva or urine CMV, PCR collected at <3 weeks of life (a negative DBS PCR does not rule out cCMV; see above). When a urine or saliva sample collected at <3 weeks of age is not
available to exclude cCMV, infants may be considered to have possible or probable pCMV if there is a clinical correlation with the detection of virus after 3 weeks of age, particularly if symptomatic improvement is temporally associated with antiviral treatment and virologic response.

**Treatment**

Evidence of the efficacy of antiviral treatment in children with pCMV infection is limited. Given the lack of clear associations with long-term complications, treatment is typically limited to severe disease compatible with pCMV. Ganciclovir is typically given at a dose of 6 mg/kg/dose IV every 12 h for at least 2 weeks, with a reevaluation of symptoms and CMV viral load. As long as clinical improvement is observed, treatment may be extended [98]. Experience with valganciclovir for treatment of pCMV in VLBW infants is even more limited but is an option (16 mg/kg PO even 12 h) for patients with resolving symptoms able to tolerate oral feeding [99]. Data on dosing and safety are limited among infants <32 weeks gestation.

**Prevention of pCMV through breast milk**

As mentioned above, the use of leukocyte-reduced blood products is highly effective in preventing transfusion-related pCMV. The use of strategies to reduce the risk of pCMV via human milk is a topic of debate. Although prevention of pCMV among VLBW infants is desirable, the benefits of methods to inactivate CMV must be weighed against potential undesirable effects on the nutritional and immunologic properties of breast milk.

**Freeze–thaw**

Freezing may reduce but does not eliminate CMV transmission through breast milk [100]. Negative effects on macro- and micronutrients in breast milk due to freezing have been described, including decreased energy content and fat [101].

**Pasteurization**

Holder pasteurization consists of heating at 62.5 °C for 30 min, effectively inactivates CMV as well as other potential pathogens, and is currently recommended for banking of human milk as well as for regular feeding preterm of infants [102]. However, pasteurization is reported to have greater negative impacts compared with freezing on host defense proteins in milk, as well as on numerous cytokines, hormones, and growth factors [103].
Other methods

Different treatments, such as short/rapid pasteurization (62 °C for 5 s), ultraviolet radiation, and high-pressure processing can also inactivate CMV, and may better preserve the beneficial attributes of human milk compared with classical pasteurization [104, 105]. Currently, however, there is no consensus among experts with respect to whether or how all breast milk for VLBW should be routinely processed [106•]. Additional research is needed to assess the potential harms and benefits of modifying breast milk in this vulnerable population, with respect to pCMV but also risks of other infections and NEC.

Conclusions

C conspicuously incurs an enormous burden of disease, which is likely even greater than previously appreciated, because of vestibular and neurobehavioral complications that are increasingly recognized among infected children who were asymptomatic at birth. The use of universal newborn CMV screening programs promises not only to improve the neurodevelopmental outcomes of large numbers of children. Until a preventive vaccine is available, education is critical to avoid maternal CMV (re)infection during pregnancy. Early evidence indicates the utility and short-term safety of high-dose valacyclovir treatment of pregnant women with primary CMV infection early in gestation. Additional studies are needed to optimize the care of children with cCMV and to identify predictors of long-term complications.

Much less is known about how best to manage pCMV, which is an important cause of acute morbidity and mortality in the neonatal intensive care unit. Though it is clear that antiviral treatment should be used in severe cases among preterm infants, additional data are needed regarding indications and optimal regimens for treatment in this vulnerable population. Furthermore, whether pCMV causes long-term sequelae is unresolved, complicating decisions regarding the routine use of strategies to inactivate the virus in human milk. Larger, well-conducted prospective studies are essential to better understand this highly prevalent and insidious infection.

Declarations

Conflict of interest
SG reports research funding and consulting fees from Moderna, Merck, GSK, VBI vaccines, and Altona Diagnostics. FK reports research funding Altona Diagnostics. ASC does not have existing conflicts of interest.
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