

Clinical Guideline: Diagnosis and Management of Congenital Cytomegalovirus

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For use in: EoE Neonatal Units, Paediatric Departments and Audiology Departments.


Guidance specific to the care of neonatal and paediatric patients.

Used by: Medical staff, Neonatal Nurse Practitioners, Newborn Hearing Screeners, Audiologists

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Neonatal Clinical Oversight Group	
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Audit Standards:

- ☐ All babies identified as having no clear response on the newborn hearing screening pathway should have a saliva swab sent within 3 weeks of life.
- ☐ All babies investigated for cCMV in the neonatal period (1st 28 days) should have a definitive management decision by 4 weeks of life with medication commenced as clinically indicated.
- ☐ All infants or children diagnosed with cCMV between 4 weeks and their 4th birthday (3 years 11 months) should be considered for entry into on-going cCMV trials.

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1. Introduction – the Burden of cCMV Disease

The 2017 European Consensus Statement for the management of cCMV¹ state that “congenital cytomegalovirus (cCMV) is the most common congenital infection in the developed world. Reported prevalence varies between cohorts but is approximately 7 per 1000 births². About half of cCMV infected babies with clinically detectable disease at birth are destined to have significant impairments in their development, and cCMV infection is implicated in approximately 25% of all children with sensorineural hearing loss (SNHL)^{2,3}. Meta-analysis shows that although long-term sequelae, especially SNHL, are more common in those with clinically detectable disease at birth, they are also found in 13% of those without clinical features attributable to cCMV on initial examination.” Of all children who develop cerebral palsy, 9.6% have been shown to have had CMV viraemia on their newborn bloodspot test, indicating cCMV infection⁴. CMV has also been associated with a potential risk for autism^{49,50}. Importantly congenital CMV can frequently cause vestibular dysfunction which can be severe⁵¹ (its severity is not linked to the severity of the hearing loss⁵¹) and affect a child’s motor skills, posture and stability.

2. Summary

This guideline (based on the “cCMV - a European Consensus Statement of Diagnosis and Management”¹, “Fifteen Minute Consultation - Diagnosis and management of congenital CMV”⁵ and the June 2015 London Consensus guideline) is for the initial diagnosis and treatment of newborn infants who may have cCMV infection. The internationally accepted GRADE system for evaluating evidence has been used to illustrate points where relevant (Appendix A).

There is an urgency to diagnose and assess infants with cCMV as antiviral treatment is only recommended if started in the first 4 weeks of life based on current research. For this reason, relevant investigations must be carried out by 3 weeks of life (which is the cut off for diagnosis of congenital infection), so parents and clinicians can make a timely and informed choice regarding treatment. Infants older than three weeks with symptoms of potential cCMV (see table 1) should still be investigated as their management may still centre around this diagnosis and recruitment into research studies may potentially be offered

There are still many areas of uncertainty surrounding the management of cCMV. Sub specialists that can be involved to help with management decisions include virologists or paediatric infectious disease specialists, to provide help considering a risk versus benefit to the individual child.

3. Acronyms

CMV Cytomegalovirus

cCMV	Congenital Cytomegalovirus infection	LFT	Liver function tests
CNS	Central nervous system	PCR	Polymerase chain reaction
DBS	Dried Blood Spot (Guthrie Card)	RCT	Randomised controlled trial
FBC	Full blood count	SNHL	Sensorineural hearing loss
G-CSF	Granulocyte-colony stimulating factor	TDM	Therapeutic Drug Monitoring
IUGR	Intrauterine growth restriction	U&E	Urea and electrolytes

4. Transmission

Babies can acquire CMV during pregnancy, at delivery or postnatally through breast milk or close family contact. The risk of transmission is higher during later stages of pregnancy; however, transmission during early pregnancy is more likely to have severe consequences for the fetus⁶. The rate of transmission during pregnancy is 30-40% in primary maternal CMV infection but only 1% when there is maternal CMV reactivation. In the UK up to 50% women of

reproductive age are CMV seronegative so can have a primary CMV infection during pregnancy, which is thought to represent the greatest threat to the foetus.

5. Who should be investigated for cCMV?

Table 1 Clinical features to trigger targeted investigation¹

Neonates
<p>Physical Examination:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Hepatosplenomegaly <input type="checkbox"/> Petechiae or purpura or blueberry muffin rash in the newborn <input type="checkbox"/> Jaundice (prolonged or conjugated) <input type="checkbox"/> Microcephaly (head circumference <-2 SD for gestational age) <ul style="list-style-type: none"> <i>Consider if symmetrically small for gestational age (<-2 SD for gestational age)</i> <p>Neurology</p> <ul style="list-style-type: none"> <input type="checkbox"/> Seizures with no other explanation <input type="checkbox"/> <i>Vestibular concerns are unlikely to show in neonates (other than, possibly, poor head control or absent Farmer's Test) and will be more obvious later as delayed gross motor skills and balance problems.</i> <p>Laboratory Parameters (cCMV affects reticuloendothelial and hepatobiliary systems)</p> <ul style="list-style-type: none"> <input type="checkbox"/> Hyperbilirubinaemia causing prolonged jaundice often associated with transaminitis <input type="checkbox"/> Conjugated hyperbilirubinaemia <input type="checkbox"/> Unexplained thrombocytopenia, especially if leucopenia or anaemia <p>Neuroimaging</p> <ul style="list-style-type: none"> <input type="checkbox"/> Intracranial calcification (often periventricular) <input type="checkbox"/> Intracranial ventriculomegaly (without other explanation) <input type="checkbox"/> <i>Consider in the case of periventricular cysts, subependymal pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriate vasculopathy</i> <p>Visual Examination</p> <ul style="list-style-type: none"> <input type="checkbox"/> Abnormal finding on ophthalmological examination consistent with congenital CMV (e.g. chorioretinitis) <input type="checkbox"/> <i>Consider if congenital cataracts</i> <p>Audiology</p> <ul style="list-style-type: none"> <input type="checkbox"/> No clear response on newborn hearing screening <p>Maternal serology</p> <ul style="list-style-type: none"> <input type="checkbox"/> Evidence of maternal primary infection (seroconversion or low avidity IgG)* <input type="checkbox"/> <i>Consider in women with known CMV infection (known IgG seropositive at start of pregnancy), particularly, if symptoms or virological examination consistent with suspected CMV reactivation/reinfection</i> <p><i>Prematurity[†]</i></p>
Other children
<p>Sensorineural hearing loss – new diagnosis</p> <p><i>Balance/ vestibular concerns</i></p> <p>Cerebral Palsy of unknown origin/cause</p>

Features in bold are those where there is consensus for testing. Features in italics are those that might lead to testing in individual circumstances.

*Seek expert clinical virology advice for interpretation of virological investigations in pregnancy.

**Baseline screening to differentiate between congenital and postnatal CMV infection is helpful for extremely premature infants (<28 weeks gestational age) who are at increased risk of symptomatic postnatal infection.*

6. Which tests are needed to confirm cCMV?

Diagnosis of cCMV is established by detection of CMV DNA by PCR in body fluids in the first 3 weeks of life (Table 2). If CMV is detected after 3 weeks then there is uncertainty whether it was congenital (antenatal infection) or acquired (postnatal infection) therefore does not confirm cCMV infection⁵. The sooner after birth the tests are performed the more confidently the diagnosis of cCMV can be made. Infants older than three weeks with symptoms of potential cCMV (see table 1&7) should still be investigated as their management may still centre around this diagnosis.

Urine and saliva are the preferred samples due to greater sensitivity, but blood (including the newborn blood spot) can also be used in addition to, but not in place of, urine or saliva (see table 2). A negative blood PCR does not exclude cCMV, it is only helpful if positive. CMV IgM is not recommended since it is not as sensitive or specific as CMV PCR. CMV IgG is less useful in under 1 year olds because it can reflect maternal antibody owing to placental transfer. Urine and saliva should be collected as a priority, blood is not a substitute, and therefore a TORCH screen should include urine/saliva for CMV.

Saliva samples should be taken at least an hour after the baby last breastfed or had a bottle containing expressed breast milk since maternal virus present in the milk may be detected. This is the reason that false-positive results have been reported⁹⁻¹² with saliva, therefore positive saliva sample results should subsequently be confirmed with a second test. There are no time restrictions for formula fed babies.

Evidence that premature babies have a higher incidence of cCMV is limited.^{13,14} Testing extremely premature babies (<28 weeks gestational age) at birth may assist in differentiating between congenital and postnatal infection. This may be very helpful in guiding the management of these babies that are particularly vulnerable to symptomatic postnatal infection¹. Further research is needed to contribute to this currently controversial area.

PCR assay of neonatal DBS can be performed retrospectively in an attempt to diagnose cCMV after the first 21 days of life. Sensitivity is around 84% in meta-analysis but is highly variable depending on the laboratory techniques used and the population being tested; a negative DBS PCR cannot therefore, be used to definitively exclude a diagnosis of cCMV.¹⁵

Table 2 Diagnostic tests

Test	Comments
CMV PCR urine in first 21 days of life	Can be obtained through a bag or cotton wool
CMV PCR saliva swab in first 21 days of life 9,11,46	Take at least one hour after breast milk. No restriction in formula-fed babies.
CMV PCR in whole blood or plasma in ideally in first 21 days of life	EDTA sample. This can be negative when other samples are positive and therefore saliva and urine are the preferred tests.
CMV PCR on the Guthrie card (dried blood spot / DBS)	This can be used for a retrospective diagnosis but a negative result does not fully exclude cCMV as the sensitivity is variable: 34-80% ^{16,17} . See appendix C for Guthrie Consent Release Form.
Maternal booking bloods	This can demonstrate timing of infection by: <ul style="list-style-type: none"> <input type="checkbox"/> Seroconversion if there are two sequential samples e.g. during pregnancy, or when comparing ante, peri or immediately post-natal blood. <input type="checkbox"/> CMV IgG Avidity testing - low avidity is consistent with a recent infection (seek virology advice)
CMV IgG - Children age over 1 year	A negative result almost certainly excludes congenital CMV. (If clinical suspicion is very high, consider sending another sample as false negative results caused by laboratory error/test sensitivity are possible). A positive result demonstrates prior exposure and the Guthrie card CMV PCR is required to distinguish congenital CMV from acquired CMV.
Maternal CMV IgG (this can be performed whatever the age of the child, and can be tested early in conjunction with/ as an adjunct to the other tests)	A negative result excludes congenital CMV (see above comment)

1. Once cCMV confirmed, what are the next steps?

a) Determine the current impact of cCMV

- i) After a diagnosis of cCMV infection has been made, additional investigations are necessary to evaluate the extent of disease (Table 3) and to assist with discussions regarding prognosis and treatment. Current research only supports the decision to treat within 4 weeks of age. Clinicians must be mindful of this target – further research is currently underway to evaluate later treatment of cCMV disease. *See Section 8 Treatment* – for further information.
- ii) Follow your local trust's flowchart for your specific pathway to ensure timely management (Appendix E)

Table 3 Essential Neonatal Investigations in congenital CMV

Test	Comments ¹⁸
Bloods	
FBC	Thrombocytopenia (< 100,000/mm ³ , nadir at 2 weeks)
Creatinine, urea & electrolytes	Baseline renal function
LFTs	ALT >80U/L, conjugated hyperbilirubinaemia, parameters increase in first fortnight
CMV viral load by PCR	Needs EDTA sample
Radiology	
Cranial USS and Brain MRI	<p>All infants with cCMV should have neuroimaging. Some centres advocate undertaking an MRI in all babies with cCMV because additional pathology can be identified as compared with CrUSS ¹⁹⁻²¹. Others are only advocating an MRI in the presence of clinically detectable disease or CrUSS abnormalities.</p> <p>The spectrum of abnormalities is wide: Periventricular calcifications, ventricular enlargement, white matter changes, cysts, neuronal migration defects, and cerebellar hypoplasia support the diagnosis of CNS cCMV disease ^{21,22}.</p>
Referrals	
Ophthalmologist review	Chorioretinitis, optic atrophy, cataracts
Diagnostic auditory assessment +/- vestibular assessment.	Thorough auditory brainstem response assessments (preferably all four frequencies and at least 1 and 4 KHz), even when there are clear responses on the newborn hearing screen, as the screen can miss a mild SNHL.

b) Plan Management

- i) For timely management, discuss with virologists and/ or discuss with a paediatric infectious diseases specialist for consideration of treatment, even while further investigations are being planned. Since all involved professionals are aware of the narrow time frame for treatment, it is expected that not all investigation results will be back before initiating these discussions.

c) Support Families

- i) All families should be offered the advice and support of the national CMV support group (<http://cmvaction.org.uk/>).

8. Treatment

Classically cCMV infection is categorised as “symptomatic” or “asymptomatic” but the European Guidelines¹ have suggested that a more useful differentiation may be to think of these babies in terms of having mild, moderate or severe disease. These categories will help direct the treatment choice for each affected infant. Each case should be discussed with the wider team to help individual categorisation of disease severity. This category guides the planning and management for the baby (see table 4 and Appendix B for further information). Evidence of benefit from randomised controlled trials is only available for treatment started in the first month of life, in infants over 32 weeks gestation, and further studies are on-going to verify whether treatment outside this period is beneficial¹.

The treating paediatrician will be able to take subspecialist advice (from infectious diseases teams, virologists, etc.) and discuss risk-benefit with the families before considering appropriate course of management.

Table 4 Guidance on treatment decision for babies with cCMV (positive CMV PCR saliva swab)

Disease Manifestation	Treatment Recommendation	Level of Evidence (Appendix A)
Severe Disease:		
CNS disease <input type="checkbox"/> Microcephaly, <input type="checkbox"/> CNS calcification, <input type="checkbox"/> chorioretinitis <input type="checkbox"/> White matter changes (or other abnormalities on MRI consistent with CMV disease) [†]	Ganciclovir/valganciclovir Duration 6 months*	Treatment: Quality A, Strength 1 (to treat) Duration: Quality B, Strength 2
Life-threatening disease Severe multiorgan non-CNS disease Severe single-organ disease* includes those with clinically significant liver enzyme abnormalities (liver “failure”) and marked hepatosplenomegaly)	Ganciclovir/valganciclovir: Duration minimum of 6 weeks, up to 6 months*‡	Treatment: Quality B, Strength 1 Duration: Quality B, Strength 2
Isolated hearing deficit*§	Ganciclovir/valganciclovir Duration 6 months*	Treatment: Quality C, Strength 1 Duration: Quality C, Strength 2
Moderate Disease		
Persistent (> 2 weeks duration) abnormalities of	Consider treatment after discussion with specialist	Treatment: Quality C, Strength 2

hematological/biochemical indices More than 2 “mild” disease manifestations	Duration: Minimum of 6 weeks and up to 6 months*	Duration: Quality B, Strength 2
Mild		
Isolated (1 or 2 at most), otherwise clinically insignificant or transient findings e.g. <input type="checkbox"/> Petechiae <input type="checkbox"/> Mild hepatomegaly or splenomegaly <input type="checkbox"/> Biochemical/hematological abnormalities (such as mild thrombocytopenia, anaemia, leukopenia, borderline raised liver enzyme abnormalities or conjugated hyperbilirubinemia) SGA (defined as weight for gestational age <-2 standard deviations) without microcephaly. No clinical or biochemical findings of disease (± detectable CMV viraemia)	No treatment	Treatment: Quality D, Strength 1 (for no treatment)

There is currently only evidence for starting treatment in the first month of life.

**Limited evidence without full consensus: see European Guidelines for further description (Appendix B).*

†In the case of isolated, nonspecific MRI findings that are not consistent with cCMV disease, it was agreed that treatment is not necessarily indicated.

‡It was suggested (without consensus) that treatment might continue in this group until the underlying clinical manifestation of disease (e.g., hepatitis) resolved because benefit of 6 months treatment is unclear.

§No studies address this particular group, although they were included in eligibility criteria for treatment in both published RCTs of treatment.

Oral valganciclovir is currently the drug of choice, although no antiviral drug is currently licensed for the treatment of cCMV. Intravenous ganciclovir should be used in babies unable to tolerate oral drug or where gastrointestinal absorption is uncertain (Evidence: Quality A, Strength 1). Neonatal pharmacokinetic data shows 16mg/kg/dose of valganciclovir oral solution administered twice daily provides ganciclovir exposure comparable to that of a 6mg/kg/dose of intravenous ganciclovir, in infants born at 32 weeks gestation or more²³.

There have been two randomised controlled clinical trials informing cCMV treatment decisions. In both trials, antiviral therapy was started in the first month of life. The first showed that 6 weeks of IV ganciclovir had a positive effect on neurological outcome in infants with CNS involvement and reduced the risk of progression or development

of hearing loss at 12 months of age^{24,25}. The second trial, compared 6 weeks versus 6 months oral valganciclovir in symptomatic cCMV disease, with and without CNS involvement, and showed that the 6-month course improves audiological and neurodevelopmental outcomes to at least 2 years of age²⁶. Infants receiving a 6-month course showed statistically significant improvement in language and receptive-communication scales. The benefit of 6 months versus 6 weeks treatment on hearing was more marked when there was baseline CNS disease compared to those infants with no CNS involvement. For example, at 24 months there was a 46% greater likelihood of having better audiological outcomes when there was baseline CNS involvement compared to 19% with no CNS involvement. The improvement in neurodevelopmental outcomes did not significantly vary between those with or without baseline CNS involvement. It should be noted that the study was relatively small and the numbers of patients recruited with only mild cCMV disease was insufficient to show benefit of treatment. In addition, despite randomisation there were some baseline differences in neurological involvement between the two groups (though this was not statistically significant).

Treatment for infants greater than 4 weeks old

Treating babies with cCMV who are older than 28 days has not been addressed in any RCTs, although it is acknowledged that the 28-day cut-off is also not evidence based. Retrospective case series of small numbers of babies treated outside the newborn period have reported good outcomes^{27,28}. No consensus was reached in the European Guidelines¹ on how late it might be acceptable to start treatment in the scenario of SNHL diagnosed after 1 month of age, or in the eventuality of hearing deterioration. Two RCTs, in the UK and France, are currently evaluating the use of treatment in older children with cCMV and SNHL (clinicaltrials.gov NCT01649869 – “Congenital CMV and Hearing Loss in Children up to 4 Years of Age: Treating with Valganciclovir Therapy – ‘Toddler Valgan’” and NCT02606266 – “Evaluation of the Benefit of Antiviral Treatment with Valganciclovir on Congenital CMV Infection-related Deafness on Hearing and Balance (GANCIMVEAR)”), which may clarify this debate. (Evidence for treating outside the newborn period Quality D, Strength 2). In the event of UK infants being diagnosed outside the 4-week treatment cut off, recruitment to Toddler Valgan should be considered (See Appendix D).

9. Monitoring

Infants receiving treatment for cCMV require regular monitoring for potential toxicity (see Table 5). Short-term toxicity, including neutropaenia can be anticipated in around half of patients treated with ganciclovir and in a fifth on valganciclovir^{26,29}. Neutropaenia generally occurs during the first month of treatment, with no increased toxicity observed after 6 weeks. This may require treatment interruption and rarely administration of granulocyte-colony stimulating factor (G-CSF).

Hepatotoxicity has been reported in up to 30% of those treated with ganciclovir and thrombocytopaenia in a similar proportion²⁹. In the most recent study of treatment with valganciclovir, deranged liver function was observed, but this was neither clinically nor statistically significant when compared with placebo. In all studies, abnormal biochemical and haematological parameters resolved after drug discontinuation.

Long-term side effects have not been evaluated in neonates treated with ganciclovir or valganciclovir. Animal studies raise the theoretical risk of gonadotoxicity and carcinogenicity^{30,31}. Although this has not been observed in humans to date, parents should be counselled about these potential risks, particularly when considering treatment in those groups in which benefit has not been clearly shown. No adverse long-term effects have been documented in a small cohort of babies treated in early neonatal studies and followed up to puberty (NCT00031421, unpublished data).

There are no data to support therapeutic drug monitoring³². Therapeutic drug monitoring may, however, have a role when toxicity is a concern (e.g. in those with impaired renal function) or where there are concerns about treatment response.

Some centres report monitoring viral load to assist in decisions regarding adequate drug dosing and detection of

potential drug resistance. The European Consensus Guidelines do not recommend this as treatment duration is not altered by any viral parameters, and rebound of virus after treatment discontinuation is well documented with no demonstrable association with long-term outcomes (Quality D, Strength 2).

10. Follow-up

Table 5 (page 12) summarises recommended follow-up of babies with cCMV (both treated and untreated).

The recommendation for audiological follow-up is based on long-term surveillance studies of SNHL in cCMV^{34,35}. Frequent follow-up is suggested during the first 2 years of life because this is the period of highest risk of development of cCMV-associated hearing loss or emergence of a vestibular disorder and a critical period for language development. The hearing loss is progressive in half of cases. The hearing loss can start in one ear and go on to affect both ears. Early detection of SNHL during this period is also most likely to improve long-term outcomes³³. Monitoring should continue into early childhood, however, because deterioration in hearing continues throughout early life³³ (Quality B, Strength 1).

Neurodevelopmental follow-up is suggested at 1- 2 years of age, ideally with formal neurodevelopmental assessment and vestibular examination. This is not, however, routinely conducted in all centres, and there is no evidence-based benefit in this particular group, although early detection of functional impairments is generally agreed to be beneficial. (The East of England Community Paediatricians Audiology Interest Group noted that assessment at 1 year is notoriously difficult and may not pick up positive signs, therefore some paediatricians may want to assess the child at 2 years old.)

Vestibular hypofunction is common in children with cCMV, and can be severe. Vestibular function can be stable or progressive, and its severity does not necessarily match the severity of the hearing loss. Recent research by Bernard et al, published in Paediatrics in Oct 2017 suggests "Screening and appropriate management of vestibular lesions is essential to initiate adapted care"⁵¹. This means better therapy services for managing paediatric vestibular problems are likely to be needed, in the region, in the future. A vestibular disorder is difficult to assess over the neonatal period but may later affect a child's motor development/ skills, coordination and posture.⁵³ Farmer's Test⁵⁴ may be used up to 6 weeks of age, after which vestibular signs may include reduced head control, poor tone, delayed gross motor milestones and an unsteady gait with greater tendency to fall. Classic vestibular symptoms of dizziness or sickness are often not seen in paediatric patients. Children can learn to compensate for vestibular hypofunction. It is helpful to inform a child's physiotherapist of any known vestibular hypofunction.

Ophthalmic follow-up is recommended annually (at least until children can talk). European guidelines suggest follow up in those with clinically detectable disease at birth, but not in those without, because deterioration in vision has not been observed in this group (Quality C, Strength 1)³⁶. However many clinicians involved in producing the London consensus guidelines arrange annual ophthalmology follow up in all children who are positive for cCMV regardless of how much the disease is clinically detectable at birth. Local ophthalmology teams can help advise.

Families should be given information about cCMV in general as well as local/national support groups where these exist (<http://cmvaction.org.uk/>). Where cCMV parent groups are not easily accessible, parents of children with hearing loss may need support from groups for those with hearing impairment (<http://www.ndcs.org.uk/>).

Our understanding of cCMV is still limited and there is an urgent need to combine information on a central database, since individual centres will have only small numbers of patients. Local approval and individual consent is required

for patient data to be shared. Further information can be found at the European Congenital CMV Initiative (ECCI) website: www.ecci.nhs.uk, www.ecci.ac.uk.

Table 5 Monitoring and follow up according to treatment status

No treatment given	Treatment given
Monitoring	Monitoring
	<p>FBC,* LFT† and U&E suggested weekly for first 4 weeks and then at least monthly until completion of treatment course (ganciclovir/valganciclovir)‡ (Quality B, Strength 2)</p> <p>Weight measurement and drug dose review at time of blood sampling</p> <p>Viral load at baseline (Quality C, Strength 2)</p> <p><input type="checkbox"/> Consider Viral load 2–4 weekly whilst on antiviral therapy (not consensus; Quality D, Strength 2)§</p> <p>Consider therapeutic drug monitoring if:</p> <p><input type="checkbox"/> Viral load increase $>1.0 \log_{10}$ during treatment¶</p> <p><input type="checkbox"/> Toxicity is suspected</p> <p><input type="checkbox"/> There is an increased risk of toxicity: e.g., prematurity <36 weeks, abnormal renal function</p> <p>(Quality D, Strength 2)</p>
Follow up	Follow up
<p>Audiology assessment every 3–6 months in the first year, then every 6 months until 3 years of age and then every 12 months until 6 years old (Quality C, Strength 1). Vestibular assessments/ management may also be indicated.</p> <p>Paediatric infectious disease clinic review (or paediatric clinic after consultation with a specialist) until at least 1 year, and ideally 2 years, of life. (Quality D, Strength 1)</p> <p>Monitor development. (Quality D, Strength 1)</p>	<p>Audiology assessment every 3–6 months in the first year, then every 6 months until 3 years of age and then every 12 months until 6 years old (Quality C, Strength 1)</p> <p>Paediatric infectious disease clinic review (or paediatric clinic after consultation with a specialist) as soon as possible in the first month, then annual review until at least age 2 years (specialist or general clinic with paediatric infectious diseases input depending on local agreements). (Quality D, Strength 1)</p> <p>European Guidelines suggest to monitor development with neurodevelopmental assessment at 1 year in a child development service (Quality D, Strength 1). The Eastern Region Community Paediatric Group suggest that widening the age (to 1-2 years) for neurodevelopmental review may be more productive. This should be locally agreed by each trust.</p>

<p>Ophthalmic assessment as directed by ophthalmologist, but baseline and annual review up to age 5 years in those with clinically detectable symptoms/signs at birth recommended.** (Quality D, Strength 2)</p>	<p>Ophthalmic assessment directed by ophthalmologist, but baseline and annual review up to age 5 years recommended.** (Quality D, Strength 2)</p>
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*Interrupt treatment or consider granulocyte colony stimulating factor (GCSF) if absolute neutrophil count $<0.5 \times 10^9/L$. Decreasing dose may be considered for less severe neutropaenia.

†LFT monitoring monthly is sufficient if sampling difficulties.

‡Increase frequency or seek advice if there is deterioration.

§Measuring viral load is not evidence based but offers some evaluation of virus response and enables detection of possible viral resistance.

¶Consider CMV resistance testing (sequencing) in unexplained elevations/breakthrough of viraemia.

∥According to current United Kingdom newborn hearing screening guidelines.

**There is limited evidence on late ocular manifestations of cCMV. They are rare and include visual impairment and strabismus.

11. CONCLUSION

Congenital CMV is an important cause of morbidity. The diagnosis and work up for cCMV needs to be timely so treatment can be considered with all relevant investigations available. Up to 15% of children with cCMV who have no clinical signs at birth may go on to develop neurological sequelae including 6-23% who will develop SNHL. All families should be offered the advice and support of the national CMV support group (<http://cmvaction.org.uk/>).

Research in this area is rapidly expanding and may alter our approach to the management of cCMV in the future. For infants who fall outside these current treatment guidelines, discussions should be had with an experienced paediatric infectious diseases team who may be able to direct clinicians to on-going research projects that families could potentially access.

12. Acknowledgement:

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- ☐ Audiologists working in East of England
- ☐ Chear, Independent Audiology Centre, East of England
- ☐ East of England Newborn Hearing Screeners
- ☐ British Association of Paediatricians in Audiology (BAPA)
- ☐ Community Paediatric East of England Audiology Working Interest Group (EARWIG)
- ☐ East of England Regional Community Paediatric Group
- ☐ Neonatal Clinical Oversight Group
- ☐ Teachers of the Deaf in the Eastern Region
- ☐ ENT (CUHFT and NNUH)
- ☐ Ophthalmology (CUHFT and NNUH)
- ☐ Pharmacy (NNUH)

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14. Appendix A

Table 6: Grade System of Evaluating Evidence¹

Quality Rating	Definition	Example Methodology	Depiction in Text
High	Further research is very unlikely to change our confidence in the estimate of effect	Randomized trials or double-upgraded observational studies	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	Downgraded randomized trials or upgraded observational studies	B
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	Double-downgraded randomized trials or observational studies.	C
Very Low	Any estimate of effect is very uncertain	Triple-downgraded randomized trials, or downgraded observational studies, or case series/case reports	D
Strength of Recommendation	Definition	Depiction in Text	
Strong recommendation for using (or not using) an intervention	Most informed patients would choose the recommended management and clinicians can structure their interactions with patients accordingly	1	
Weak recommendation for using (or not using) an intervention	Patients' choices will vary according to their values and preferences and clinicians must ensure that patients' care is in keeping with their values and preferences	2	

Strength of recommendations is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence, variability in values and preferences and resource use.

15. Appendix B

“Definitions of Symptomatic Disease” further information extracted from European Consensus Guidelines¹

Classically, cCMV infection is categorised as “symptomatic” or “asymptomatic” at birth. Differing definitions and opinions on what constitutes “symptomatic” CMV infection, however, makes interpreting the literature challenging. Indeed, some of the largest cohort studies include babies with SNHL at birth in the group described as being “asymptomatic” because no “clinically apparent disease” was detectable during newborn examination.⁴ In modern healthcare systems, whereby cCMV is increasingly detected through screening for other conditions, alongside increased accessibility of investigations, such as magnetic resonance imaging (MRI), the traditional dichotomy between clinically “apparent” and “inapparent” disease is becoming less meaningful. Appendix B table summarises the accepted clinical features of cCMV disease with those symptoms detectable on newborn examination listed separately to those detectable only if specific investigations are conducted, for example, when cCMV is already suspected.^{24, 36-38}

Table 7

Possible Signs and Symptoms in Children with Congenital CMV ^{24, 36-38}	
Clinically detectable symptoms/signs	
<input type="checkbox"/> Physical Examination	<ul style="list-style-type: none"> ○ Small for gestational age (birth weight <−2 SD for gestational age) ○ Microcephaly (head circumference <−2 SD for gestational age) ○ Petechiae or purpura (usually found within hours of birth and persist for several weeks) ○ Blueberry muffin rash (intra dermal haematopoiesis) ○ Jaundice* ○ Hepatomegaly ○ Splenomegaly ○ Neurological signs (lethargy, hypotonia, seizures, poor sucking reflex)
Abnormalities detected incidentally or through subsequent investigation/specialist examination	
<input type="checkbox"/> Laboratory results	<ul style="list-style-type: none"> ○ Anaemia ○ Thrombocytopaenia (occurs in the first week but platelets often increase spontaneously after the second week) ○ Leucopaenia, isolated neutropaenia ○ Elevated liver enzymes (ALT/AST) ○ Conjugated hyperbilirubinaemia
<input type="checkbox"/> Cerebrospinal fluid	<ul style="list-style-type: none"> ○ Abnormal cerebral fluid indices, positive CMV DNA
<input type="checkbox"/> Neuroimaging	<ul style="list-style-type: none"> ○ Calcifications, periventricular cysts, ventricular dilatation, subependymal pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriatal vasculopathy
<input type="checkbox"/> Hearing test	<ul style="list-style-type: none"> ○ Sensorineural hearing loss uni- or bilaterally
<input type="checkbox"/> Visual examination	<ul style="list-style-type: none"> ○ Chorioretinitis, retinal haemorrhage, optic atrophy, strabismus, cataracts

*CMV-associated jaundice can be present at the first day after birth and usually persists longer than physiological jaundice. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviations.

Full Consensus Within This Expert Group Was That:

- For the purposes of research and publication, newborns identified as having cCMV disease after abnormal clinical examination at birth (such as microcephaly, small for gestational age (SGA), widespread petechiae, hepatosplenomegaly) should be differentiated from those babies identified through screening or investigation for other disorders, for example, those tested for CMV after known/likely maternal infection or abnormal newborn hearing screening. This differentiation would allow for more accurate assessment of the prognostic value of individual manifestations of “symptomatic” disease on longer- term outcomes as already shown in other publications.³⁹
- “Symptomatic” cCMV should be considered as “severe,” “moderate” or “mild” disease.
 - “Mild” disease includes those with isolated (1 or 2 at most), otherwise, clinically insignificant or transient findings, such as petechiae, mild hepatomegaly or splenomegaly or bio- chemical/hematological abnormalities (such as thrombocytopaenia, anaemia, leukopaenia, borderline raised liver enzyme abnormalities or conjugated hyperbilirubinaemia) or SGA (defined as weight for gestational age <-2 standard deviations) without microcephaly.
 - “Severe” disease includes those with central nervous system (CNS) involvement (abnormal neurological or ophthalmological examination, microcephaly or neuroimaging consistent with cCMV disease such as calcifications, moderate to severe ventriculomegaly, cysts, white matter changes, cerebral or cerebellar hypoplasia, hippocampal dysplasia, neuronal migration abnormalities)⁴⁰ or with life-threatening disease.

The Majority Agreed That:

- “Severe” disease also includes babies with evidence of severe single-organ disease (including those with clinically significant liver enzyme abnormalities [liver “failure”] and marked hepatosplenomegaly) or those with significant multi-organ involvement. Babies with transient or otherwise clinically insignificant abnormalities (i.e., the babies are not “sick”) that resolve spontaneously over a few weeks are not included in this group even if these abnormalities are multiple.
- A further group exists that may be considered to have “moderate” disease. This group is heterogeneous and includes, for example, those with persistent (e.g., more than 2 weeks duration) abnormalities of haematological/biochemical indices or more than 2 “mild” disease manifestations (as listed earlier). Because of lack of evidence, full consensus could not be reached on how to approach this group, and treatment decisions are currently made on a case by case basis. Development of a validated clinical scoring system for disease severity at presentation and risk of sequelae would be beneficial for both counselling parents and informing treatment decisions.
- Defining CNS involvement
 - It remains uncertain whether some, nonspecific findings detected on cranial ultrasound (CrUSS) and MRI (particularly isolated lenticulostriatal vasculopathy [LSV]) constitute clinically significant CNS disease. LSV has been detected in 0.4%–5.8% of all neonates undergoing an ultrasound, and only 5% has been associated with cCMV ^{41,42}. Some have suggested isolated LSV as a marker of risk for SNHL⁴¹. Others have found only more extensive neuroimaging abnormalities to be of prognostic value ^{43,44}. The majority at this meeting would not consider LSV in isolation to be a notable CNS manifestation of disease. It is suggested that neuroradiological abnormalities not known to be clearly associated with CMV disease and adverse outcomes are discussed with a suitably experienced neuroradiologist, particularly, if the results of these discussions might influence treatment decisions.
 - The exact pathophysiology of SNHL is not clear but is likely secondary to infection and degradation of sensory structures within the inner ear^{35,45}. It is therefore debated whether isolated SNHL should truly be considered a CNS manifestation of infection and, as a consequence, whether such children should be considered comparable to those with CNS disease included in published clinical trials. No studies have addressed this specific population, but a nonrandomised cohort study observing the effects of valganciclovir in isolated SNHL is in progress (clinicaltrials.gov NCT02005822). The majority of experts at this meeting would categorise babies with isolated, confirmed SNHL in the “severe”/CNS group because bilateral SNHL is not only associated with likely long-term impairments but was also included in the criteria for recruitment in the only randomised controlled trials (RCTs) in cCMV. However, consensus was

not reached because the spectrum of hearing loss is wide, and treatment of isolated SNHL has not been evaluated in any RCTs.

16. Appendix C

Request for The Release of a Newborn Screening Card for Further Testing

This form must be completed before a blood spot card can be released from the Newborn Screening Laboratory, Addenbrookes Hospital, Cambridge, for analyses additional to those undertaken by the Neonatal Screening Programme. The medical practitioner responsible for the patient should complete this form.

Please indicate the reason for the request and sign below.

Patient Details (including any alternate names, by which the infant was known)

Surname: _____ NHS number: _____

First Name: _____

Date of Birth: __/__/__

Sex: M / F

Address: _____

Reason for request

Release of a blood spot sample from the individual identified above is requested for the following reason:

The consent of the individual's parents (or legal guardians) has been obtained.

Name (printed): _____ Signed: _____

Designation: _____

Please release the card to: _____

Return form to: Newborn Screening Laboratory, Box 247, Addenbrookes Hospital, Hills Road, Cambridge. CB2 0QQ. **Fax: 01223 216867.**

FOR LAB USE

Release of Guthrie card agreed on: __/__/__ Episode number:

Signed _____ Date sample rec'd:

Dr. J. Calvin / Miss S. Hogg

Neonatal Screening, Addenbrookes Hospital, Cambridge.

Tel: 01223 257130

17. Appendix D

Treatment for infants greater than 4 weeks old – Toddler Valgan Study

At the time of writing these guidelines (March 2018), children with cCMV infection and hearing loss who are between the ages of 4 weeks old and their 4th birthday (i.e. up to age 3 years 11 months) can be recruited into a research trial: This is a phase II randomised and controlled investigation of six weeks of oral valganciclovir therapy in infants and children with congenital cytomegalovirus infection and hearing loss.

Subject Inclusion Criteria:

- Signed informed consent from parent(s) or legal guardian(s)
- Sensorineural hearing loss (greater than or equal to 21dB in one or both ears, documented within 12 weeks prior to study entry).
- Children from 1 month through 3 years of age (up to the 4th birthday)

Subject Exclusion Criteria:

- Imminent demise
- Profound sensorineural hearing loss (>90dB in both ears)
- Patients receiving other antiviral agents or immunoglobulin
- Gastrointestinal abnormality which might preclude absorption of an oral medication (e.g., a history of necrotising enterocolitis)
- Documented renal insufficiency, as noted by a creatinine clearance < 10 mL/min/1.73m² at time of study enrollment
- Breastfeeding from mother who is receiving ganciclovir, valganciclovir, foscarnet, cidofovir, or maribavir
- Infants known to be born to women who are HIV positive (but HIV testing is not required for study entry).
- Current receipt of other investigational drugs
- Previous receipt of ganciclovir or valganciclovir
- Known hypersensitivity to ganciclovir, valganciclovir, or components of the product
- Inability to attend follow-up hearing and clinical assessments
- Infants with auditory neuropathy/dyssynchrony.
- Children with another known aetiology for SNHL (e.g. connexin 26, syndrome or metabolic disorder associated with SNHL, inner ear malformation and widened vestibular aqueducts, meningitis). Exclusion of each of these conditions is not required for trial enrollment.

The study is on the <https://clinicaltrials.gov/ct2/show/NCT01649869?term=11-0069&rank=1>

The website for the study is on <http://www.networks.nhs.uk/> please join this (Top right hand corner 'Register').

When done and passwords adjusted, then login again and search for DMID 11.0069 Valgan Toddler Study and click on "Apply to join" this study.

Professor Paul Griffiths is the CI for the UK and Emily Rothwell is the Clinical Trials Coordinator/ RN. Emily Rothwell can be contacted on:

UCL Medical School | Royal Free Campus

Centre for Virology | Division of Infection and Immunity

Rowland Hill Street | Hampstead | London NW3 2PF

Tel: 020 7794 0500 Ext: 34943 | Fax: 020 7830 2854 | Bleep: 1320

www.ucl.ac.uk/infection-immunity/

Emil Rothwell's Postal Address for package deliveries to the Royal Free:

Royal Free London NHS Foundation Trust

Royal Free Hospital

Department of Virology | Ground Floor | Pond Street | London NW3 2QG

18. Example of a local cCMV Proforma

Parents/Guardian Contact Details:

Neonatal Review Clinic Date:			
Date of Birth:	Age in days at clinic review:	<u>Date when 3 weeks old:</u>	<u>Date when 4 weeks old:</u>
History			
CMV Saliva swab	Date sent:	Date result available:	
Clinical Suspicion of cCMV?	Y/N	Date:	

Details:

No clear response new-born hearing screening?	AOAE1 Date: AOAE2 Date: AABR Date:	Result: Left Result: Left Result: Left	Right Right Right
Clinical Examination:	Include presence or absence of <input type="checkbox"/> microcephaly <input type="checkbox"/> hepatosplenomegaly <input type="checkbox"/> jaundice <input type="checkbox"/> petechiae, purpura, blueberry muffin rash		
Cranial Imaging	Document presence of:	CUSS Result:	
USS All infants with cCMV should have a CUSS at neonatal review clinic. <u>And/or</u> MRI See guidelines (Table 2) for advice.	Intracranial calcification (often periventricular), Intracranial ventriculomegaly, periventricular cysts, subependymal pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriate vasculopathy.		
		MRI Result:	

Investigations:	<p>FBC (thrombocytopenia, anaemia, leucopaenia)</p> <p>LFTs (elevated transaminases, conjugated bilirubin)</p> <p>U&Es (baseline renal function)</p> <p>CMV PCR – blood (EDTA)</p> <p>CMV PCR - urine (Plain bottle)</p>	
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Ophthalmology review:	Document presence or absence of Chorio-retinitis, optic atrophy, cataracts	Date:
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Result:

Diagnostic auditory assessment	Auditory brainstem response result (normal / unilateral / bilateral deafness)	Date:
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Result:

Parental Information and Consent	
<p>I have</p> <p><input type="checkbox"/> I have been given the cCMV leaflet and had an opportunity to ask questions.</p> <p><input type="checkbox"/> Clinical information about infants with cCMV is held on a central database to allow more information to be gathered about this condition. I agree for my baby's data to be held securely on this database and used anonymously.</p> <p>Signature</p> <p>Relationship to infant:</p>	<p>initial</p> <p>Date:</p>