CONGENITAL CYTOMEGALOVIRUS INFECTION

Megan H Pesch,1 Katie Kuboushek,2 Michael M McKee,3 Marc C Thorne,2 Jason B Weinberg4

What you need to know

- Congenital cytomegalovirus (cCMV) is common, occurring in one in every 100-200 live births.
- The mainstay of prevention is prenatal education about behaviour change to reduce contact with saliva and urine of young children who may be shedding CMV.
- cCMV most often presents with no visible signs at birth, yet infected infants are at increased risk for sensorineural hearing loss in childhood.
- cCMV can be diagnosed shortly after birth using polymerase chain reaction to detect viral DNA in urine or saliva, or later in life by testing residual newborn dried blood spot (Guthrie card).
- All children with cCMV require close monitoring of their hearing and development.

Congenital cytomegalovirus (cCMV) infection is a common congenital infection, affecting one in every 100-200 live births globally. Long term neurodevelopmental sequelae occur in a quarter of children affected. This article provides a clinical update of the literature on the prevention, diagnosis, treatment, and anticipatory management of infants and children with cCMV. Recommendations from the 2015 European Society of Paediatric Infectious Diseases (ESPID) Expert Consensus Group (largely based on expert opinion) are presented along with more recent literature relevant to the general practitioner.

What is congenital cytomegalovirus infection?

Cytomegalovirus (CMV) can cause self-limited generalised symptoms such as fatigue and lymphadenopathy in most healthy individuals, including pregnant people. cCMV infection occurs when CMV transplacentally infects a developing fetus. The virus can cause damage to the placenta, and replicate in fetal central nervous system (CNS) cells, which may result in disrupted fetal development, miscarriage, or intrauterine fetal demise. Neonates with cCMV may experience a wide range of signs, symptoms, and long term sequelae (fig 1), although most experience no recognisable signs or symptoms.
Neonates born with visible signs or CNS involvement, commonly referred to as symptomatic, make up 10% of cCMV cases and are at increased risk for long term neurodevelopmental sequelae.\(^5\)

Neonates born without visible signs of infection or CNS involvement, referred to as asymptomatic, make up 90% of cases.\(^2\)\(^3\)

Approximately 15% of asymptomatic neonates develop isolated...
sensoneural hearing loss (SNHL), which may progress. Recent research has found an increased prevalence of cCMV in children with autism spectrum disorder, suggesting a possible association, although this remains an area of continued research.5-8

Who is at risk of having an infant with cCMV?

All people of childbearing age are at risk of contracting CMV and transmitting the virus to a fetus when pregnant. Primary infections occur when CMV is contracted for the first time just before or during pregnancy, posing a 30-35% risk of fetal transmission.1 Non-primary infections occur when the childbearing parent has pre-existing CMV immunity but is exposed to a different strain, or has a reactivation of a latent infection. The risk for fetal transmission is lower (~1%) with non-primary infections.9 Primary infections (versus non-primary) and those that occur earlier (versus later) in gestation are associated with poorer fetal outcomes.

CMV is transmitted through bodily fluids, most commonly through the saliva or urine of young children. Children who attend nursery or daycare may shed high levels of the CMV in their saliva or urine for weeks to months after acute symptoms resolve.10 Pregnant people in contact with young children (eg, parents, nursery teachers, paediatric healthcare providers) are at heightened risk of having pregnancies complicated by cCMV.11 12

How is it prevented, diagnosed, and managed during pregnancy?

While the focus of this clinical update is diagnosis and management of cCMV in the newborn, general practitioners should also know about the prevention, diagnosis, and management of CMV in pregnancy. General practitioners can play an important role in counselling for prenatal CMV risk reduction, which includes basic hygiene and behavioural change practices to avoid contact with potentially infectious bodily fluids (box 1).1-3 An expert review of CMV in pregnancy recommended counselling and subsequent behaviour changes beginning in the weeks before conception.13 Prenatal CMV antibody screening can be performed in individuals with symptoms; routine screening remains controversial.13 A congenital infection may be suspected based on fetal imaging findings (eg, intrauterine growth restriction, intracranial calcifications) or maternal seroconversion.

Box 1: Advice on ways to reduce the risk of CMV in pregnancy

- Avoid contact with children’s saliva—young children, especially those at daycare or nursery, commonly shed CMV in their bodily fluids. Avoid kissing on the lips; offer a cheek or forehead instead
- Avoid sharing food or utensils—including straws, utensils, or cups, especially with young children. Avoid sharing food with young children.
- Wash hands after nappy/diaper changes and wiping a child’s nose—washing hands thoroughly for at least 20 seconds or using hand sanitiser can reduce CMV transmission
- Avoid putting pacifiers in your mouth—avoid “cleaning” a child’s pacifier in your mouth if it falls on the floor

Refer cases of suspected cCMV infection in utero to a specialist in maternal fetal medicine.1 A prenatal diagnosis of cCMV can be made by polymerase chain reaction (PCR) detection of virus in amniotic fluid obtained via amniocentesis.3 14 Surveillance by ultrasound may help to identify potential cCMV related sequelae in the fetus; fetal brain abnormalities are associated with adverse outcomes, although studies have been limited by loss to follow-up and terminations of pregnancy.13 14 No licensed treatments exist to prevent vertical transmission or fetal disease, although valaciclovir has shown promise.13 15 16 Individuals who have previously had a child with cCMV are not at an increased risk in subsequent pregnancies.17

Two articles provide further discussion of perinatal cCMV prevention, management, and recommended counselling practice.14 18

How does neonatal cCMV infection present?

At birth, roughly 90% of neonates with cCMV have no overt signs of infection.2 19 Of the 10% who are symptomatic, most have a combination of one or more findings (fig 1).19 Classical signs of CMV in neonates include small for gestational age, microcephaly, jaundice, hepatosplenomegaly, petechial rash, seizures, or intracranial abnormalities (eg, calcifications). Sensoneural hearing loss (unilateral or bilateral) is also common (fig 2). Neonates with no overt symptoms may be diagnosed through systematic neonatal screening or retrospectively after sensorineural hearing loss is diagnosed later in childhood. A differential diagnosis for infants presenting with signs concerning for cCMV is shown in box 2.
### Box 2: Differential diagnosis for infants with signs suggestive of cCMV

- Congenital rubella
- Congenital toxoplasmosis
- Herpes simplex virus infection
- Inborn errors of metabolism
- Connexin 26 mutation
- Congenital Zika virus infection
- Intrauterine alcohol or substance use
- Biliary atresia or obstruction
- Sepsis

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**How is cCMV infection diagnosed in the neonate or child?**

cCMV may be diagnosed by urine or saliva PCR in the first 21 days of life. After that time it becomes difficult to distinguish congenital infection from postnatal infection.

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When based on clinical suspicion alone, 90% of symptomatic cases go undiagnosed at birth. Implementation of systematic neonatal cCMV screening, either universal or targeted to infants with hearing loss, increases diagnosis of both symptomatic and asymptomatic cases. Incidental findings or delayed onset symptoms may also lead to a diagnosis later in infancy or childhood.

**Neonates**

Test neonates with clinical signs suggestive of cCMV or with confirmed SNHL. CMV testing may be performed in the hospital after birth or as an outpatient, using urine or saliva PCR before 21 days of age, and ideally before 14 days. After 21 days, it is challenging to distinguish congenital from postnatal CMV infection, which is not typically associated with long term sequelae.

The ESPID consensus guidelines give preference to the use of urine rather than saliva for CMV PCR because of possible false positives in saliva from CMV shed in breastmilk. However, the difficulty...
of collecting urine from a neonate may be prohibitive. Saliva PCR is performed on a sample obtained from a cheek swab, and it can be performed as a point-of-care test. False positives can be reduced by collecting the sample 60 minutes or more after breastmilk consumption. A positive saliva PCR result should be confirmed with urine PCR.

**Infants and children older than 21 days**

Clinical suspicion for cCMV may be raised by a delayed onset or recognition of symptoms (fig 1), particularly SNHL. CMV PCR can be performed on a stored residual dried blood spot left over from newborn screening. The sensitivity of this approach is low (30-85%); a negative result cannot definitively rule out cCMV. If no dried blood spot is available, a definitive diagnosis of cCMV cannot be made.

No consensus recommendations exist for the presumptive diagnosis of cCMV. A definitive diagnosis of cCMV in an otherwise asymptomatic infant allows for close monitoring of hearing and development, and early intervention should concerns arise. However, close monitoring can still be implemented if only a presumptive diagnosis can be made.

If definitive diagnosis of cCMV cannot be made, additional testing may lend support for or against a presumptive diagnosis. While the ESPID guidelines do not address how to rule out cCMV in children older than 21 days, we find the following tests and parameters useful in our own clinical practice based on existing literature. First, evaluate for findings consistent with cCMV through cranial imaging, eye examination, and/or laboratory studies. Second, rule out other possible contributors to the clinical presentation (eg, genetic causes of hearing loss). Third, test for previous exposure to CMV by measuring CMV IgG. A positive result cannot differentiate between congenital and postnatal disease, but a negative result substantially diminishes the likelihood of cCMV. For children <18 months, a positive urine or saliva CMV PCR confirms previous exposure to the virus (we caution against using IgG in this age group because of the potential for persistence of maternal antibodies in the infant). For children older than 18 months, a positive CMV IgG suggests previous exposure to the virus. Shedding of CMV in urine and saliva of a child with cCMV may not persist indefinitely, making those tests less reliable in older children.

**How is congenital CMV infection managed?**

ESPID recommendations for the initial evaluation, scheduled monitoring, and ongoing surveillance of an infant with cCMV are summarised in fig 3. Additional recommendations based on more recent studies and the authors’ expert opinion are presented in table 1.
Fig 3 | Overview of the diagnosis, evaluation, treatment, and follow-up of infants with congenital cytomegalovirus

- **Diagnosis**
  - Patient suspected of having congenital CMV
    - Yes: Age >21 days
      - Urine or saliva CMV PCR
        - Positive: Confirm saliva results with urine PCR
          - Confirms diagnosis of congenital CMV
        - Negative: Rule out cCMV
      - No: Dried blood spot CMV PCR
        - Approximately 84% sensitive, varies between labs
          - Negative: Cannot rule out cCMV
  
- **Additional Evaluation**
  - Ophthalmology
    - Dilated exam with renal evaluation
  - Infectious diseases
    - Discuss treatment, oversee evaluation
  - Audiology
    - Brainstem-evoked response
  - Laboratory evaluation
    - Complete blood count, liver enzymes, bilirubin, renal function
  - Cranial imaging
    - Cranial ultrasound then MRI if abnormalities identified

- **Treatment**
  - Symptomatic
    - Signs at birth and/or intracranial abnormalities
      - Consider antiviral medication
        - Refer to or consult with a paediatric infectious disease specialist
        - Initiate <1 month of age if possible
        - Oral valganciclovir (16mg/kg PO BID for 6 months) is the current preferred drug
        - Side effects include neutropenia and hepatic dysfunction
      - Check baseline CBC with differential weekly for six weeks, then every other week for a month, then monthly thereafter
      - Check baseline LFTs and monthly thereafter
  - Asymptomatic
    - Continue close follow-up and monitoring as below
  - Asymptomatic with isolated SNHL
    - Continue close follow-up and monitoring as below

- **Monitoring**
  - Ophthalmology
    - Symptomatic children should be seen annually until 5 years. Asymptomatic children can follow up as needed from baseline exam
  - Audiology
    - All children require hearing exams every 3-6 months until age 3, then annually through at least 6 years
  - Developmental surveillance
    - Routine surveillance by primary care provider; refer those treated with valganciclovir for specialist testing at 12 and 24 months
  - Subspecialists and therapies
    - If treated with antiviral medication, follow with ID until 2 years. Subspecialists care on a case-by-case basis, including speech, occupational, and physical therapies

CBC: complete blood count; LFT: liver function test
Table 1 | Primary care considerations for infants and children with cCMV

<table>
<thead>
<tr>
<th>Age</th>
<th>Potential clinical concerns*</th>
<th>Possible physical examination findings*</th>
<th>Disease growth, developmental surveillance</th>
<th>Referrals and other considerations</th>
</tr>
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<tbody>
<tr>
<td>Initial evaluation Birth to 1 month</td>
<td>Feeding difficulties, seizures, lethargy</td>
<td>Laboratory studies to assess extent of disease: complete blood count, liver enzymes, conjugated bilirubin</td>
<td>Refer to paediatric ophthalmology (rule out chorioretinitis) Refer to audiology, even if the newborn hearing screen was passed, to establish care and hearing monitoring Refer to or consult with a paediatric infectious diseases specialist to consider additional investigations and antiviral medication Brain MRI for those with clinically detectable CNS involvement or cranial ultrasound abnormalities. Consider referral to a paediatric neurologist if concerned for substantial CNS involvement</td>
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<tr>
<td>1 month to 1 year</td>
<td>Feeding difficulties, seizures, SNHL, chorioretinitis, developmental delays, sleep difficulties</td>
<td>Monitor growth trajectories, including trends in head circumference (recovery from or persistence of microcephaly) Routine developmental screening at well visits</td>
<td>Paediatric ophthalmology (annually through age 5 for symptomatic infants) Continued monitoring by audiology (every 3-6 months until age 3, annually until age 6) Continued follow-up with a paediatric infectious disease specialist (until 24 months) Refer to a specialist for developmental assessment at 12 months in infants treated with valganciclovir Refer to early intervention services if available*</td>
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<tr>
<td>1-6 years</td>
<td>Feeding difficulties, seizures/epilepsy, SNHL, vision loss, developmental delay, learning difficulties, sleep difficulties, behaviour problems, balance problems, mobility needs</td>
<td>Monitor growth trajectories, including trends in head circumference Routine developmental screening at well visits, including autism screening*</td>
<td>Continued monitoring by paediatric ophthalmology (annual through age 5 for symptomatic infants) Continued monitoring by audiology (every 6 months) Continued follow-up with a paediatric infectious disease specialist (until 24 months) Consider vestibular testing and physical therapy if balance concerns arise Refer to a specialist for developmental assessment at 24 months in infants treated with valganciclovir Continued involvement with early intervention services if available* Transition to special education supports as needed*</td>
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<td>6-18 years</td>
<td>Feeding difficulties, seizures/epilepsy, SNHL, vision loss, developmental delay, learning difficulties, sleep difficulties, behaviour problems, balance problems, mobility needs, increasing independence in self-care</td>
<td>Monitor growth trajectories, including trends in head circumference as needed Routine developmental screening at well visits, including autism screening*</td>
<td>Continued vision and hearing monitoring as needed. Consider neuropsychological testing for cognitive concerns* Consider special education supports as needed* Consider vestibular testing and physical therapy if balance concerns arise* Slowly increase the child’s autonomy over their own medical needs (eg, daily hearing aid care, or stretches) as appropriate*</td>
</tr>
</tbody>
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Recommendation from Luck et al, 2017, unless otherwise indicated.

MRI=magnetic resonance imaging, SNHL=sensorineural hearing loss

* Denotes authors’ recommendation not formally supported by guidelines at this time.
Antiviral therapy

Treatment with a six month course of valganciclovir starting in the first month of life has been associated with improved hearing and developmental outcomes at 24 months.²⁸ Owing to the risk of associated toxicities, particularly neutropenia, ESPID experts recommend valganciclovir treatment for infants with symptomatic disease (full consensus) and those with isolated sensorineural hearing loss (majority consensus), but not for asymptomatic infants.² Infants should be monitored for toxicities by a paediatric infectious disease specialist throughout the treatment course.²³ ²⁸

Hearing surveillance

Serial audiological evaluations—starting at baseline and continuing every 3-6 months until 3 years, and then annually until 6 years—are recommended by ESPID because of the high risk of hearing deterioration in this period.² ²⁹ Others recommend continuing routine audiological evaluations through adolescence.³ Hearing amplification and early access to oral or sign language can improve educational and communication outcomes in children with hearing loss.³⁰ ³¹

Developmental surveillance

Children with cCMV, even those who are asymptomatic, may be at increased risk for neurodevelopmental sequelae; this remains an area of active research.³³ In addition to routine developmental monitoring, general practitioners should keep a heightened suspicion for autism spectrum disorder, although evidence to support formal screening recommendations is lacking. Refer children who received antiviral treatment for formal neurodevelopmental assessments at ages 12 months and 24 months.²

What are the long term outcomes for children with cCMV infection?

The range of possible neurodevelopmental outcomes in children with cCMV is wide, and is associated with CNS involvement (fig 2).⁵ Hearing loss

Sensorineural hearing loss occurs in 40-60% of symptomatic and 10-14% of asymptomatic infants with cCMV.¹⁹ ³³ Factors predictive of delayed onset hearing loss have not been identified.

Cognitive

Cognitive outcomes are strongly tied to the presence of intracranial involvement,³⁴ with just under half (43%) of those with such involvement having an intellectual disability. Asymptomatic children do not appear to have functional differences in cognitive or academic skills compared with controls, although this remains an area of active inquiry.³³ ³⁵

Gross motor

Intracranial abnormalities at birth (occurring in 5-9% of all cases) are associated with increased risk of major motor disability, including cerebral palsy.³⁶ Vestibular, gaze, and balance disorders are also common.³⁷ Consider referrals for vestibular testing, physical therapy, supportive bracing, or mobility assistance in those with gross motor delays.

What can we expect in the future?

Prevention

Promising CMV vaccine platforms are currently in phase II and III clinical trials.³⁸ An efficacious, safe, and widely accepted CMV vaccine could have a substantial impact on public health, hypothetically reducing the incidence of cCMV related pregnancy loss, SNHL, and neurodevelopmental disabilities.

Early detection

Universal and targeted screening approaches for cCMV are gaining traction.⁶ Reflexive testing of infants who fail their newborn hearing screen increases detection of infants with cCMV associated SNHL, but it fails to identify nearly half of cases.²¹ The cost-benefit analysis of universal screening remains a topic of debate.³⁹

Development

Studies of large cohorts of universally screened infants are ongoing.²² The granulnar characterisation of neurodevelopmental outcomes from these studies will be important to inform policy and clinical care guidelines.

Treatment

An ongoing phase II trial in the US is exploring the use of valganciclovir in asymptomatic infants with isolated sensorineural hearing loss, which has previously been studied in Europe.³⁰ Aside from antiviral medication, disease specific behavioural interventions and family support systems need to be developed.

Education into practice

- Think about awareness regarding prevention and diagnosis of cCMV in your practice. To what extent do you counsel individuals of childbearing potential about prevention of cCMV?
- How might you alter your practice to diagnose, monitor, and (if needed) manage more infants with cCMV?

Information resources for patients

- National CMV Foundation. Free resource about congenital CMV from the National CMV Foundation (USA). This website includes educational resources, including flyers about CMV prevention for clinical and public settings in many different languages. Information is evidence based and written largely for non-healthcare professionals. https://www-nationalcmv.org
- CMV Action. Free resource that provides straightforward information about congenital CMV, from prevention to treatment, from CMV Action (UK). Offers direct support from other CMV parent volunteers, a listing of social media support groups and international CMV organisations, in addition to webinars, fundraisers, and events. Information is written largely for parents and caregivers. https://cmvaction.org.uk/
- The Israeli Association for CMV Pregnancy. Free informational resources for pregnant people about congenital CMV, including detailed information about diagnosis and monitoring during pregnancy and after delivery. Recommendations for parents about cCMV. Information is written largely for non-healthcare professionals. https://www-cmvco-il/en/

Additional educational resources (for healthcare providers)

How this article was created

We obtained sources for this article from a Medline search (search terms: congenital cytomegalovirus + diagnosis + prevention + treatment + sequelae, and congenital cytomegalovirus + hearing + cognitive + development + outcomes). Cochrane reviews were also consulted around prevention and treatment of congenital CMV, although these reviews were relatively dated (2003 and 2011). The 2015 International and the European Society for Paediatric Infections Diseases expert consensus guidelines were also consulted.

How patients were involved in the creation of this article

Megan Pesch is the mother of a young daughter with congenital CMV. She contributed in drafting and revising this manuscript and recommended emphasising the importance of prenatal education around cCMV prevention in this article.


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