Archives of
Disease in Childhood

Managing Challenges in Congenital CMV: Current Thinking

Journal:	*Archives of Disease in Childhood*
Manuscript ID	archdischild-2022-323809.R1
Article Type:	Review
Date Submitted by the Author:	31-Oct-2022
Complete List of Authors:	Jones, Christine; University of Southampton Faculty of Medicine, Clinical and Experimental Sciences; University Hospital Southampton NHS Foundation Trust, Clinical Research Facility and Biomedical Research Centre bailey, heather; University College London, Institute for Global Health Bamford, Alasdair; Great Ormond Street Hospital For Children NHS Foundation Trust, Paediatric infectious diseases; UCL Great Ormond Street Institute of Child Health Library, Calvert, Anna; St George's University of London, Centre for Neonatal and Paediatric infection Dorey, Robert; University of Southampton Faculty of Medicine Drysdale, Simon; St George's University of London, Centre for Neonatal and Paediatric infection Khalil, Asma; St George's University Hospitals NHS Foundation Trust, Fetal Medicine Unit; St George's University of London, Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute Heath, Paul; St George's University of London, Centre for Neonatal and Paediatric infection Lyall, Hermione; Imperial College Healthcare NHS Trust, Department of Paediatrics Ralph, Kate; University of Southampton Faculty of Medicine, Faculty of Medicine Sapuan, Shari; St George's University of London, Centre for Neonatal and Paediatric infection Vandrevala, Tushna; Kingston University, Centre for Applied Health and Social Care Research, Faculty of Health, Social Care and Education Walter, Simone; St George's University Hospitals NHS Foundation Trust, Department of Audiovestibular Medicine whittaker, elizabeth; Imperial College Healthcare NHS Trust, Department of Paediatrics Wood, Sharon; CMV Action
Keywords:	Infectious Disease Medicine, Neonatology

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Managing Challenges in Congenital CMV: Current Thinking

Christine E Jones[1]*, Heather Bailey[2], Alasdair Bamford[3], Anna Calvert[4], Robert B Dorey[5], Simon B Drysdale[4], Asma Khalil[6], Paul T Heath[4], Hermione Lyall[7], Kate MI Ralph[5], Shari Sapuan[4], Tushna Vandrevala[8], Simone Walter[9], Elizabeth Whittaker[7], Sharon Wood[10] for the UK Congenital CMV Infection Collaboration (UKCCIC)

[1] Clinical and Experimental Sciences, University of Southampton and NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[2] Institute for Global Health, University College London, UK

[3] Great Ormond Street Hospital for Children NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health, London, UK

[4] Centre for Neonatal and Paediatric infection, St George's, University of London, London

[5] Faculty of Medicine, University of Southampton, Southampton, UK

[6] Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust and Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK

[7] Department of Paediatrics, Imperial College Healthcare NHS Trust, London, UK

[8] Centre for Applied Health and Social Care Research, Faculty of Health, Social Care and Education, Kingston University, London, UK

[9] Department of Audiovestibular Medicine, St George's University Hospitals NHS Foundation Trust, London, UK

[10] CMV Action, London, UK

[*] Correspondence to Dr Christine E Jones, Clinical and Experimental Sciences, University of Southampton, University Hospital Southampton NHS Foundation Trust, Southampton, UK; c.e.jones@soton.ac.uk

Abstract

Congenital human cytomegalovirus (CMV) infection is the most common congenital infection, affecting around 1 in 200 infants in high-income settings. It can have life-long consequences for up to 1 in 4 children, including sensorineural hearing loss and neurodisability. Despite the frequency of congenital CMV and the severity for some children, it is a little-known condition by pregnant women, families, and healthcare providers. Timely diagnosis of CMV infection in pregnancy is important to facilitate consideration of treatment with valaciclovir, which may reduce the risk of transmission to the fetus or reduce the severity of the outcomes for infected infants. Recognition of features of congenital CMV is important for neonatologists, paediatricians, and audiologists to prompt testing for congenital CMV within the first 21 days of life. Early diagnosis gives the opportunity for valganciclovir treatment, where appropriate, to improve outcomes for affected infants. Further research is urgently needed to inform decisions about antenatal and neonatal screening, long-term outcomes for asymptomatic and symptomatic infants, predictors of these outcomes, and optimal treatment for women and infants.

Congenital human cytomegalovirus (CMV) infection is the most common congenital infection globally, affecting an estimated 0.48% of all live born infants in high-income countries and 1.42% in low- and middle-income countries.[1] There are life-long consequences for as many as 1 in 4 infants with congenital CMV infection, including sensorineural hearing loss and neuro-disability.[2] Congenital CMV impacts the health-related quality of life of the individual and the family, even for those infants who are less severely affected.[3,4] There is an appreciable cost of congenital CMV, estimated at £732 million per year in the UK.[5] Despite the prevalence of congenital CMV infection and the consequences for individuals, families and society, awareness is low amongst pregnant women and healthcare professionals. Pregnant individuals and healthcare providers strongly agree that CMV risk reductions measures should be included in antenatal care.[6,7] Behavioural adaptions to avoid direct contact with saliva and urine of young children – the most common source of infection to pregnant women - can reduce the risk of CMV infection.[8] Here, we review the challenges associated with screening, diagnosis, and treatment of CMV infection in pregnancy and infancy. 'Woman' or 'mother' are used throughout; these terms should be taken to include people who do not identify as women, but who are pregnant or a birthing parent, where relevant.

DIAGNOSIS OF MATERNAL CMV INFECTION IN PREGNANCY

Maternal CMV infection in pregnancy can be primary or non-primary (re-infection or reactivation) and is commonly asymptomatic but may manifest as an influenza-like illness; both primary and non-primary maternal CMV can result in infection of the fetus, with similar consequences for the infant. The infrequency of clinical symptoms in most adults makes the diagnosis of CMV infection challenging, particularly in the absence of routine antenatal screening.

Serological testing can only diagnose primary infection and is unhelpful in non-primary infection. Testing of CMV-specific immunoglobulin (Ig) G, IgM, and IgG avidity in maternal serum, with

comparison to a sample collected previously, if available, is performed to determine primary infection and estimate the timing of infection. Detection of CMV IgG and IgM, with low avidity IgG, implies primary infection in the last 3 months; high avidity IgG implies infection more than 3 months earlier.

The timing of maternal CMV infection in pregnancy influences the risk of vertical transmission and severity of symptoms in the infant. Infection in the first trimester of pregnancy is associated with the highest risk of severe outcomes for the infant, whereas transmission is more common in later pregnancy but is significantly less likely to result in significant sequalae.[9]

Routine antenatal serological screening of pregnant women is not recommended in most countries, including the UK, but is applied at a local or regional level in some.[10] Where antenatal screening is not recommended, testing is offered only to pregnant women who have suggestive clinical symptoms or signs on antenatal ultrasound testing, Table 1.

DIAGNOSIS OF FETAL CMV INFECTION

CMV DNA detected by polymerase chain reaction (PCR) in a sample of amniotic fluid or cord blood is diagnostic of fetal infection. Amniocentesis should be performed after 17 weeks of gestation, and at least 6-8 weeks after the suspected maternal infection. Failure to detect CMV DNA in amniotic fluid does not completely rule out the possibility of congenital infection, as later transplacental transmission of CMV can occur.[11] However, transmission which occurs later in pregnancy is not associated with severe disease in the infant, so a negative CMV DNA PCR in amniotic fluid or cord blood can provide reassurance to women and their families.

MANAGEMENT OF MATERNAL AND FETAL CMV INFECTION IN PREGNANCY

Prevention of vertical transmission of CMV

Administration of valaciclovir (8g/day) initiated after confirmed maternal primary infection in early pregnancy has been shown in a randomised, double-blind, placebo-controlled trial (RCT) to reduce the rate of fetal infection by 71%[11] Treatment was most effective when commenced soon after primary maternal infection. Valaciclovir provides an opportunity to prevent transmission of CMV, however the absence of antenatal screening to identify primary maternal infection in the first trimester of pregnancy limits the potential for benefit. Screening recommendations therefore need to be kept under review as new evidence emerges.

Management of the CMV-infected fetus

Ultrasound features, Table 1, may evolve as late as 12 weeks after maternal infection, so serial fetal ultrasound scans for the remainder of pregnancy are warranted.[12] Ultrasound and magnetic resonance imaging (MRI) are complementary imaging modalities.

An observational study has demonstrated that valaciclovir treatment (2g four times/day) of women carrying a CMV-infected infant was associated with an increased proportion of CMV-infected infants who were asymptomatic at birth (82%, 95% confidence interval [CI] 67-88%) compared to untreated historical controls (43%, 95% CI 29-57%)[13]. Subsequently, maternal valaciclovir has been recommended on a case-by-case basis in some centres.[12]

DIAGNOSIS OF CONGENITAL CMV IN INFANTS AND CHILDREN

A confirmed diagnosis of congenital CMV can only be made on a sample collected before 21 days of age, as a positive CMV DNA PCR collected after this point may reflect postnatal acquisition of infection. Delayed diagnosis means missed opportunities for improving outcomes in those eligible for treatment.

Screening newborn infants for congenital CMV is not currently recommended in most countries, including the UK. However, the Canadian provinces of Ontario and Saskatchewan implemented

universal screening using the dried blood spot in July 2019 and February 2022. Minnesota, United States of America, is due to begin universal screening using dried blood spots in January 2023. The impact of these programmes are keenly awaited to inform policies in other settings.

What are the clinical indications for postnatal investigation for congenital CMV?

In the absence of universal screening, all infants should be tested for congenital CMV infection where there is suspicion of maternal or fetal CMV infection, or if they have suggestive symptoms or signs, or sensorineural hearing loss, Table 1.

Most infants with congenital CMV have no clinically detectable features at birth. However around 1 in 6 of these 'asymptomatic' infants will have long-term sequalae, and around 1 in 2 infants who present with clinical features of congenital CMV will have life-long problems, Figure 1. The number of children with congenital CMV in the UK is not known, however, using data from a retrospective cohort study in the Netherlands and projecting this onto population figures for the UK, an estimated 3750 children with congenital CMV are born each year in the UK, of which 931 would be expected to have long-term sequalae, however 536 would not have been diagnosed at birth using clinical features alone, Figure 1. Therefore, in the absence of neonatal screening, many of these children will remain undetected, unless they present with hearing loss or neurodisability later in infancy or childhood.

Newborn hearing screening provides an important opportunity to identify infants with congenital CMV, who would not have been identified by routine clinical examination. Targeted testing of infants for congenital CMV may be offered for infants who have no clear responses on the newborn hearing screen. This approach ensures a diagnosis is made within a suitable timeframe to enable antiviral treatment to be initiated, if appropriate. Routine targeted testing for CMV in Utah and Connecticut, in the United States, has been shown to be cost-effective.[14] Targeted testing has been implemented within a few local centres in the UK. Integration of

targeted CMV testing within the newborn hearing programme would be cost-effective and acceptable to UK parents.[15]

Whilst this approach cannot detect all children with CMV who develop sensorineural hearing loss (as up to 33-50% of cases of hearing loss present after the newborn period), it does provide a vital opportunity for early diagnosis to enable treatment to prevent further hearing loss in those eligible for treatment.[16] Not all infants with clinically significant CMV infection will have hearing loss, therefore targeted CMV testing alongside newborn hearing screening will not identify all children significantly affected by CMV.[17]

What newborn samples should be collected to confirm a diagnosis of congenital CMV?

Urine or saliva are the optimum specimens to collect, as the viral load is often significantly higher than in the blood.[18] PCR testing of saliva may be falsely positive due to breast milk exposure, so sampling should ideally be performed an hour after a breast-feed. However, the viral load of a positive PCR test due to contamination with breast milk is significantly lower than that observed in infants with congenital CMV, making identification of true positives relatively easy.[19]

If a urine or saliva sample has not been collected before 21 days of life, a retrospective diagnosis can be made by CMV PCR testing of the newborn dried blood spot. The sensitivity of this test (85.7%; 95% CI 74.3 – 92.6) and practicalities of retrospectively obtaining consent, retrieval and testing of the sample, means that it is not optimal for a rapid diagnosis.[18] Despite these difficulties, it is the only test which can diagnose congenital CMV in children presenting after the age of 3 weeks with hearing loss or vestibular dysfunction, and / or neurodevelopmental difficulties, providing families with an explanation for the difficulties their child experiences.

What investigations should be done to determine effect of congenital CMV on the infant?

To assess for CMV-associated end organ disease, all infants should have the following performed: clinical examination, including growth parameters; diagnostic auditory brain stem responses; ophthalmological examination for retinitis or scarring; full blood count to assess bone marrow function; and renal and liver function tests.

Cranial ultrasound and brain MRI are considered complementary tests. MRI is the most sensitive imaging to detect disorders of neuronal migration, cysts, ventricular dilatation or volume loss, and abnormalities of white matter signal.[20] Cranial ultrasound is more sensitive for the detection of calcification. A finding of disordered neuronal migration, not easily detected on ultrasound scan, is indicative of fetal infection before 18-20 weeks of gestation, and suggestive of a worse neurological outcome. The ability of neonatal imaging to predict neuro-developmental outcomes at 5-6 years of age is not yet clear.

CHALLENGES IN THE MANAGEMENT OF CONGENITAL CMV

Which infants should be treated for congenital CMV and what is the evidence for treatment?

Infants diagnosed with congenital CMV should be referred to the regional Paediatric Infectious Diseases service.

RCTs of treatment for infants with congenital CMV have focused on those with clinically apparent disease, as opposed to those who are asymptomatic at birth or have isolated sensorineural hearing loss. The first RCT of 6 weeks of IV ganciclovir versus placebo included infants with symptomatic congenital CMV involving the central nervous system.[21,22] Treatment with IV ganciclovir was shown to improve hearing and neurodevelopmental outcomes, compared to placebo, Table 2.

A subsequent trial of a 6-months versus 6-weeks course of oral valganciclovir showed modest benefits in hearing and neurodevelopmental outcomes, with a 6-month course of oral valganciclovir compared to 6 weeks, Table 2.[23] Compared to IV ganciclovir treatment there was a lower incidence of significant neutropenia.

In both these RCTs, participants were over 32 weeks of gestation at birth and started treatment before 4 weeks of age. Given there are no licenced anti-viral therapies for congenital CMV, clinicians must interpret the inclusion criteria of RCTs when assessing whether to start a patient on treatment, Table 2. Further research is urgently needed to fill the evidence gaps for infants – particularly pre-term infants – and less symptomatic children, for whom there is little data to guide treatment.

Treatment dilemmas

Isolated sensorineural hearing loss

Consensus statements vary on the treatment of congenital CMV in patients with isolated sensorineural hearing loss, with some recommending treatment and others not.[24,25] These differing statements are a result of limited high-quality evidence of anti-viral treatment in infants with isolated sensorineural hearing loss.

The randomised controlled trials of anti-viral treatment of infants with congenital CMV included few infants with isolated sensorineural hearing loss, making it difficult to draw firm conclusions from the highest-quality evidence.[23] The evidence for benefit is from retrospective studies showing better outcomes in those treated with oral valganciclovir compared to published data from untreated populations.[26] Uncontrolled assessments of treatment efficacy are difficult to interpret due to the fluctuating nature of hearing loss in congenital CMV, and it is difficult to compare outcomes between centres unless similar, rigorous, protocols for ascertaining hearing

thresholds are employed. The demonstrated benefits of oral valganciclovir are stabilisation of hearing and language outcomes. In the absence of conclusive evidence for the treatment of infants with isolated sensorineural hearing loss, many experts recommend treatment, however this should be done on a case-by-case basis, after full discussion with the parents about the potential benefits and toxicities of treatment.

Infants with asymptomatic congenital CMV

In the absence of universal neonatal screening, most infants without clinically apparent congenital CMV will not be diagnosed in the first month of life, however an appreciable number will develop life-long problems, Figure 1. It is not known whether early treatment could prevent hearing loss or neurodisability in these children. A single-arm open-label trial set up to investigate this has recently been halted (ClinicalTrials.gov Identifier: NCT03301415).

There are significant challenges to studying sequelae attributable to congenital CMV among this population: determining gestational timing of infection in the absence of maternal screening programmes; the non-specific outcomes which may change over time or only become apparent later in childhood; the need for appropriate controls and a low tolerance for treatment-related side effects in healthy children.[27] Study designs that address these challenges are needed to improve our understanding of congenital CMV-related outcomes for asymptomatic children and inform trials and then enable potential screening and treatment strategies for this group.

Treatment of children over 4 weeks of age

The pivotal treatment studies of infants with symptomatic congenital CMV disease were based on starting therapy within the first month of life, although two small retrospective observational series have reported improved hearing outcomes in treating older infants.[28,29] A recently published multi-centre, single-arm, open-label study showed similar best ear and total ear

assessments based on auditory brainstem responses after six months of treatment in 7 infants 14-28 days of age and 17 infants 31-66 days of age.[30] However, a phase II, double-blind, randomised placebo-controlled trial of children 1 month to 4 years of age with virologically-confirmed congenital CMV infection and hearing loss was established to specifically address this issue (ClinicalTrials.gov Identifier: NCT01649869). Infants received oral valganciclovir or placebo for 6-weeks and outcome was assessed at 6-month follow-up. The study is not yet published, but data presented on clinicaltrials.gov indicate that of the 35 children who were enrolled (median age of 18.7 months), there was no impact of treatment on hearing outcomes. Data from the prospective CONCERT trial (ClinicalTrials.gov Identifier: NCT02005822) which compared hearing outcomes in infants treated with 6 weeks of valganciclovir before the age of 13 weeks and a non-randomised control group is awaited.

Therefore, at the current time, there is no published evidence from high-quality studies to inform treatment in older infants and discussion with parents must therefore acknowledge the lack of proven benefit in commencing therapy beyond the first month of life and the potential toxicities of treatment.

Current and future treatments for congenital CMV

There is no licensed antiviral treatment for congenital CMV. Randomised trial evidence supports the use of valganciclovir or ganciclovir. Current guidelines favour valganciclovir as first line treatment, unless oral administration is contraindicated. Reversible neutropenia is one of the main treatment-limiting toxicities of both drugs, although less common with valganciclovir, and should be monitored for throughout treatment with temporary dose reductions made as needed.[24,25]

Foscarnet and cidofovir have been used for treatment of CMV disease in immunocompromised patients, but experience in treating congenital CMV is minimal. The requirement for intravenous administration and high rates of toxicity limits their use.

Promising newer antivirals, letermovir and maribavir, have recently been approved for prevention or treatment of CMV in the transplant setting. Studies investigating their use in congenital CMV are being planned.

Although ganciclovir and valganciclovir have been used for many years, there are potential concerns about longer-term toxicities, such as impact on fertility, although there is no evidence in humans that this occurs. Recording health outcomes following treatment in infancy, through national and international registries, is important to monitor rare and long-term outcomes. One such registry is the European CCMVNET registry, which is enrolling patients in the UK and throughout Europe.

How long should infants with congenital CMV be treated for?

Only one randomised controlled trial has investigated the impact of duration of treatment for congenital CMV, Table 2.[23] This study showed a benefit of six months compared to six weeks of valganciclovir in hearing and neurodevelopmental outcomes. Most centres now routinely treat infants with congenital CMV for 6 months.

There are some observational data from infants that have been treated for up to a year with valganciclovir suggesting extending the course is safe, with improved outcomes compared with a historical cohort who received six weeks of IV ganciclovir.[21,31] However, this is not recommended practice at the current time.

As valganciclovir is not a licensed treatment for congenital CMV in the UK, it is important that all parents are fully informed about short-term and potential long-term side effects.

CONCLUSIONS

Congenital CMV has a significant impact on the individual child, wider family, and society. To date, there is no licensed vaccine for primary prevention of congenital CMV, although promising candidate vaccines are in clinical trials. Antenatal education to reduce the risk of CMV in pregnancy should be provided to all pregnant women, Table 3. First trimester diagnosis to facilitate consideration of treatment with valaciclovir to prevent transmission to the infant is important. Delays in considering CMV infection in pregnancy and early life have a significant impact on children and families, and all antenatal healthcare providers, audiologists, neonatologists and paediatricians should be aware of pathways for diagnosis and early treatment to reduce the harm associated with CMV, Box 1. Families affected by a diagnosis of CMV infection in pregnancy or childhood may benefit from support from CMV Action (cmvaction.org.uk). Further research is urgently needed to inform decisions about antenatal and neonatal screening in the UK, long-term outcomes for asymptomatic and symptomatic infants and predictors of these outcomes, and optimal treatment for women and infants.

Acknowledgements

Claire Atkinson, Institute of Immunity and Transplantation, University College London for critical appraisal of the manuscript; Members of the UK Congenital CMV Infection Collaboration (UKCCIC) who have collaborated on studies cited in this manuscript and discussed ideas contain herein.

Competing Interest Statement

Provided consultancy and /or investigator roles in relation to product development for MSD (AK, CJ, PTH, SD), Sanofi Pasteur (AK, CEJ, PTH, SD), Gilead (AB), Janssen (PTH), AstraZeneca (PTH), Moderna (CJ, PTH, SD) Pfizer (CJ, PTH), Valneva (PTH) on behalf of their institutions. Chair of CCMVNet (provider of European Registry for Congenital CMV infection) (HL). Co-chair of the European Congenital CMV Initiative (ECCI) (CJ).

[Box providing patient perspective to run alongside article]***Parent perspective – importance of diagnosis and clear information about treatment***

Clear diagnosis of CMV infection and clear information on treatment have important implications for parents, providing reassurance that their situation is not unique or inexplicable and that there is a professional body of knowledge and experience that can be exercised in providing help. However, too many parents seeking advice from CMV Action, the UK charity for congenital CMV, have experienced protracted delays in diagnosis, and apart from the very real missed opportunities for effective treatment, this causes much distress and uncertainty. Indeed, many children living with life-long impairments as a consequence of cCMV may never have CMV identified as the cause due to a lack of testing in clinical practice.

Given the far-reaching consequences for children, CMV Action recommends minimum standards of care and the implementation of clinical guidelines and pathways for testing, improved diagnosis and management for pregnant women and babies affected. GPs, midwives and obstetricians can advise women about reducing the risks of CMV infection in pregnancy; antenatal healthcare professionals, neonatologists and paediatricians can be more aware of the potential signs of CMV infection in a fetus or newborn to improve diagnosis and treatment within the first four weeks of life. Paediatricians and others working with families must understand the guidelines for managing CMV so that more families receive the monitoring and support their child needs.

The introduction of antenatal or neonatal screening would identifying babies who would benefit from early diagnosis and timely treatment, would dramatically improve our knowledge of long-term outcomes.

Parents would welcome tests at birth that could provide guidance on the severity of symptoms their child is likely to develop. We would also support research into the efficacy and cost of new drugs, with attention given to diagnostic techniques such as foetal MRI or blood sampling for early identification of babies who may benefit from antiviral treatment.

CMV Action

Tables

Antenatal features	Postnatal features
Maternal Symptomatic CMV infection Cholestasis of pregnancy Placental dysfunction CMV IgG seroconversion	**Features found on clinical examination** Birth weight <2nd centile Petechial or blueberry muffin rash Thrombocytopenia Prolonged jaundice (often conjugated) Hepatitis +/- Hepatosplenomegaly Microcephaly Retinitis (rare) Abnormal neurological examination **Features found on clinical testing** Confirmed sensorineural hearing loss **Additional features which prompt testing in some centres** No clear responses on newborn hearing screening Extreme prematurity Intrauterine growth restriction
Fetal Antenatal abnormalities on USS or MRI • Cerebral abnormalities: Ventriculomegaly, intracranial calcifications, microcephaly, sub-ependymal cysts • Extracerebral abnormalities: Fetal growth restriction, hyperechogenic bowel, hepatomegaly, liver calcifications, pericardial effusion	

Table 1: Presenting features of congenital CMV which should prompt consideration of testing for congenital CMV.

MRI: Magnetic resonance imaging; USS: Ultrasound

Study and setting	Inclusion and exclusion criteria	Number included	Intervention	Outcome
Kimberlin 2003 [21] 1991-1999, multi-centre	Inclusion: Neonates (<1 month of age) with symptomatic congenital CMV involving CNS Exclusion: <1200g birth weight <32 weeks of gestation at birth	100 enrolled 42 completed follow-up (25 treatment, 17 no treatment	IV ganciclovir (6mg/kg BD) 6 weeks versus no treatment	• Improved or maintained normal hearing at 6 months: n= 21/25 (84%) treatment group vs n= 10 /17 (59%) control group (p=0.06) • Worsened hearing at 6 months compared to baseline: n=0 (0%) treatment group vs n=7/17 (41%) control group (P < .01)
Oliver 2009 [22] 1991-1999, multi-centre	As Kimberlin 2003	60 completed all assessments (29 treatment, 31 no treatment)	As Kimberlin 2003	• Average number of delayed milestones at 12 months: 10.06 in treatment group vs 17.14 in control group (p=0.007)
Kimberlin 2015 [23] 2008-2011, multi-centre	Inclusion: Neonates (<30 days of age) with symptomatic congenital CMV, including: haematological, organomegaly, intrauterine growth restriction, hepatitis,	109 enrolled, 96 randomised 68 completed 24 months of follow-up (37 in 6-month group and 31 in 6-week group)	Oral valganciclovir (16mg/kg BD) 6-months versus 6-weeks (followed by 4.5 months of placebo)	• No significant difference in “best-ear” hearing at 6 months • “Total ear” hearing remained normal or improved: 73% in the 6-month group vs 57% in 6-week group

	central nervous system involvement, sensorineural hearing loss Exclusion: <1800g birth weight, <32 weeks of gestation			(p=0.01) at 12 months and was maintained at 24 months 77% vs. 64%, P=0.04 • Higher Bayley-III language-composite scores at 24 months in 6-months vs 6-weeks (P=0.005) • Higher receptive-communication scale scores at 24 months in 6-months vs 6-weeks (P=0.003)
NCT01649869[a] 2015 -2019	Inclusion: Children aged 1 month to 4 years with congenital CMV and sensorineural hearing loss Exclusion: Profound sensorineural hearing loss, previous ganciclovir or valganciclovir	Target 54 32 children completed	Oral valganciclovir 16mg/kg BD 6-weeks versus placebo	• Awaiting formal publication • At 6 months, no difference in hearing change (neither improvement, nor deterioration

Table 2. Randomised controlled trials of anti-viral therapy for congenital CMV.

Oliver 2009 performed Denver II developmental assessment on the participants enrolled in the Kimberlin 2003 study to determine the effects of IV ganciclovir for 6 weeks on neurodevelopmental outcome at 6 weeks, 6 months, and 12 months. CMV: cytomegalovirus; CNS: central nervous system; CSF: cerebrospinal fluid. [a]Available from: https://clinicaltrials.gov/ct2/show/NCT01649869

Table 3: Recommendations for diagnosis and treatment of CMV in pregnancy and infancy

Recommendations for diagnosis and treatment of CMV infection in pregnancy

- All women should be given advice about how to reduce their risk of CMV infection in pregnancy
- Continue to review the evidence to inform decisions about antenatal serological screening in pregnancy
- Offer serological testing for CMV in women with symptoms or clinical or radiological signs suggestive of infection
- Discuss amniocentesis with women with confirmed primary CMV infection or suspected non-primary infection to determine fetal infection
- Consider antenatal valaciclovir for the prevention of transmission of CMV infection and for the treatment of mildly- and moderately affected fetuses, on a case-by-case basis

Recommendations for diagnosis and treatment of infants with congenital CMV

- Continue to evaluate the evidence to review neonatal universal screening decisions
- Infants should be tested for congenital CMV infection where there is suspicion of maternal or fetal infection, or neonatal symptoms or signs of congenital CMV or sensorineural hearing loss are present
- Urine or saliva (or blood) should be collected before 21 days of age to confirm congenital CMV infection
- In infants > 21 days of age, retrospective CMV PCR testing of the dried blood spot should be performed. It is essential that dried blood spots are stored appropriately and long enough to allow retrospective diagnosis of congenital CMV-related sequalae
- Consider targeted testing for congenital CMV for those infants who are referred from newborn hearing screening for diagnostic hearing tests to allow earlier diagnosis
- Where this is not in place, CMV testing should be offered for all infants at the first diagnostic audiology showing results indicative of sensorineural hearing loss
- Infants diagnosed with congenital CMV should be referred to the regional Paediatric Infectious Diseases service
- Infants with congenital CMV with central nervous system abnormalities are eligible for treatment, after discussion with the parents about the risks and benefits of treatment
- Infants with isolated sensorineural hearing loss may be considered for treatment on a case- by-case, after full discussion with the parents about the risks and potential benefit of treatment
- Treatment is currently not advised for infants with no clinical or radiological features of CMV and without sensorineural hearing loss
- Treatment with valganciclovir (or IV ganciclovir where oral administration is contraindicated) should be started before 4 weeks of age in those infants where treatment is indicated
- Parents of infants with congenital CMV should be offered enrolment of their infant in a national CMV registry, such as CCMVNet
- Families affected by CMV should be given information about the national charity CMV Action (cmvaction.org)

References

1 Ssentongo P, Hehnly C, Birungi P, *et al.* Congenital Cytomegalovirus Infection Burden and Epidemiologic Risk Factors in Countries With Universal Screening. *Jama Netw Open* 2021;4:e2120736. doi:10.1001/jamanetworkopen.2021.20736

2 Korndewal MJ, Oudesluys-Murphy AM, Kroes ACM, *et al.* Long-term impairment attributable to congenital cytomegalovirus infection: a retrospective cohort study. *Dev Med Child Neurol* 2017;59:1261–8. doi:10.1111/dmcn.13556

3 Ralph KMI, Bull K, Trotter C, *et al.* Paediatric health-related quality of life in congenital cytomegalovirus. *Arch Dis Child* 2022;:archdischild-2022-324007. doi:10.1136/archdischild-2022-324007

4 Vandrevala T, Barber V, Mbire-Chigumba E, *et al.* Parenting a child with congenital cytomegalovirus infection: a qualitative study. *bmjpo* 2020;4:e000844. doi:10.1136/bmjpo-2020-000844

5 Retzler J, Hex N, Bartlett C, *et al.* Economic cost of congenital CMV in the UK. *Arch Dis Child* 2019;104:559–63. doi:10.1136/archdischild-2018-316010

6 Montague A, Vandrevala T, Calvert A, *et al.* Experiences of Pregnant Women and Healthcare Professionals of Participating in a Digital Antenatal CMV Education Intervention. *Midwifery* 2022;:103249. doi:10.1016/j.midw.2022.103249

7 Vandrevala T, Barber V, Calvert A, *et al.* Understanding pregnant women's readiness to engage in risk-reducing measures to prevent infections during pregnancy. *J Health Psychol* 2019;:1359105319884609. doi:10.1177/1359105319884609

8 Barber V, Calvert A, Vandrevala T, *et al.* Prevention of Acquisition of Cytomegalovirus Infection in Pregnancy Through Hygiene-based Behavioral Interventions: A Systematic Review and Gap Analysis. *PIDJ* 2020;39:949–54. doi:10.1097/inf.0000000000002763

9 Chatzakis C, Ville Y, Makrydimas G, *et al.* Timing of primary maternal cytomegalovirus infection and rates of vertical transmission and fetal consequences. *American Journal of Obstetrics and Gynecology* 2020;223:870-883.e11. doi:10.1016/j.ajog.2020.05.038

10 Faure-Bardon V, Fourgeaud J, Stirnemann J, *et al.* Secondary prevention of congenital cytomegalovirus infection with valacyclovir following maternal primary infection in early pregnancy. *Ultrasound Obst Gyn* 2021;58:576–81. doi:10.1002/uog.23685

11 Shahar-Nissan K, Pardo J, Peled O, *et al.* Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial. *The Lancet* 2020;396:779–85. doi:10.1016/s0140-6736(20)31868-7

12 Khalil A, Sotiriadis A, Chaoui R, *et al.* ISUOGPractice Guidelines: role of ultrasound in congenital infection. *Ultrasound Obstet Gynecol* 2020;56:128–51. doi:10.1002/uog.21991

13 Leruez-Ville M, Ghout I, Bussières L, *et al.* In utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study. *American Journal of Obstetrics and Gynecology* 2016;215:462.e1-462.e10. doi:10.1016/j.ajog.2016.04.003

14 Bergevin A, Zick CD, McVicar SB, *et al.* Cost–benefit analysis of targeted hearing directed early testing for congenital cytomegalovirus infection. *Int J Pediatr Otorhi* 2015;79:2090–3. doi:10.1016/j.ijporl.2015.09.019

15 Williams EJ, Kadambari S, Berrington JE, *et al.* Feasibility and acceptability of targeted screening for congenital CMV-related hearing loss. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F230–6. doi:10.1136/archdischild-2013-305276

16 Fowler KB. Congenital Cytomegalovirus Infection: Audiologic Outcome. *Clin Infect Dis* 2013;57:S182–4. doi:10.1093/cid/cit609

17 Stehel EK, Shoup AG, Owen KE, *et al.* Newborn Hearing Screening and Detection of Congenital Cytomegalovirus Infection. *Pediatrics* 2008;121:970–5. doi:10.1542/peds.2006-3441

18 Dollard SC, Dreon M, Hernandez-Alvarado N, *et al.* Sensitivity of Dried Blood Spot Testing for Detection of Congenital Cytomegalovirus Infection. *Jama Pediatr* 2021;175:e205441. doi:10.1001/jamapediatrics.2020.5441

19 Blázquez-Gamero D, Soriano-Ramos M, Vicente M, *et al.* Prevalence and Clinical Manifestations of Congenital Cytomegalovirus Infection in a Screening Program in Madrid (PICCSA Study). *Pediatr Infect Dis J* 2020;39:1050–6. doi:10.1097/inf.0000000000002808

20 Kachramanoglou C, Jan W, Jones B, *et al.* Diagnostic analysis of baseline brain MRI features in infants with congenital cytomegalovirus infection: a simplified scoring system. *Clin Radiol* 2021;76:942.e7-942.e14. doi:10.1016/j.crad.2021.09.015

21 Kimberlin DW, Lin C-Y, Sánchez PJ, *et al.* Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003;143:16–25. doi:10.1016/s0022-3476(03)00192-6

22 Oliver SE, Cloud GA, Sánchez PJ, *et al.* Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol* 2009;46 Suppl 4:S22-6. doi:10.1016/j.jcv.2009.08.012

23 Kimberlin DW, Jester PM, Sánchez PJ, *et al.* Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med* 2015;372:933–43. doi:10.1056/nejmoa1404599

24 Luck SE, Wieringa JW, Blázquez-Gamero D, *et al.* Congenital Cytomegalovirus. *PIDJ* 2017;36:1205–13. doi:10.1097/inf.0000000000001763

25 Rawlinson WD, Boppana SB, Fowler KB, *et al.* 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

26 Pasternak Y, Ziv L, Attias J, *et al.* 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

27 Bartlett AW, McMullan B, Rawlinson WD, *et al.* Hearing and neurodevelopmental outcomes for children with asymptomatic congenital cytomegalovirus infection: A systematic review. *Rev Med Virol* 2017;27:e1938. doi:10.1002/rmv.1938

28 Dorfman L, Amir J, Attias J, *et al.* Treatment of congenital cytomegalovirus beyond the neonatal period: an observational study. *Eur J Pediatr* 2020;179:807–12. doi:10.1007/s00431-019-03558-7

29 Suganuma E, Sakata H, Adachi N, *et al.* Efficacy, safety, and pharmacokinetics of oral valganciclovir in patients with congenital cytomegalovirus infection. *J Infect Chemother* 2021;27:185–91. doi:10.1016/j.jiac.2020.08.019

30 Morioka I, Kakei Y, Omori T, *et al.* Oral Valganciclovir Therapy in Infants Aged ≤2 Months with Congenital Cytomegalovirus Disease: A Multicenter, Single-Arm, Open-Label Clinical Trial in Japan. *J Clin Medicine* 2022;11:3582. doi:10.3390/jcm11133582

31 Amir J, Wolf DG, Levy I. Treatment of symptomatic congenital cytomegalovirus infection with intravenous ganciclovir followed by long-term oral valganciclovir. *Eur J Pediatr* 2010;169:1061–7. doi:10.1007/s00431-010-1176-9

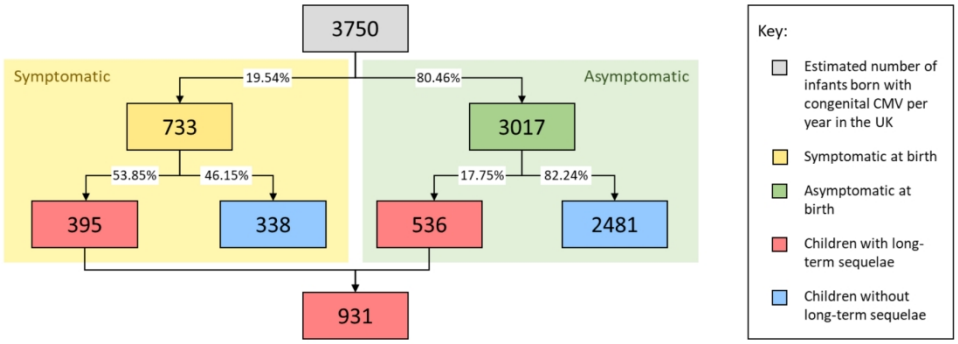

Figure 1: Estimation of the number of children affected by short- and long-term adverse outcomes attributable to congenital cytomegalovirus (cCMV) per year in the UK

Extrapolation of the results of a retrospective cohort study in the Netherlands which assessed outcomes in 133 children with cCMV (identified by retrospective testing of neonatal dried blood spots) to the UK setting (750,000 live births per year, with estimated birth prevalence of congenital CMV of 0.5%) in order to estimate the number of infants that would be affected by short- and long-term adverse outcomes of cCMV per year in the UK.[2]

167x68mm (300 x 300 DPI)