[1] Department of Pediatrics, Division of Developmental and Behavioral Pediatrics, University of Michigan, Ann Arbor, MI, USA

[2] Department of Otolaryngology and Head and Neck Surgery, Division of Pediatric Otolaryngology, University of Michigan, Ann Arbor, MI, USA

[3] Department of Family Medicine, University of Michigan, Ann Arbor, MI, USA

[4] Department of Pediatrics, Division of Pediatric Infectious Diseases, University of Michigan, Ann Arbor, MI, USA

Correspondence to M H Pesch
pesch@umich.edu
http://orcid.org/0000-0002-8212-2241

Cite this as: *BMJ* ${year};373:n1212
http://dx.doi.org/10.1136/bmj.n1212
Published:

CLINICAL UPDATES

Congenital cytomegalovirus infection

Megan H Pesch, [1] Katie Kuboushek, [2] Michael M McKee, [3] Marc C Thorne, [2] Jason B Weinberg[4]

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.[1] 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.[2]

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.[3] 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.[4] 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.[3]

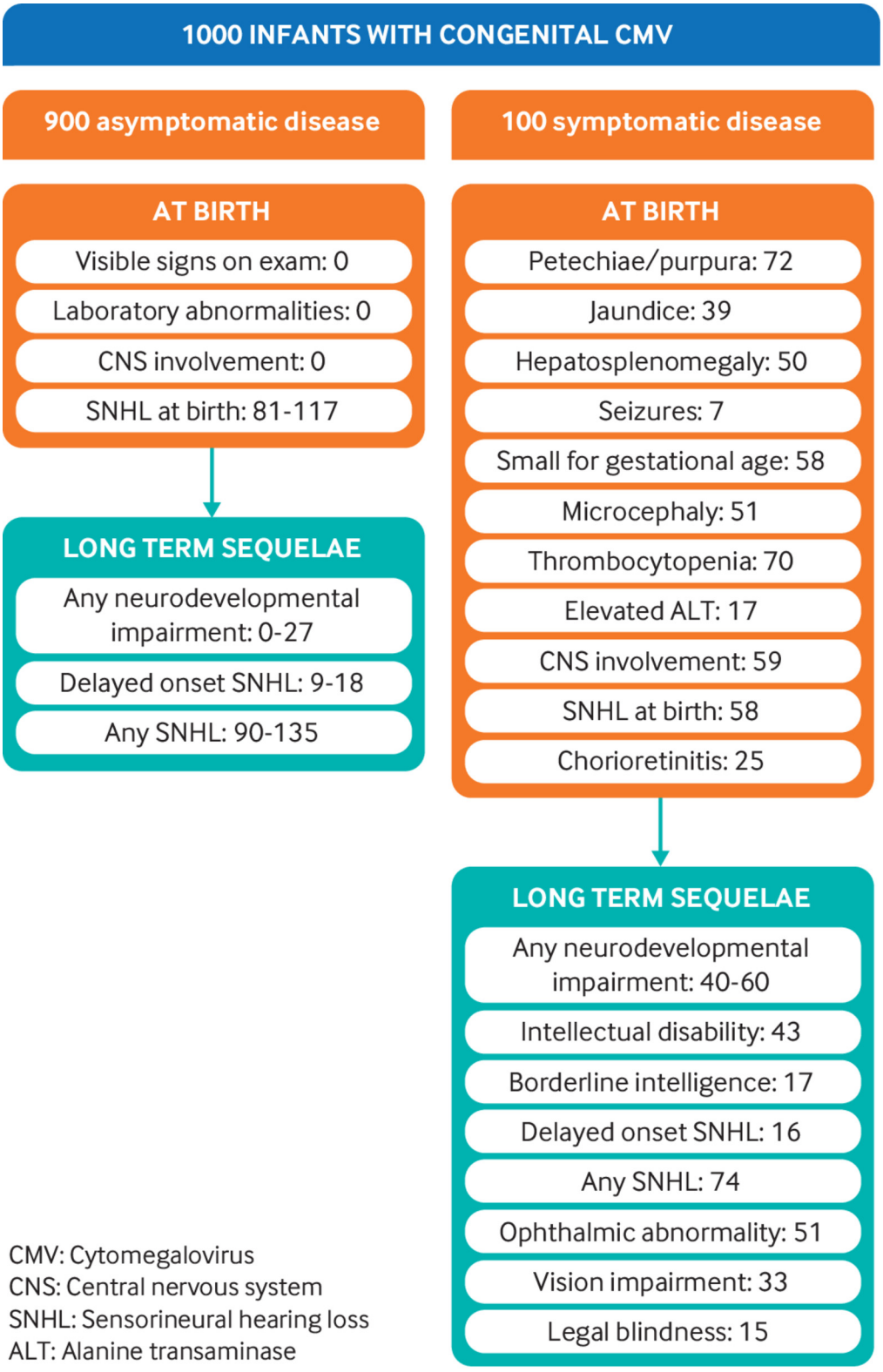


Fig 1 | Expected incidence of disease manifestations and developmental outcomes of infants with congenital cytomegalovirus demonstrated in 1000 hypothetical infants born with congenital cytomegalovirus

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

sensorineural 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.[6-8]

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 cCMV in pregnancy. General practitioners can play an important role in counselling for prenatal cCMV 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.[3] A prenatal diagnosis of cCMV can be made by polymerase chain reaction (PCR) detection of virus in amniotic fluid obtained via amniocentesis.[3 13] 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 cCMV in neonates include small for gestational age, microcephaly, jaundice, hepatosplenomegaly, petechial rash, seizures, or intracranial abnormalities (eg, calcifications). Sensorineural 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.

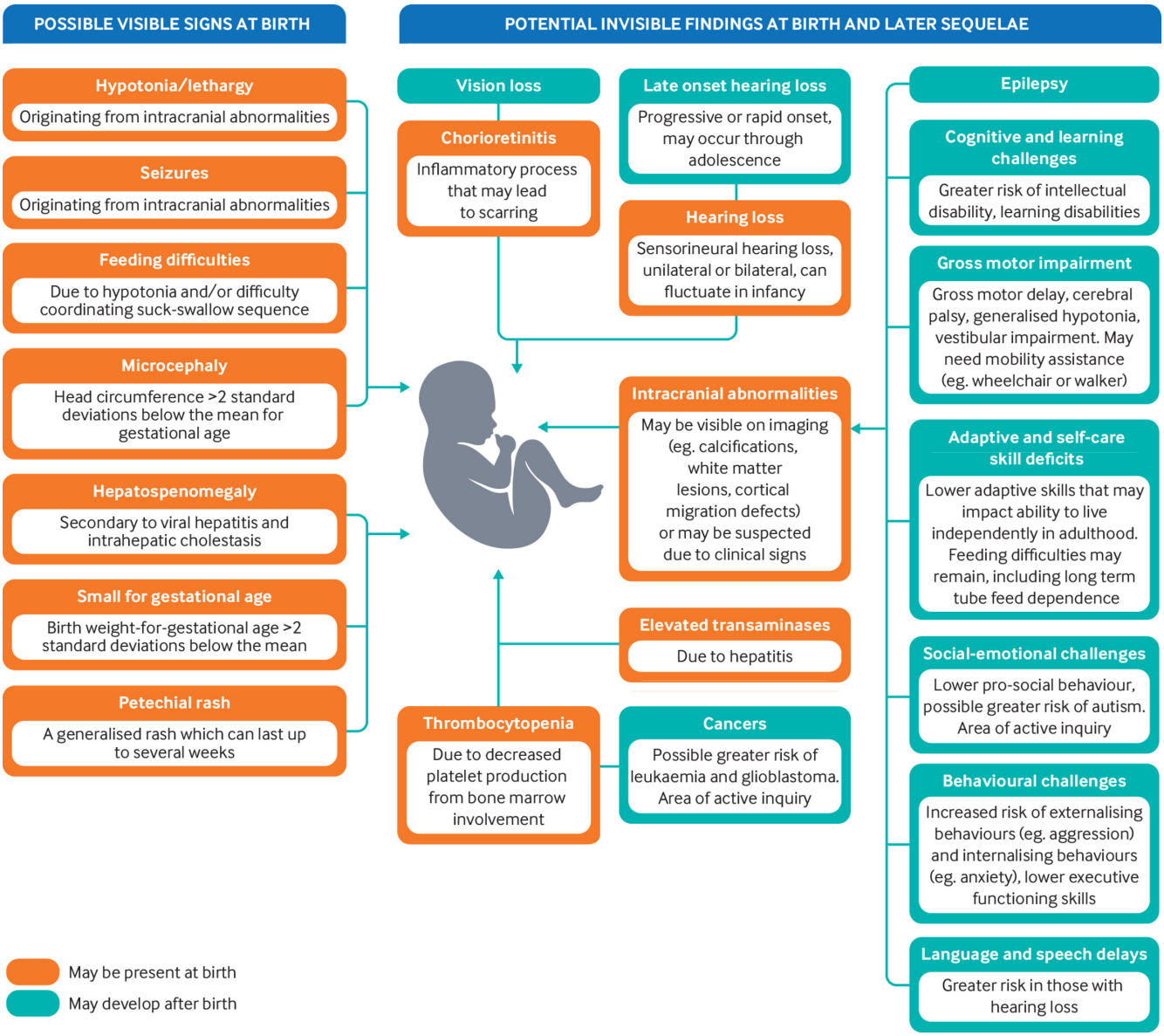


Fig 2 | Potential clinically visible and invisible signs and sequelae of cCMV at birth and later in life

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

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.

When based on clinical suspicion alone, 90% of symptomatic cases go undiagnosed at birth.[20] Implementation of systematic neonatal cCMV screening, either universal or targeted to infants with hearing loss, increases diagnosis of both symptomatic and asymptomatic cases.[21] 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.[2] CMV testing may be performed in the hospital after birth or as an outpatient,[22] using urine or saliva PCR before 21 days of age, and ideally before 14 days.[2 3] After 21 days, it is challenging to distinguish congenital from postnatal CMV infection,[23] 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.[2 24 25] 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.[26] 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.[2]

Infants and children older than 21 days

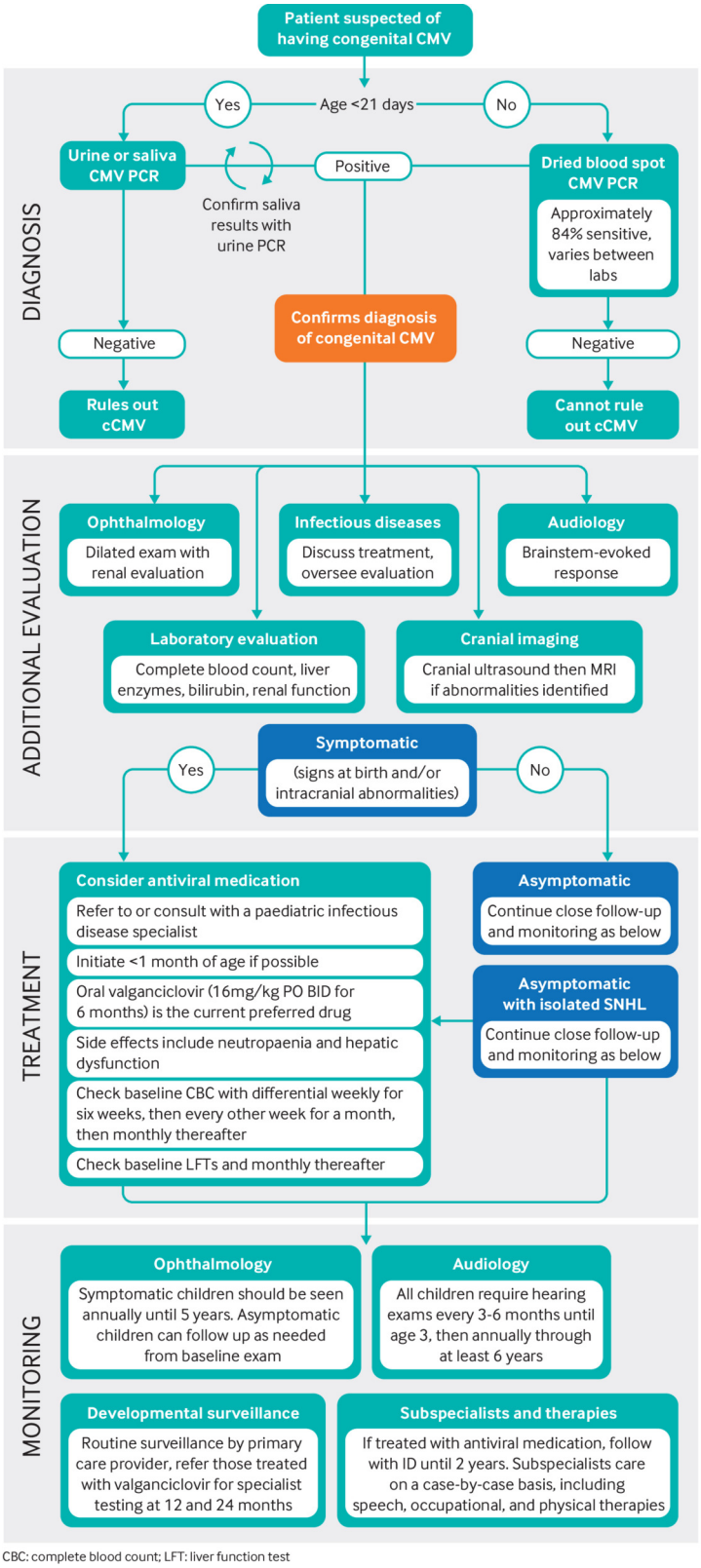
Clinical suspicion for cCMV may be raised by a delayed onset or recognition of symptoms (fig 1), particularly SNHL. CMV PCR can be performed on a stored residual dried blood spot left over from newborn screening. The sensitivity of this approach is low (30-85%); a negative result cannot definitively rule out cCMV.[2 22] 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,[2] we find the following tests and parameters useful in our own clinical practice based on existing literature.[27] 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.[27]

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.[2] Additional recommendations based on more recent studies and the authors' expert opinion are presented in table 1.



CBC: complete blood count; LFT: liver function test

Fig 3 | Overview of the diagnosis, evaluation, treatment, and follow-up of infants with congenital cytomegalovirus

Table 1 | Primary care considerations for infants and children with cCMV

Age	Potential clinical concerns*	Possible physical examination findings*	Disease growth, developmental surveillance	Referrals and other considerations
Initial evaluation Birth to 1 month	Feeding difficulties, seizures, lethargy	Small for gestational age, microcephaly, low tone, petechial or purpuric rash, absent red reflex, jaundice, hepatosplenomegaly, diminished or absent startle or response to sound	Laboratory studies to assess extent of disease: complete blood count, liver enzymes, conjugated bilirubin Cranial ultrasound to evaluate for visible calcifications or anomalies that would indicate symptomatic disease Monitor for appropriate weight gain and growth	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
1 month to 1 year	Feeding difficulties, seizures, SNHL, chorioretinitis, developmental delays, sleep difficulties	Persistent low tone or developing spasticity, low core strength, microcephaly, persistent hepatosplenomegaly	Monitor growth trajectories, including trends in head circumference (recovery from or persistence of microcephaly) Routine developmental screening at well visits	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 Referral to early intervention services if available*
1-6 years	Feeding difficulties, seizures/epilepsy, SNHL, vision loss, developmental delay, learning difficulties, sleep difficulties, behaviour problems, balance problems, mobility needs	Persistent low tone or developing spasticity, restricted range of motion from spasticity, low core strength	Monitor growth trajectories, including trends in head circumference Routine developmental screening at well visits, including autism screening*	Continued monitoring by paediatric ophthalmology (annual through age 5 for symptomatic) Continued monitoring by audiology (every six 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*
6-18 years	Feeding difficulties, seizures/epilepsy, SNHL, vision loss, developmental delay, learning difficulties, sleep difficulties, behaviour problems, balance problems, mobility needs, increasing independence in self-care	Persistent low tone or developing spasticity, restricted range of motion from spasticity, low core strength	Monitor growth trajectories, including trends in head circumference as needed Routine developmental screening at well visits, including autism screening*	Continued vision and hearing monitoring as needed. Consider neuropsychological testing for cognitive concerns* Continue 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*

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.[2 3 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]

Vision surveillance

Refer infants with cCMV for an ophthalmologic evaluation at diagnosis followed by yearly surveillance until age 5 in those with symptomatic disease.[2] Delayed onset chorioretinal sequelae are rare.[32]

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.[16] 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 granular 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.[40] 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.cmv.co.il/en/

Additional educational resources (for healthcare providers)

- Australian Government Department of Health pregnancy care guidelines—cytomegalovirus. Free resource from the Australian government for healthcare providers caring for women of childbearing age and expectant mothers around antenatal prevention and testing for CMV. https://www.health.gov.au/resources/pregnancy-care-guidelines/part-g-targeted-maternal-health-tests/cytomegalovirus .

- Centers for Disease Control and Prevention. CMV fact sheet for healthcare providers. Free fact sheet for healthcare providers of young children, basic facts and guidance around congenital CMV diagnosis, treatment, and monitoring. https://www.cdc.gov/cmv/downloads/identifying-cmv.pdf

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 Infectious 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.

Provenance and peer review: commissioned; externally peer reviewed.

Contributor and guarantor information: The idea for this article, the literature search and drafting of this article is attributed to Megan Pesch who accepts full responsibility for the finished article. Katie Kuboushek, Michael McKee, Marc Thorne and Jason Weinberg contributed to the conceptualisation of the scope and focus of this article, contributed expert knowledge, critically reviewed and edited the final article. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interests disclosed: We have read and understood the *BMJ* policy on declaration of interests and declare the following interests: MP is an unpaid board member of National CMV Foundation.

1 Marsico C, Kimberlin DW. Congenital cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment. *Ital J Pediatr* 2017;43:38. doi: 10.1186/s13052-017-0358-8 pmid: 28416012

2 Luck SE, Wieringa JW, Blázquez-Gamero D, etalESPID Congenital CMV Group Meeting, Leipzig 2015. Congenital cytomegalovirus: a European expert consensus statement on diagnosis and management. *Pediatr Infect Dis J* 2017;36:1205-13. doi: 10.1097/INF.0000000000001763 pmid: 29140947

3 Rawlinson WD, Boppana SB, Fowler KB, etal. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis* 2017;17:e177-88. doi: 10.1016/S1473-3099(17)30143-3 pmid: 28291720

4 Page JM, Bardsley T, Thorsten V, etal. Stillbirth associated with infection in a diverse US cohort. *Obstet Gynecol* 2019;134:1187-96. doi: 10.1097/AOG.0000000000003515 pmid: 31764728

5 Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. *Clin Infect Dis* 2013;57(Suppl 4):S178-81. doi: 10.1093/cid/cit629 pmid: 24257422

6 Zhang XY, Fang F. Congenital human cytomegalovirus infection and neurologic diseases in newborns. *Chin Med J (Engl)* 2019;132:2109-18. doi: 10.1097/CM9.0000000000000404 pmid: 31433331

7 Maeyama K, Tomioka K, Nagase H, etal. Congenital cytomegalovirus infection in children with autism spectrum disorder: systematic review and meta-analysis. *J Autism Dev Disord* 2018;48:1483-91. doi: 10.1007/s10803-017-3412-x pmid: 29185167

8 Slawinski BL, Talge N, Ingersoll B, etal. Maternal cytomegalovirus sero-positivity and autism symptoms in children. *Am J Reprod Immunol* 2018;79:e12840. doi: 10.1111/aji.12840 pmid: 29520885

9 Coppola T, Mangold JF, Cantrell S, Permar SR. Impact of maternal immunity on congenital cytomegalovirus birth prevalence and infant outcomes: a systematic review. *Vaccines (Basel)* 2019;7:129. doi: 10.3390/vaccines7040129 pmid: 31561584

10 Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit?*Rev Med Virol* 2014;24:291-307. doi: 10.1002/rmv.1790 pmid: 24760655

11 Leruez-Ville M, Guilleminot T, Stirnemann J, etal. Quantifying the burden of congenital cytomegalovirus infection with long-term sequelae in subsequent pregnancies of women seronegative at their first pregnancy. *Clin Infect Dis* 2020;71:1598-603. doi: 10.1093/cid/ciz1067 pmid: 31665306

12 Fowler KB, Stagno S, Pass RF. Maternal immunity and prevention of congenital cytomegalovirus infection. *JAMA* 2003;289:1008-11. doi: 10.1001/jama.289.8.1008 pmid: 12597753

13 Leruez-Ville M, Foulon I, Pass R, Ville Y. Cytomegalovirus infection during pregnancy: state of the science. *Am J Obstet Gynecol* 2020;223:330-49. doi: 10.1016/j.ajog.2020.02.018 pmid: 32105678

14 Bartlett AW, Hamilton ST, Shand AW, Rawlinson WD. Fetal therapies for cytomegalovirus: What we tell prospective parents. *Prenat Diagn* 2020;40:1681-92. doi: 10.1002/pd.5692 pmid: 32271956

15 Shahar-Nissan K, Pardo J, Peled O, etal. Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial. *Lancet* 2020;396:779-85. doi: 10.1016/S0140-6736(20)31868-7 pmid: 32919517

16 Rawlinson WD, Palasanthiran P, Hall B, etal. Neonates with congenital cytomegalovirus and hearing loss identified via the universal newborn hearing screening program. *J Clin Virol* 2018;102:110-5. doi: 10.1016/j.jcv.2018.03.006 pmid: 29571077

17 Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol* 2007;17:253-76. doi: 10.1002/rmv.535 pmid: 17579921

18 Kilby MD, Ville Y, Acharya G. Screening for cytomegalovirus infection in pregnancy. *BMJ* 2019;367:l6507. doi: 10.1136/bmj.l6507 pmid: 31744814

19 Lanzieri TM, Leung J, Caviness AC, etal. Long-term outcomes of children with symptomatic congenital cytomegalovirus disease. *J Perinatol* 2017;37:875-80. doi: 10.1038/jp.2017.41 pmid: 28383538

20 Sorichetti B, Goshen O, Pauwels J, etal. Symptomatic congenital cytomegalovirus infection is underdiagnosed in British Columbia. *J Pediatr* 2016;169:316-7. doi: 10.1016/j.jpeds.2015.10.069 pmid: 26597435

21 Fowler KB, McCollister FP, Sabo DL, etalCHIMES Study. A targeted approach for congenital cytomegalovirus screening within newborn hearing screening. *Pediatrics* 2017;139:e20162128. doi: 10.1542/peds.2016-2128 pmid: 28049114

22 Dollard SC, Dreon M, Hernandez-Alvarado N, etal. Sensitivity of dried blood spot testing for detection of congenital cytomegalovirus infection. *JAMA Pediatr* 2021;175:e205441. doi: 10.1001/jamapediatrics.2020.5441 pmid: 33523119

23 Weimer KED, Kelly MS, Permar SR, Clark RH, Greenberg RG. Association of adverse hearing, growth, and discharge age outcomes with postnatal cytomegalovirus infection in infants with very low birth weight. *JAMA Pediatr* 2020;174:133-40. doi: 10.1001/jamapediatrics.2019.4532 pmid: 31790557

24 Exler S, Daiminger A, Grothe M, Schalasta G, Enders G, Enders M. Primary cytomegalovirus (CMV) infection in pregnancy: Diagnostic value of CMV PCR in saliva compared to urine at birth. *J Clin Virol* 2019;117:33-6. doi: 10.1016/j.jcv.2019.05.015 pmid: 31176209

25 Ross SA, Michaels MG, Ahmed A, etal. Contribution of breastfeeding to false-positive saliva polymerase chain reaction for newborn congenital cytomegalovirus screening. *J Infect Dis* 2018;217:1612-5. doi: 10.1093/infdis/jiy057 pmid: 29401303

26 Gantt S, Bitnun A, Renaud C, Kakkar F, Vaudry W. Diagnosis and management of infants with congenital cytomegalovirus infection. *Paediatr Child Health* 2017;22:72-4. doi: 10.1093/pch/pxx002 pmid: 29479184

27 Cannon MJ, Hyde TB, Schmid DS. Review of cytomegalovirus shedding in bodily fluids and relevance to congenital cytomegalovirus infection. *Rev Med Virol* 2011;21:240-55. doi: 10.1002/rmv.695 pmid: 21674676

28 Kimberlin DW, Jester PM, Sánchez PJ, etalNational Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med* 2015;372:933-43. doi: 10.1056/NEJMoa1404599 pmid: 25738669

29 Fletcher KT, Horrell EMW, Ayugi J, etal. The natural history and rehabilitative outcomes of hearing loss in congenital cytomegalovirus: a systematic review. *Otol Neurotol* 2018;39:854-64. doi: 10.1097/MAO.0000000000001861 pmid: 29912824

30 World Health Organization. Deafness and hearing loss. 2019. https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss

31 Ching TYC, Dillon H, Leigh G, Cupples L. Learning from the Longitudinal Outcomes of Children with Hearing Impairment (LOCHI) study: summary of 5-year findings and implications. *Int J Audiol* 2018;57(suppl 2):S105-11. doi: 10.1080/14992027.2017.1385865 pmid: 29020839

32 Jin HD, Demmler-Harrison GJ, Coats DK, etalCongenital CMV Longitudinal Study Group. Long-term visual and ocular sequelae in patients with congenital cytomegalovirus infection. *Pediatr Infect Dis J* 2017;36:877-82. doi: 10.1097/INF.0000000000001599 pmid: 28399055

33 Bartlett AW, McMullan B, Rawlinson WD, Palasanthiran P. Hearing and neurodevelopmental outcomes for children with asymptomatic congenital cytomegalovirus infection: A systematic review. *Rev Med Virol* 2017. doi: 10.1002/rmv.1938. pmid: 28876493

34 Pinninti SG, Rodgers MD, Novak Z, etal. Clinical predictors of sensorineural hearing loss and cognitive outcome in infants with symptomatic congenital cytomegalovirus infection. *Pediatr Infect Dis J* 2016;35:924-6. doi: 10.1097/INF.0000000000001194 pmid: 27195603

35 Lopez AS, Lanzieri TM, Claussen AH, etalCongenital Cytomegalovirus Longitudinal Study Group. Intelligence and academic achievement with asymptomatic congenital cytomegalovirus infection. *Pediatrics* 2017;140:e20171517. doi: 10.1542/peds.2017-1517 pmid: 29066580

36 Noyola DE, Demmler GJ, Nelson CT, etalHouston Congenital CMV Longitudinal Study Group. Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *J Pediatr* 2001;138:325-31. doi: 10.1067/mpd.2001.112061 pmid: 11241037

37 Pinninti S, Christy J, Almutairi A, Cochrane G, Fowler KB, Boppana S. Vestibular, gaze, and balance disorders in asymptomatic congenital cytomegalovirus infection. *Pediatrics* 2021;147:e20193945. doi: 10.1542/peds.2019-3945 pmid: 33419867

38 Schleiss MR, Permar SR, Plotkin SA. Progress toward development of a vaccine against congenital cytomegalovirus infection. *Clin Vaccine Immunol* 2017;24:e00268. doi: 10.1128/CVI.00268-17 pmid: 29046308

39 Economic assessments of the burden of congenital cytomegalovirus infection and the cost-effectiveness of prevention strategies. In *Seminars in perinatology*. Grosse SD, Dollard SC, Ortega-Sanchez IR, ed. Elsevier. 2021.

40 Pasternak Y, Ziv L, Attias J, Amir J, Bilavsky E. Valganciclovir is beneficial in children with congenital cytomegalovirus and isolated hearing loss. *J Pediatr* 2018;199:166-70. doi: 10.1016/j.jpeds.2018.02.028 pmid: 29605391