Clinical Guideline: Diagnosis and Management of Congenital Cytomegalovirus

Authors: F Walston, K McDevitt, S Walter, R Brown, S Luck, T Holland Brown

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	
Clinical Lead Matthew James	*Matthew James*

Audit Standards:

- TIMELY SALIVA SWABS: 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. (Note that saliva swabs taken after this ideal timeframe, can still be valuable for investigation and management)

- MANAGEMENT DECISIONS BY 4 WEEKS - 3 MONTHS: All babies investigated for cCMV in the neonatal period (1st 28 days) should ideally have a definitive management decision by 4 weeks of life with medication commenced as clinically indicated. However where services or circumstances result in the 4 week time frame being missed, an upper limit of 3 months is used for a management decision and medication where indicated (See the CONCERT study, 2021 *)

- CONSIDERATION OF RESEARCH TRIALS: All infants or children diagnosed with cCMV after 3 months should be considered for entry into ongoing cCMV trials where available.

* *Chung PK Schornagel, F Soede, W Kroes, A Oudesluys-Murphy, A Vossen The CONCERT Study: Treatment of infants with congenital cytomegalovirus infection and isolated hearing loss, detected through newborn hearing screening. 39th Annual Meeting of the European Society for Paediatric Infectious Diseases. Geneva, Switzerland; 2021*

1. Introduction – the Burden of cCMV Disease

The 2017 European Consensus Statement for the management of congenital CytoMegaloVirus (cCMV)[1] 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 births[2]. About half of cCMV infected babies with clinically detectable disease at birth are more likely to have significant impairments in their development, and cCMV infection is implicated in up to 25% of all children with sensorineural hearing loss (SNHL)[2,3]. Meta-analysis shows that although long-term sequelae, especially Sensorineural Hearing Loss (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 (congenital CMV) infection[4]. CMV has also been associated with a potential risk for autism[5,6.] Importantly congenital CMV can frequently cause vestibular dysfunction which can be severe[7] (its severity is not necessarily linked to the severity of the hearing loss[52]) 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"[8] , the June 2015 London Consensus guideline and the BMJ 2021 publication 'Congenital cytomegalovirus infection' by MH Pesch, K Kuboushek, MM McKee, MC Thorn and JB Weinberg) 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).

The British Academy of Audiology quality standards 2022 define an expectation for departments to have a CMV pathway : "Quality standards section 1a. 3. *The Service has defined triage criteria for designating routine and urgent referrals. Urgent referrals should include…babies with congenital CMV*".

"Standard 3c. 4. *The service must have clearly defined pathways and protocols for the early diagnosis and management of congenital CMV as progression of the hearing loss associated with this can be prevented by early diagnosis and treatment*." (British Academy of Audiology: Quality Standards in Paediatric Audiology, July 2022)00

"3c. 5. *The service must meet clearly defined timescales for newborns, infants, children and young people to see the medic for carrying out aetiological investigations. In the case of newborns, diagnosing and starting treatment for congenital CMV within four weeks of life is vital and as such there must be well defined pathways to achieve this*." (British Academy of Audiology: Quality Standards in Paediatric Audiology, July 2022)

There is an urgency to diagnose and assess infants with cCMV as antiviral treatment is recommended if started ideally within the first 4 weeks of life based on current randomised controlled trials (RCT's) and evidence available by the start of 2024. However there are several individual examples of hospital teams treating beyond this timeframe up to around 3 months, after discussions with paediatric infectious diseases teams and shared decision making with parents. In line with the World Report on Hearing 2021[9], hearing care should be incorporated into universal health care services and include prevention measures[9]. 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 that 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. Some children who are asymptomatic at birth may develop late onset sensorineural hearing loss and potentially other sequelae of cCMV which has raised the question of

universal screening programs to enable detection and treatment of asymptomatic neonates at birth. In the absence of universal programs, this guideline is used across many health organisations.

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 and 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

CMV is transmitted via close contact with bodily fluids e.g. saliva. 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 fetus[10]. The rate of transmission during pregnancy is 30-40% in primary maternal CMV infection and it is important to confirm infection at birth before considering anti-viral treatment for any antenatally detected maternal CMV infections. In the UK, up to 50% women of reproductive age are CMV seronegative so can have a primary CMV infection during pregnancy.

5. Who should be investigated for cCMV?

Whilst most services are focused on detecting CMV in the neonate at birth, there are some areas where antenatal screening for CMV is becoming more widely available, and therefore will identify mothers with detected or suspected CMV during pregnancy. These newborns have the advantage of potentially being alerted to audiology and neonatal services early (or in-advance) and targeted for investigation and early testing at birth. Therefore in the table below there is reference to babies being investigated early whose mothers show evidence of maternal primary infection (seroconversion or low avidity IgG) or mothers with known IgG seropositivity at the start of pregnancy with confirmed or suspected CMV reactivation/ reinvention.

Table 1 Clinical features to trigger targeted investigation[1]

Neonates

Physical Examination:

- **Hepatosplenomegaly**
- **Petechiae or purpura or blueberry muffin rash in the newborn**
- **Jaundice (prolonged or conjugated)**
- **Microcephaly (head circumference <−2 SD for gestational age)**
    - *Consider if symmetrically small for gestational age (<−2 SD for gestational age), or IUGR (IntraUterine Growth Restriction) concerns.*

Neurology

- **Seizures with no other explanation**
- *Vestibular concerns are unlikely to show in neonates (other than, possibly, poor head control or absent Farmer's rotation test) and will be more obvious later as delayed gross motor skills and balance problems.* (Note: Farmer's test is where the neonate is rotated in a circle inducing eye widening and eye deviation in the direction of turn.)

Laboratory Parameters (cCMV affects reticuloendothelial and hepatobiliary systems)

- Hyperbilirubinaemia causing **prolonged jaundice often associated with transaminitis**
- **Conjugated hyperbilirubinaemia**
- **Unexplained thrombocytopenia,** *especially if leucopenia or anaemia*

Neuroimaging

- **Intracranial calcification (often periventricular)**
- **Intracranial ventriculomegaly (without other explanation)**
- *Consider in the case of periventricular cysts, subependymal pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriate vasculopathy*

Visual Examination

- **Abnormal finding on ophthalmological examination consistent with congenital CMV (e.g. chorioretinitis)**
- *Consider if congenital cataracts*

Audiology

- **No clear response on newborn hearing screening**

Maternal serology

- **Evidence of maternal primary infection (seroconversion or low avidity IgG)**[*]
- *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*

Prematurity[†]

Note that some hospitals investigate ALL premature babies admitted to their Neonatal Intensive Care Units (NICU) for CMV.

Other children

Sensorineural hearing loss – new diagnosis
Balance/ vestibular concerns
Neurodevelopmental delay of unknown origin/cause

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), perinatal or acquired (postnatal infection) therefore does not confirm cCMV infection[8]. 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 reported [11-16] with saliva, therefore positive saliva sample results should subsequently be confirmed with a second test. There are no time restrictions for formula fed babies.

Some hospitals investigate all premature babies being admitted to Neonatal Intensive Care Units (NICU). Evidence that premature babies have a higher incidence of cCMV is limited. [17,18] 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 infection[1]. Further research is needed.

Polymerase Chain Reaction (PCR) assay of neonatal Dried Blood Spot (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	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: Quoted as being between 34 - 84% [19,20,21] in the past. Detection has improved over the years with several departments (such as the Royal Free) boasting sensitivity levels consistently nearer to 85%. See appendix C for Guthrie Consent Release Form (note that the example Guthrie Consent Release Form was available in 2021 and therefore more up to date forms are likely to be available locally or on hospital computer systems).
Maternal booking bloods	This can demonstrate timing of infection by: • Seroconversion if there are two sequential samples e.g. during pregnancy, or when comparing ante, peri or immediately post-natal blood. • 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)

(Note regarding example of managing test results: The Cambridge neonatal hearing screening team lead on taking and coordinating saliva swabs from babies that have concerns raised on their OAE screening test. Training materials for those taking saliva swabs have been developed with colleagues at NNU. The neonatal team send out negative results letters while positive results from virology are alerted to the neonatal screeners as well as audiology and acute paediatric teams for rapid assessment.)

7. 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, on balance, supports the decision to treat within 4 weeks of age, with some paediatric, infectious diseases, specialists, considering treatment up to age 3 months in light of concert trial data (non-randomised study). Clinicians must be mindful of the ideal timeframe for diagnosis and treatment window target. All cases, including those falling outside this timeframe should be discussed with local/national specialists to ensure optimal and personalised care. *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	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 [22-26]. Others are only advocating an MRI IAM. (Further information available in appendix D). Babies can sometimes be fed and wrapped to sleep through the MRI if imaging can be arranged within the first couple of months (with some arguing it is possible up to three months) of life. Some papers demonstrate an association between neuroimaging results and prognosis for hearing MRI grading Cannie et al • Grade 1, no abnormality • Grade 2, isolated periventricular T2-weighted signal hyperintensity in the frontal and parieto-occipital areas Grade 3, isolated T2-weighted hyperintense signal in the temporal lobes • Grade 4, cysts and/or septa in the temporal and/or occipital lobes • Grade 5, migration disorders, cerebellar hypoplasia, microcephaly Lvall et al • 0 normal • 1 structural abnormality alone • 2 white matter abnormality alone • 3 white matter abnormality plus structural lesion 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 [24,25]. (Readers may find the following paper valuable: C. Kachramanoglou, W. Jan, B. Jones, E. Papachatzi, L. Zombori, F. Khan, P. Gaur, N. Basheer, P. Randell, H. Lyall, Diagnostic analysis of baseline brain MRI features in infants with congenital cytomegalovirus infection: a simplified scoring system, Clinical Radiology, Volume 76, Issue 12, 2021,Pages 942.e7-942.e14, ISSN 0009-9260,https://doi.org/10.1016/j.crad.2021.09.015. (https://www.sciencedirect.com/science/article/pii/S0009926021004499) which states “study describes the notable intracranial MRI findings in cCMV in a given study period and categorises those into a simplified scoring system. In addition, the use of MRI as a diagnostic tool in cCMV is assessed and the reasons why MRI proves essential in determining the presence of intracranial cCMV infection is outlined to support the need of MRI in all suspected cases in the early postnatal period. This study also advocates that recognition of intracranial abnormalities related to cCMV infection will assist in the decision to commence treatment and may help to identify the

	timing of transmission, as it is well known that first trimester infection is more likely to lead to structural brain anomalies and is linked to worse outcomes.”)
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). Confirmed congenital CMV is now an exception to the newborn hearing screen, therefore a child may have already had an ABR.

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. For those infants who fall outside of this timeframe, specialist colleagues should still be consulted to ensure most up to date personalised care is delivered.

c) **Support Families**

i) All families should be offered advice and support such as the national CMV support group (http://cmvaction.org.uk/).

8. Treatment

Classically cCMV infection is categorised as “symptomatic” or “asymptomatic” but the European Guidelines[1] 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). There is some evidence of benefit from randomised controlled trials for treatment started in the first month of life, in infants over 32 weeks gestation, and further research will provide more information[1].

The treating paediatrician will be able to take specialist 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 • Microcephaly, • CNS calcification, • chorioretinitis • 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*§	valganciclovir Duration 6 months*	Treatment: Quality C, Strength 1 Duration: Quality C, Strength 2
Moderate Disease		
Persistent (> 2 weeks duration) abnormalities of hematological/biochemical indices More than 2 "mild" disease manifestations	Consider treatment after discussion with specialist Duration: Minimum of 6 weeks and up to 6 months*	Treatment: Quality C, Strength 2 Duration: Quality B, Strength 2
Mild		
Isolated (1 or 2 at most), otherwise clinically insignificant or transient findings e.g. • Petechiae • Mild hepatomegaly or splenomegaly • Biochemical/hematological abnormalities (such as mild thrombocytopenia, anemia, 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)

Currently the only available evidence is supportive of 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 (eg, 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 more[27].

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 [27,28,29]. 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 age[29,30]. 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

Retrospective case series of small numbers of babies treated outside the newborn period have reported good outcomes[31,32]. No consensus was reached in the European Guidelines[1] 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.

The results of a recent RCT treating babies with cCMV who are older than 28 days by Kimberlin et al ("Congenital CMV and Hearing Loss in Children up to 4 Years of Age: Treating with Valganciclovir Therapy – 'Toddler Valgan'") have been presented to the wider scientific community but not yet been published. They suggest that valganciclovir was no better than placebo in this group. Larger multicenter studies could give more information.

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 [30,33]. 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 proportion[30]. 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 [34,35]. 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 monitoring[36]. 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[37,38,39]. 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, other studies suggest this should be extended to 3-4 years of age. Hearing loss is progressive in around 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 outcomes[37]. Monitoring should continue into early childhood, however, because deterioration in hearing continues throughout early life[37] (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 centers, 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 in 2021 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. Research by Bernard et al, published in Pediatrics in Oct 2017 suggests "Screening and appropriate management of vestibular lesions is essential to initiate adapted care" [7]. 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[7]. Farmer's rotational test[7] 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. A systematic review published on. This topic also includes

simple screening assessments which may be carried out in the outpatient clinic. 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.

There are often very limited resources to provide vestibular assessments for patients and variable vestibular assessment practices in young children[40,41,42]. S Martens et al, 2022, suggest vestibular assessment using Video Head Impulse Testing and cervical vestibular evoked myogenic potentials screening for children over 6 months[40] to aid management of motor development, postural skills, balance and rehabilitation. However it is acknowledged that many services do not have access to these clinics or assessments in 2024.

Ophthalmic follow-up is recommended annually (at least until children can talk and communicate). 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)[43]. 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 [44-55] 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).

Table 5 Monitoring and follow up according to treatment status

No treatment given	Treatment given
Monitoring	**Monitoring**
	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) Weight measurement and drug dose review at time of blood sampling Viral load at baseline (Quality C, Strength 2) • Consider Viral load 2–4 weekly whilst on antiviral therapy (not consensus; Quality D, Strength 2)§ Consider therapeutic drug monitoring if: • Viral load increase >1.0 $\log_{10}$ during treatment¶ • Toxicity is suspected • There is an increased risk of toxicity: e.g., prematurity <36 weeks, abnormal renal function (Quality D, Strength 2)
Follow up	**Follow up**

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. 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) Monitor development. (Quality D, Strength 1) 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)	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). (In 2024 it is noted that some services do a full audiological assessment and some limit assessments to OAE's and tympanometry depending on the case or hearing status.) 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) 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. Ophthalmic assessment directed by ophthalmologist, but baseline and annual review up to age 5 years recommended.** (Quality D, Strength 2)

**Interrupt treatment or consider granulocyte colony stimulating factor (GCSF) if absolute neutrophil count <0.5×10^9/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.*

The CCMVnet registry

CMV Network and Registry is a group of healthcare professionals with an interest in cCMV. The aim is to collate epidemiology and clinical characteristics, evaluate risk factors for long term sequelae, evaluate prognostic value of neonatal variables (eg microbiological & imaging), document treatment strategies and outcomes, document short & long term adverse events (including malignancy, teratogenicity, etc). The data collected will help to provide more information about cCMV.

Advocacy for targeted screening in more Trusts:

"Every week in the UK, several infants narrowly miss out on the opportunity to benefit from antiviral treatment to improve their long-term outcomes. A national, targeted screen for CMV based on the NHSP would address this; enabling timely CMV testing and the opportunity for treatment and tailored follow-up for infants in all regions. We appreciate the programme will require training for newborn hearing screeners and information for parents. These have already been designed, trialled and refined, with screener and parent input, and are in operation in several Trusts. A phased regional uptake, or stepwise introduction, may be practical approaches to implementation." (Excerpt from a letter headed ' NSC Proposal: Targeted Screening for Congenital CMV' from heads of audiology and paediatric services in UK to the National Screening committee in Nov 2022)

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 offer expert advice.

12. Acknowledgement:

This guideline has been put together by Dr Tamsin Holland Brown (Community Paediatrician with expertise in childhood hearing, Cambridge); Dr Florence Walston (Neonatologist with a special interest in vertical transmission of infectious diseases, Norfolk and Norwich), Dr Simone Walter (Audiovestibular physician St George's London), Dr Sue Luck (consultant in paediatric infectious diseases, Jersey), Dr Katherine McDevitt, (Consultant Paediatrician Peterborough), Dr Richard Brown (Consultant Paediatrician Addenbrookes).

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Valuable comments and feedback was taken from the following groups or individual professionals :

- cCMV and Hearing Loss Regional Working Group
- East of England Virology
- 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)
- World Hearing Forum (WHF)

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14. Appendix A

Table 6: Grade System of Evaluating Evidence[1]

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 Guidelines[1]***

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
• Physical Examination
  ○ 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 hematopoiesis)
  ○ Jaundice*
  ○ Hepatomegaly
  ○ Splenomegaly
  ○ Neurological signs (lethargy, hypotonia, seizures, poor sucking reflex)
Abnormalities detected incidentally or through subsequent investigation/specialist examination
• Laboratory results
  ○ 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
• Cerebrospinal fluid
  ○ Abnormal cerebral fluid indices, positive CMV DNA
• Neuroimaging
  ○ Calcifications, periventricular cysts, ventricular dilatation, subependymal pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriatal vasculopathy
• Hearing test
  ○ Sensorineural hearing loss uni- or bilaterally
• Visual examination
  ○ Chorioretinitis, retinal hemorrhage, 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 (eg, 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 [42,43]. Some have suggested isolated LSV as a marker of risk for SNHL[41]. Others have found only more extensive neuroimaging abnormalities to be of prognostic value [44,45]. The majority of teh expert group 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[36,46]. 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

Cambridge University Hospitals
NHS Foundation Trust
Newborn Screening Laboratory, Box 247
Addenbrooke's Hospital
Hills Road, Cambridge, CB2 0QQ

Email: add-tr.newbornscreening@nhs.net
Tel: 01223 217160

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, Addenbrooke's Hospital, Cambridge, for analyses additional to those undertaken by the Newborn Blood Spot Screening Programme. The medical practitioner responsible for the patient should complete this form.

Following completion of screening, dried blood spot cards are stored at room temperature and blood spots may come into contact with blood spots from adjacent cards. The newborn screening laboratory takes no responsibility for confirming that storage conditions are adequate for the requested purpose. Wherever possible, it is therefore usually preferable to collect a fresh sample rather than using a retrieved newborn screening card.

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

Surname:	Enter surname		First Name:	Enter first name	
NHS Number:	Enter NHS no	Gender:	Select Gender	Date of Birth:	Select date
Address:	Enter address				

- **Reason for request**

Known CMV. To identify congenital CMV	☐		
Other *(provide details)*	☐	Details:	Enter reason

- **Where should the blood spot card be sent?**

Addenbrooke's virology lab	☐	
Other laboratory	☐	Enter laboratory

- **Information for receiving laboratory:**

Please send results and invoice to:	Enter address for results and invoice

I confirm the consent of the individual's parents (or legal guardians) has been obtained ☐

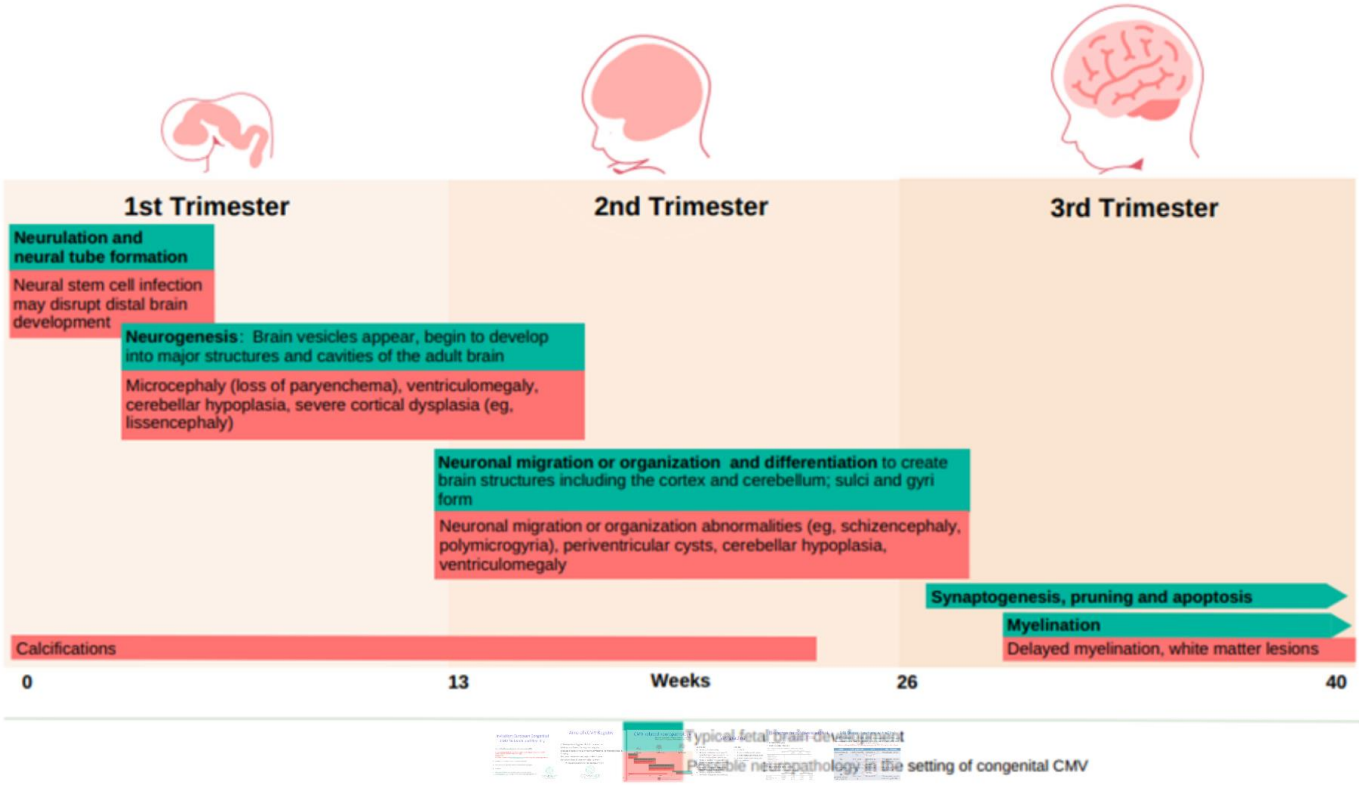
Requesting Clinician:	Enter name	Designation:	Enter job title
Email:	Enter Email address	Telephone:	Enter telephone number
Signed:		(or send from named email address)	

Please return completed form to the newborn screening laboratory by email or post *(see details above)*.

Screening lab use Register on Omnilab as External Document > Blood Spot Release Request, scan form and pass to clinical scientist.

CMV-related neuropathology

Pesch MH, Schleiss MR. Emerging Concepts in Congenital Cytomegalovirus. Pediatrics. 2022;150(2):e2021055896



1. **Example of a local cCMV Proforma in 2021**

Parents/Guardian Contact Details:

Neonatal Review Clinic Date:			
Date of Birth:	Age in days at clinic review:	***Date when 3 weeks old:***	***Date when 4 weeks old:***
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 • microcephaly • hepatosplenomegaly • jaundice • petechiae, purpura, blueberry muffin rash		
Cranial Imaging **USS** All infants with cCMV should have a CUSS at neonatal review clinic. And/or **MRI** See guidelines (Table 2) for advice.	Document presence of: Intracranial calcification (often periventricular), Intracranial ventriculomegaly, periventricular cysts, subependymal pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriate vasculopathy.	CUSS Result: MRI Result:	

Investigations:	FBC (thrombocytopenia, anaemia, leucopaenia) LFTs (elevated transaminases, conjugated bilirubin) U&Es (baseline renal function) CMV PCR – blood (EDTA) CMV PCR - urine (Plain bottle)	

Ophthalmology review:	Document presence or absence of Chorio-retinitis, optic atrophy, cataracts	Date:

Result:

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

Result:

Parental Information and Consent

I have • **I have been given the cCMV leaflet and had an opportunity to ask questions.** • **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.** **Signature** **Relationship to infant:** **Date:**	**initial**

Appendix D

MRI Brain in Newborns with cCMV

ICHT Cohort n = 71 (2012-20) (acknowledgement Prof Lyall)

Kachramanoglou C et al Clin Radiol. 2021 Dec;76(12):942.e7-942.e14. doi: 10.1016/j.crad.2021.09.015. Epub 2021 Oct 9. PMID: 34642043

Abnormal brain MRIs – 57% of asymptomatic & 78% of symptomatic infants

Cases	SNH Loss / NH	MRI	MRI Findings
Asymptomatic at birth 35	Normal hearing 19	Abnormal 8	White matter / cysts
		Normal 11	
	SNH Loss 16	Abnormal 12	White matter / cysts / polymicrogyria (4)
		Normal 4	
Symptomatic at birth 36 (one died without MRI or SNHT)	Normal hearing 24	Abnormal 17	White matter / cysts / polymicrogyria
		Normal 7	
	SNH Loss 11	Abnormal 11	White matter / cysts / polymicrogyria (all)

Further information (with thanks to Dr S Walter)

References

Exceptional Circumstances Form

Form to be completed in the **exceptional** circumstances that the Trust is not able to follow ODN approved guidelines.

Details of person completing the form:	
Title:	Organisation:
First name:	Email contact address:
Surname:	Telephone contact number:
Title of document to be excepted from:	
Rationale why Trust is unable to adhere to the document:	
Signature of speciality Clinical Lead: Date:	Signature of Trust Nursing / Medical Director: Date:
Hard Copy Received by ODN (date and sign):	Date acknowledgement receipt sent out:

Please email form to: kelly.hart5@nhs.net requesting receipt.

Send hard signed copy to:

Kelly Hart
EOE ODN Office Manager
Box 402
Rosie Hospital
Robinson Way
Cambridge University Hospital
Hills Road
Cambridge CB2 0SW