East Midlands Neonatal
Operational Delivery Network

Congenital Cytomegalovirus – Framework for screening, investigation and management

Guideline	**Congenital Cytomegalovirus – Framework for investigation and management**
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Review and Amendment Log

Version	Type of Change	Date	Description of Change

This document is a framework for practice and a summary of clinical guidelines for individual units to incorporate into their local governance processes. Its interpretation and application remains the responsibility of the individual clinician, particularly in view of its applicability across the different Trusts in the Yorkshire & Humber and East Midlands Neonatal Operational Delivery Networks. Where they exist, please also consult any local policy/guideline document where appropriate for the clinical management of babies at risk of congenital cytomegalovirus and if in doubt contact a senior colleague. This policy was written in collaboration between the 2 neonatal networks.

1. Scope

1.1. This guideline applies to all infants at risk of congenital cytomegalovirus (cCMV) infection and was developed with pan network agreement across Y&H NODN and EMNODN.

All guidelines listed are based on recommendations in 2015 London consensus guideline[i] and the 2017 European Consensus Statement[ii] for the management of cCMV [1,2]. https://www.piernetwork.org/congenital-cmv

2. Aim of the Guideline

2.1. To provide and outline clinical guidance for the identification of, options for initial investigation, management and requirements for follow up and monitoring of treatment.

2.2. To provide additional resources for reference and to share links to other key local guidelines that have been considered in the development of this pan network guidance [3-5].

2.3. To support local services in adoption of appropriate guidelines for their service and to outline issues for practical implementation through local referral pathways and governance processes.

2.4. To recommend routine audit standards for evaluation of effective implementation of guidelines for this condition

3. Keypoints

3.1. All Neonatal services should have access to an approved guideline and where necessary develop additional guidance based on local processes to assist implementation

3.2. Relevant investigations need to be performed before three weeks of life in order to diagnose cCMV versus postnatally acquired CMV.

3.3. Early diagnosis allows clinicians and parents to make timely decisions regarding treatment which needs to be started before an affected baby is 4 weeks old.

3.4. Defined local care pathways can assist follow up of results, counselling of parents and monitoring of treatment.

3.5. Effective implementation requires monitoring and audit

4. Acronyms and abbreviations

CMV	Cytomegalovirus Infection
cCMV	Congenital Cytomegalovirus Infection
CNS	Central Nervous System
DBS	Dried blood spot (Guthrie)
FBC	Full blood count
G-CSF	Granulocyte-Colony Stimulating Factor
ID	Infectious Diseases
IUGR	Intrauterine Growth Restriction
LFT	Liver function tests
PCR	Polymerase Chain Reaction
PNW	Postnatal ward
SCH	Sheffield Children's Hospital
SNHL	Sensorineural Hearing Loss
STH	Sheffield Teaching Hospitals
TDM	Therapeutic Drug Monitoring
U&E	Urea & Electrolytes

5. Summary of Recommendations

5.1. Table1. Broad summary of steps for implementation.

Examples of Triggers for cCMV screening (this list is not exhaustive but represents a summary from the referenced guidelines)

- Intracranial abnormalities without other explanation
- e.g. intracranial ventriculomegaly, periventricular calcification, white matter abnormality
- Opthalmological abnormalities
  - Congenital cataracts, optic disc atrophy, choriorentinitis
- Neonatal seizures without other explanation
- Failed newborn hearing screening
- Haematological abnormalities
  - Petechiae or purpura with thrombocytopenia, unexplained thrombocytopenia, hepatosplenomegaly
- Prolonged jaundice with transaminitis / conjugated hyperbilirubinaemia
- Maternal infections
  - Primary maternal CMV infection in pregnancy, babies of HIV positive mothers
- IUGR < 2nd centile ***and*** OFC < 2 SD for gestational age

Confirmatory Tests

- At least 2 tests in the first 21 days are preferred to confirm diagnosis
  - CMV PCR saliva swab taken at least 1 hour after a breast feed (no time restriction for formula fed babies)
  - CMV PCR Urine test
- Ensure there is a robust local process for clinician review of results and communication to parents

If PCR positive

- Refer to local team with expertise to discuss with family and decide on treatment options
- Document clinical evidence of cCMV
- Take bloods if not already sent for FBC, U&E, LFT, Coagulation, CMV viral load
- Perform cranial ultrasound and MRI
- Refer to audiology, ophthalmology and for neurodevelopmental follow up

Examples of Treatment options & duration of follow up

- Valgancyclovir 16mg/kg twice daily PO/NG
- Gancyclovir 6mg/kg twice daily IV if baby unwell or unable to take medication orally
- Monitor baby regualryl throughout treatment
- Treatment is needed for up to 6 months
- Other follow up is needed for up to 6 years (audiology) and developmental until at least 2 years

5.2. Table 2. Birth measurements for weight and head circumference and corresponding centiles and for assessment of eligibility for screening

Gestation in completed weeks	2nd centile weight (Boys) - Kg	- 2SD OFC (boys) - cm	2nd centile weight (girls) - Kg	- 2SD (2nd centile) OFC (girls) - cm
32	1.2	27	1.1	27
33	1.3	28	1.2	27.5
34	1.5	28.5	1.4	28.5
35	1.7	29.25	1.6	29
36	1.9	30	1.8	29.75
37	2.1	30.5	2.0	30.5
38	2.3	31.5	2.2	31
39	2.5	32	2.45	31.5
40	2.7	32.5	2.6	32
41	2.8	33.25	2.75	32.5
42	2.95	33.75	2.85	33

* < 32 weeks – treatment is not recommended but diagnosis and later monitoring for SNHL is still appropriate[5]

5.3. Practicalities for identifying babies requiring testing

5.3.1. Babies meeting the criteria of birth weight on or below the 2nd centile will usually be easily identified as those monitored after birth for neonatal hypoglycaemia. These babies will have their head circumference measured at NIPE assessment where the need for CMV screening can be identified using the figures in Table 2.

5.3.2. Babies on NNU who meet criteria for testing are should have their weight and head circumference measured and plotted on a growth chart eg in Badger as soon after admission as is practical

5.3.3. Babies meeting the criteria based on birth weight and head circumference should be referred to medical staff for assessment for testing.

5.3.4. Information for parents is available in the appendix of this guideline.

6. Guideline Notes

6.1. Rationale for identifying affected babies

6.1.1. cCMV is a significant cause of neurodevelopmental impairment and a leading cause of non-genetic sensorineural hearing loss (SNHL)

6.1.2. Mother to child transmission is about 30-40% in primary maternal CMV infection, with recent data suggesting a similar risk in non-primary infection[6,7,8]

6.1.3. 10% of congenitally infected neonates are symptomatic at birth, a third of whom have SNHL and up to two thirds have neurologic deficits [9].

6.2. Severity of cCMV[11]

6.2.1. cCMV may be considered as mild in babies with 1 or 2 transient or clinically insignificant symptoms e.g. mild thrombocytopenia, mild hepatomegaly or splenomegaly, transient biochemical abnormalities, SGA (<2SD) without microcephaly. These symptoms may overlap with more severe manifestations, however the difference is they occur in isolation.

6.2.2. cCMV is considered severe if symptoms include at least one of the following:
- CNS or eye involvement with or without microcephaly
- Hepatosplenomegaly with worsening LFTs
- deranged LFTs,
- multiple manifesations attributable to CMV

6.2.3. Moderate: There is no consensus on the babies in between mild and severe – but there is a spectrum where symptoms may fall between a clear definition of severity e.g. mild abnormalities lasting > 2 weeks. These babies

6.3. Confirmatory Tests

6.3.1. For prognosis and treatment, it is important to distinguish between congenital and postnatally acquired CMV [10,11].

6.3.2. The gold standard for testing is using saliva and urine sample as they are more reliable than blood PCR for the diagnosis. They are diagnostically equal but salivary testing is usually logistically easier to carry out.

6.3.3. Information for parents on the reasons for testing is available in Appendix 2 of this guideline.

6.3.4. Not all Trusts will offer saliva and urine PCR testing so local policies should reflect availability of local testing

6.3.5. Blood PCR (EDTA) can be useful but may give a false negative result. A positive result is diagnostic and it may be possible to have information on viral load. Virology advice should guide use of this test.

6.3.6. A positive CMV PCR on bloodspot testing may offer a restrospective diagnosis of congenitally acquired CMV infection though a negative result does not exclude cCMV

6.3.7. Serology testing is not recommended, CMV IgM is not as sensitive or specific as CMV PCR. Interpretation of IgG is difficult in infants under 1 year as it may represent transplacental transmission.

6.4. Actions if PCR is positive

6.4.1. Assess baby for other clinical signs as treatment choices will depend on symptoms including ophthalmology and audiology assessment even if newborn hearing screening has been passed. Discuss findings with the responsible consultant.

6.4.2. Complete all relevant other investigations including FBC, LFT, clotting, PCR viral load, cranial imaging, auditory brain response (ABR)

6.4.3. Discuss options for treatment and monitoring with local virology and/or infectious diseases services (according to local agreed pathways). A full clinical picture should be available for these discussions.

6.4.4. Discuss treatment options with parents including benefits, potential side effects and follow up required.

6.5. Infection Prevention and control Measures [12]

6.5.1. Spread of CMV is via direct contact with infected bodily fluids and is not airborne.

6.5.2. Babies testing positive for CMV do not require isolating either within the Postnatal ward setting or in a neonatal unit.

6.5.3. Please refer to local policies with regards to pregnant staff caring for babies with cCMV infection. They may need a risk assessment.

6.5.4. Simple PPE (apron and gloves) can be worn by staff when performing cares but is not required for parents.

6.5.5. A high level of hand washing measures should be in place and monitored for all carers following contact with bodily fluids such as saliva, urine and stool. Parents and carers should be advised not to share food utensils with their baby or put a used dummy in their mouth. Friends and family potentially at risk should avoid kissing the baby directly on the lips when having cuddles.

6.5.6. Advice to parents on discharge home should include information on contact for the first 3 months with family and friends who are pregnant. This is principally around hand hygiene following nappy changes.

6.6. Rationale for treatment

6.6.1. There is a need to diagnose and assess severity in infants with cCMV as antiviral treatment is only recommended if started in the first 4 weeks of life based on current research[4].

6.6.2. There is limited evidence to support the potential benefits of treatment of mildly affected infants or those with isolated sensorineural hearing loss[10]

6.6.3. There is lack of evidence to support initiating treatment of cCMV with antiviral treatment after 4 weeks of age.[11] For babies where the confirmed diagnosis of cCMV is made after 4 weeks, a discussion of the potential benefits of treatment with the local virology team or CCMVNET (see section 6.9.1) may be useful.

6.6.4. Research for treating preterm neonates for cCMV is sparse. With the toxicity associated with antiviral treatment, especially in babies under 32 weeks gestation, antiviral treatment for cCMV is not routinely warranted.[13] Discussion with local virology teams may be helpful in case of severe cCMV in preterm infants < 32 weeks.

6.6.5. Examples of parental consent forms for treatment and a proforma for treatment plans and monitoring are available from the Sheffield Children's Hospital Guidance.

6.7. Treatment regimes

6.7.1. The decision to offer treatment will usually be made with a Virology and/or Infectious diseases Consultant. Choices should be made in conjunction with parents following discussion of risks and benefits.

6.7.2. Drugs of choice are oral Valganciclovir or intravenous Ganciclovir in significantly unwell babies and may be required for up to 6 months[4, 13-15]

6.7.3. Monitoring should include screening for viral load, myelosuppression and hepatotoxicity and doses modified where there is a known renal impairment.

6.7.4. Withhold treatment where neutrophil count < 0.5 X 10^9/L or there is evidence of hepatotoxicity. Discuss possible complications of treatment with local virology services in order to create an ongoing treatment plan.

6.7.5. Therapeutic drug monitoring may be appropriate where viral load remains high, in higher risk groups < 36 weeks gestation and in babies with renal impairment

6.8. Advice for parents for medications

6.8.1. A summary of advice for parents is included in the appendix 2 – Information for Parents section. This guidance can be used to guide discussion and shared decision making about treatment.

6.8.2. Provide parents with a copy of this written advice as testing is initiated.

6.8.3. Benefits include a potential prevention of hearing loss or prevention of deterioration of hearing if this is detected on newborn screening and potentially better neurodevelopmental outcome in patients with symptomatic cCMV.[15]

6.8.4. Side effects of treatment with antivirals include: neutropenia, thrombocytopenia, and hepatotoxicity.

6.8.5. The following national group provides useful information for parents where a baby has tested positive for CMV https://cmvaction.org.uk/

6.9. Advice for professionals

6.9.1. CCMVNET.ORG – Congenital CMV Network links to CMVnet – a European initiative promoting international collaboration, research and educational activities for cCMV. In 2020 the Network established the European cCMVNET registry of children collecting data on epidemiology, clinical characteristics, long term sequelae, and treatment of infants born with cCMV.

6.9.2. Professionals can access advice through CCMVnet monthly meetings where more complicated cases can be discussed to support decision making on treatment and management e.g. for significant early but postnatally acquired infections and for symptomatic babies.

6.10. Follow up [4]

6.10.1. All symptomatic babies (whether treated or not) require comprehensive follow up. Regular audiology assessment should be done to 6 years (consider at least 6 monthly for the first 3 years and annually thereafter), ophthalmology to 5 years(higher risk of strabismus, chorioretinal scars, cortical visual impairment, nystagmus and optic atrophy) and developmental follow up for at least 2 years are particularly important.[16]

6.10.2. Asymptomatic babies will also benefit from longer term surveillance for developmental assessment (to 2 years of age) and annual assessment for hearing loss (to 6 years of age) as there is still a risk of childhood developmental problems or deafness. A baseline assessment for ophthalmology should also be done.

6.10.3. Arrangements for follow up should be clearly defined within local processes

7. Audit Recommendations

7.1. Individual neonatal services should audit local implementation of their approved cCMV guideline and consider the following recommended parameters

- All babies with no response on newborn hearing screening pathway should be tested for cCMV within 3 weeks
- Rates of testing of babies with clinical symptoms as listed in tables in section 5.1
- Diagnosis by 21 days of age in cases of proven symptomatic cCMV
- Treatment of cCMV by 28 days of age If recommended

7.2. Local results should be shared with associated services (ophthalmology, audiology and neurology/developmental paediatrics)

8. References

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2. Luck S. et al., A European Expert Consensus Statement on Diagnosis and Management The Pediatric Infectious Disease Journal: December 2017 - Volume 36 - Issue 12 - p 1205-1213

3. Nottingham University Hospitals - Congenital Cytomegalovirus (cCMV) – Diagnosis and Management. Accessed through the following link or the NUH guidelines app. https://www.nuh.nhs.uk/clinical-guidelines

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12. Babies born with congenital CMV https://www.cdc.gov/cmv/congenital-infection.html

13. Kimberlin DW, Lin CY, Sanchez PJ et al. Congenital Cytomegalovirus Disease involving the Central Nervous System: A randomized controlled trial. *J Pediatr 2003:143:16-25*

14. Oliver S.E., et al., *Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system.* J Clin Virol, 2009. 46 Suppl 4: p. S22-6.

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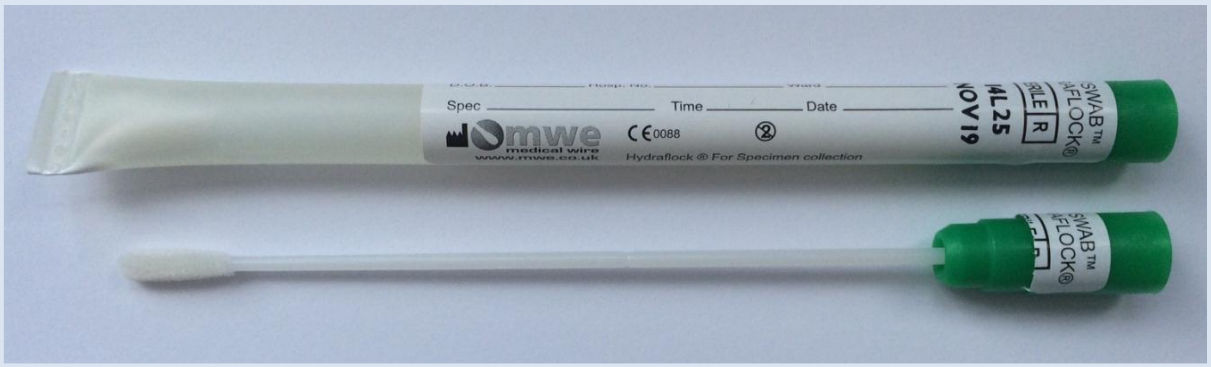
Appendix 1 Adapted from Sheffield Children's Hospital Guidance – Congenital Cytomegalovirus Infection (Neonates)

Appendix 1 - How to take a Saliva Swab for Testing for CMV

Equipment needed:

- Gloves
- Specimen bag
- Example: Hydraflock (dry) green swab as below – individual Trusts should check the swab recommended by their local testing laboratory
- Virology request form



Procedure:

- Ensure baby has not been breastfed within the last 1-2 hours
- Check expiry date of swab (see picture above), and that the label on the swab is intact. If expired/label broken, discard and get new swab
- Check baby's ID
- Complete details on swab/ apply the label with barcode
- Perform hand hygiene and put on gloves
- Open swab, and place in baby's mouth – there is no specific method/site advised but it can be helpful to aim under the tongue and roll the swab to try to catch plenty of saliva.
- Remove and place swab back into tube
- Remove gloves and perform hand hygiene
- Complete request form as per local policy and place in specimen bag
- Place swab in specimen bag and then leave at designated specimen collection point/ send by pod
- Document in clinical notes the time of sampling and that the sample has been sent
- Ensure communication about the sample being sent is made with staff responsible for acting on the result of the test eg add a note in a doctors job book

Appendix 2 – Parent Information

(Adapted from Nottingham University Hospitals - Congenital Cytomegalovirus (cCMV) – Diagnosis and Management. Accessed through the following link or the NUH guidelines app. https://www.nuh.nhs.uk/clinical-guidelines)

Cytomegalovirus (CMV)

What is Cytomegalovirus (CMV)?

Cytomegalovirus (CMV) is a fairly common virus which, in adults, may cause flu-like symptoms (fever, headaches, and tiredness) which resolve by themselves. This means that many adults can have a CMV infection without ever realising, and in most adults this does not pose a significant risk (except in some groups, for example people with impaired immunity). However, some women may contract CMV infection while they are pregnant. If a baby is infected with CMV (this is called 'congenital CMV') while growing and developing in the womb, it may cause problems related to the way their brains develop. It can also cause other symptoms which may show up after the baby is born.

How do I know if I had CMV in pregnancy?

You may have had a fever and flu-like symptoms, but it doesn't always cause symptoms in adults, so it isn't always possible to know. It may be possible to test your blood for CMV, but sometimes it can be difficult to know if a positive result means that you had a new infection for the first time during pregnancy, a reinfection or whether the blood test is just picking up evidence of old CMV infection. If your blood test is positive, we will usually test your baby as well. Sometimes we also detect signs on your baby's ultrasound scans that can suggest that the baby has been infected with CMV, and so we would do further tests to confirm this. In most cases signs are not visible on antenatal scans.

What kind of symptoms or problems might my baby have?

One of the main problems CMV can cause is hearing loss. This may be picked up on your baby's newborn hearing screen. It can also cause problems in terms of your baby's development, and they may not meet their milestones, with the possibility of long-term disability. Because babies and young children take months and years to reach certain milestones, it may not be possible to know the extent of these problems at the time of birth. Your child may have a brain scan, but this will not necessarily be able to make long term predictions.

Other potential problems include issues with growth, eye health, jaundice, liver function, and blood problems such as low platelets (a type of cell that helps form blood clots).

Alternatively, your child might not have any symptoms at all.

A birth weight below the 2nd centile on the growth chart and especially if this is in conjunction with a head circumference measurement that is also low may be the only signs of congenital CMV. Therefore screening will normally be offered to parents of babies who measure small at birth irrespective of the results of the newborn hearing screening.

How do you test for CMV in babies?

Most of the time, we take a sample of urine. In some cases a sample of your babies saliva can provide an equally good sample for testing. We can also do a blood test, but sometimes this is falsely negative. If we need urine, we can put cotton wool or a bag in your baby's nappy.

Is it treatable?

Based on your baby's symptoms, treatment may be required. For babies with very mild symptoms or isolated hearing loss, it is not clear if treatment can offer any benefit (based on the available research). Your doctors will discuss with you the pros and cons of offering oral treatment if your baby is only mildly affected. Even if your baby is not having medication, they will still receive follow up to monitor progression of their development, hearing and vision.
If treatment is to be used, it would need to be initiated within the first 3-4 weeks of life. The treatment is an antiviral called Valganciclovir, which has been shown to prevent hearing loss (or worsening of hearing loss), as well as improving the baby's development. Valganciclovir is given by mouth, but if your baby is unwell or cannot take medicine by mouth for any reason, we can give an alternative medicine intravenously (injected into the veins). The treatment must be started within the first four weeks of life, and taken for up to six months in order to provide the best chance of a good treatment effect.

Are there any risks with this treatment?

There can be some risks, such as a low number of neutrophils (one of the different types of white blood cells your baby's body produces). If this falls particularly low, your baby may be at increased risk of infection. We will monitor this with blood tests while your baby is receiving treatment. Your baby may also have low platelets, or changes to liver function (seen on blood tests) – however, these effects can also happen as part of the picture of CMV infection so would require further monitoring.

How will my baby be looked after?

Your baby will need an eye examination by a specialist as well as a hearing screen. Further regular hearing tests will be done by the audiology department. Your baby will also need an ultrasound scan of their brain which will be organised to be done in the first few weeks of life. If your baby has symptoms of concern involving the neurological system (including unusual findings on cranial ultrasound or seizures), an MRI scan (which provides more detail) may also be performed. While on treatment, your baby will have blood tests to check for side effects of the medicine. We will also need to follow your baby up over time to see how their development progresses.

What happens if my baby is exposed to CMV after birth?

The highest risk to the baby is during pregnancy, particularly during the first trimester. After the baby is born, it is very possible for the infection to be transmitted in saliva and breastmilk, but the risks in terms of growth and development are much lower, and most babies who get a CMV infection after they are born will not have any symptoms at all