DIAGNOSIS AND MANAGEMENT OF CONGENITAL CYTOMEGALOVIRUS (cCMV)





Trust reference: B8/2022

1. Introduction and scope:

Prevalence of congenital Cytomegalovirus (cCMV) in developed countries is 0.4-0.64% of all births. Up to 90% are asymptomatic at birth but 10-15% will develop Sensorineural Hearing Loss (SNHL) in the first 5 to 7 years of life. cCMV is the commonest non-genetic cause of childhood SNHL (10-25%). 50% of children with cCMV related SNHL are progressive – many are asymptomatic at birth and pass their newborn hearing screen. Children with profound SNHL related to cCMV will require cochlear implantation.

Up to 50% with symptomatic cCMV have neurodevelopmental sequelae which require extensive multidisciplinary input from: audiology and audiovestibular clinics, implant centres; paediatrics (including general paediatrics, neurology, gastroenterology, orthopaedics, community paediatrics and infectious disease specialists); physiotherapists; ophthalmologists; orthoptists, occupational therapists; dietitians; sensory integration therapists; speech and language therapists; psychologists and psychiatrists; teachers of the deaf and special educational needs support and social workers.

This guideline is for Clinicians and Health Professionals within UHL Children's Hospital & Neonatal unit assessing and managing neonates and children under 16 years old with suspected or proven cCMV.

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2. Congenital Cytomegalovirus screening, diagnosis and management

2.1 Maternal Diagnosis and Transmission:

Primary CMV infection during pregnancy is usually detected during routine U/S scanning, when any abnormality found is then followed by a Congenital Infection screen. Primary maternal CMV infection is then diagnosed by CMV IgG seroconversion between the earlier booking blood and a current blood, and/or a rise from low to high CMV IgG avidity.

About 5-10% of babies with cCMV will be born with overt signs of cCMV, the rest will be born with no apparent symptoms (https://www.cdc.gov/cmv/clinical/congenital-cmv.html), but then of the remainder, 10-15% will develop some degree of developmental delay and sensorineural deafness (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4471438/).

Note that maternal CMV reactivation can also lead to cCMV, but this risk is very low and it is not cost-effective or safe to screen for this (e.g. offering amniocentesis to every woman who is CMV IgG positive in the absence of seroconversion during pregnancy).

Congenital CMV occurs due to transplacental transmission. The earlier the transmission, the more severe the disease. Perinatal and postnatal transmission of CMV is through cervicovaginal secretion and blood, and breast milk. The risk of maternal transplacental CMV transmission is shown in the **Table 1** below:

Table 1. Risk of CMV transplacental transmission related to maternal CMV infection

Maternal infection	Risk
Primary	30-40%
	(30% in 1st trimester, 47% in 3rd trimester)
Secondary	1-2%
 reactivation 	
o reinfection with different strain	

2.2 How to screen for Congenital Cytomegalovirus

- 1. Once decided on screening do not delay sample collection the earlier the sample is taken the more reliable the test result is. It is crucial to establish the diagnosis of cCMV in the first 3 weeks of life because a positive urine CMV PCR after 21 days old may be due to perinatal or postnatal transmission instead of congenital infection. This is further compounded by the narrow window of opportunity for antiviral treatment which must be instituted within 28 days of life as per current evidence.
- 2. Send urine for CMV PCR testing these can be the same or different mediums

Urine CMV PCR (within the first 3 weeks of life)

- Sensitivity 100% and specificity 99%
- One negative urine specimen is sufficient

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- Positive result >21 days of age could be postnatally acquired (passage through the birth canal or through breast milk)
- Recommended testing <14 days of age

Dried blood spot (DBS) CMV PCR (if beyond the 3 week post-natal sampling window)

- Retrospective method of diagnosis
- Sensitivity 84% and highly variable depending on the laboratory techniques and population
- Negative result cannot definitively exclude cCMV

A urine sample is currently the main sample type for CMV PCR diagnostic investigation in a newborn. If the urine is CMV PCR positive, then the Parents Information Leaflet (PIL) on cCMV should be given to parents upon neonatal sample collection. Parents/family should be counselled by a senior paediatric clinician who will be briefed if required by other specialists (e.g. virologists, neonatologist, audiologists) assigned to oversee the entire program of screening, investigations and management of cCMV.

DO NOT send CMV serology testing

CMV IgM is not recommended because it is neither sensitive nor specific. CMV IgG is less useful in under 1 year olds because it reflects maternal antibody owing to placental transfer. A negative CMV IgG result after the first year of life almost certainly excludes cCMV. However, one should consider testing for cCMV in children with cerebral palsy of unknown cause or delayed onset of SNHL by doing CMV IgG and DBS CMV PCR.

2.3 Management of confirmed cCMV

If the screening sample (urine) is CMV PCR positive, all investigations listed in **Table 2** including blood tests, neuroimaging and ophthalmology review should happen **before 4** weeks of age.

Infants should be offered auditory brainstem response (ABR) testing **before 4 weeks** of age. As the time available to test is very short any baby with a confirmation of cCMV should be referred immediately to the Electrodiagnostics Service, Level 0, Sandringham Building, LRI for a diagnostic hearing assessment even if they have passed their newborn hearing screen. For speed referrals should be made ideally via e-mail (EDS.Audiology@uhl-tr.nhs.uk) or telephone (x15686) with a named consultant given for reporting purposes.

The decision to start valganciclovir should be made with the parents wherever possible and counselling of the expected course of treatment and monitoring is required. The recommended treatment length is 6 months, based on recent data. Please note that the information contained within the BNFc may be different for this indication. Please follow the dosing detailed in this guideline.

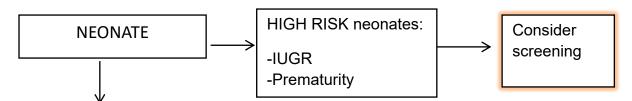
The child should be seen as soon as possible in Dr Bandi's clinic (clinic code SBRINF) who will also address any questions that the parents may have (in consultation with Virology, as needed). It is important for parents to understand even if the child does not

have treatment they will require follow up assessments for at **least 6 years**. 2 years for General Paediatrics, 5 years for ophthalmology and 6 years for Audiology.

Table 2. Essential investigations in neonatal cCMV

Test	Comments		
Full blood count	Thrombocytopaenia (<100 000/mm3,		
	nadir at 2 weeks)		
Creatinine, urea and electrolytes	Baseline renal function		
Liver function tests	ALT >80 U/L, conjugated		
	hyperbilirubinaemia, parameters increase in		
	first fortnight		
Blood CMV viral load by PCR	To monitor response to antiviral treatment		
Neuroimaging (should be	Ultrasound is the preferred initial study but all		
completed within 4 weeks of life	infants with neurological examination		
to impact on treatment decision	findings, seizures, abnormal/equivocal		
making)	ultrasound findings or features of CMV		
	diseases should have an MRI (although this		
	should not delay treatment if ultrasound or		
	other investigations already suggest CMV		
	disease).		
Ophthalmologist review	Assessment for chorioretinitis, optic atrophy,		
	cataracts		
Diagnostic auditory assessment	Diagnostic auditory brainstem response		
	(ABR)		

Figure 1. Indications for CMV neonatal screening flowchart



ANY OF THE FOLLOWING:

1. Clinical features of CMV infection present :

- Failed hearing screen (or diagnostic assessment if screen contraindicated)
- Neurology signs (seizure/hemiparesis/hypotonia/microcephaly)
- Symmetrical SGA
- Congenital cataracts/eye abnormalities
- Petechiae or Purpura in the newborn
- Prolonged jaundice with transaminitis
- Unexplained thrombocytopaenia
- Hepatosplenomegaly
- Extreme prematurity (in combination with other cCMV features)

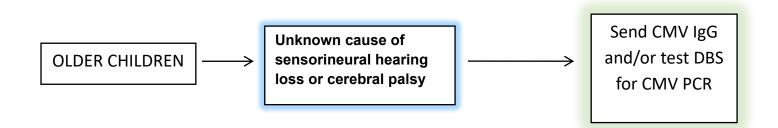
2. Abnormal cranial imaging (on USS/MRI)

- Intracranial calcification (often periventricular)
- Intracranial ventriculomegaly without other explanation
- Periventricular cysts, subependymal pseudocysts, germinolytic cysts,
- White matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriate vasculopathy

3. Abnormal laboratory results

- Transaminitis
- Conjugated hyperbilirubinemia
- Unexplained thrombocytopenia, consider if leukopenia or anaemia

4. Evidence of primary maternal CMV infection/reactivation during pregnancy



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Send urine for

CMV PCR

Figure 2: Decision to treat CMV

SYMPTOMATIC CHILD? Yes Significant irreversible organ involvement: No Mildly symptomatic child without CNS https://ep.bmj.com/content/101/5/232 disease e.g.: ANY CNS disease including isolated sensorineural hearing loss or significant CNS abnormality found in **Isolated IUGR** USS or MRI head (where USS is suggestive but not Hepatomegaly with normal liver definitive) enzymes Mild, transient thrombocytopenia Isolated elevated liver enzymes OFFER TREATMENT Should start in first month of life PO/NG Valganciclovir 16mg/kg/dose BD if enterally fed 6 months treatment with monthly dose adjustment for weight DO NOT OFFER TREATMENT OR: Keep under Paediatric review for first year IV Ganciclovir 6mg/kg/dose BD until enteral route of life. available.(Can also consider IV therapy in severe disease) **Monitor development** IV Ganciclovir: FBC, U&E and LFT weekly Consider viral load testing if initial viral load PO/NG Valganciclovir: FBC, U&E and LFT at week 2 and week 4 was high then monthly until completed Audiology testing regularly until 6 years Viral load week 2, week 4 and then monthly until completed old Drug level if any of (Discuss with Virology): 1. Toxicity suspected 2. Viral load increasing 3. Prematurity<36 weeks 4. Abnormal renal function 1. Paediatric infectious diseases clinic ASAP

- 1. Paediatric infectious diseases clinic ASAP (See in Children's Daycare if no clinic capacity) then:
 - 2 weeks
 - 1 month
 - Then monthly until completes therapy
 - Annually for minimum of two years after completion of therapy.
- 2. Audiology testing regularly until 6 years old
- 3. Neurodevelopmental assessment in clinic at one and two years
- 4. Ophthalmic assessment at least annually until 5 years of age

3. Education and Training

No further training is required to implement this guideline.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Diagnosis of cCMV by 21 days old in neonates with clinical features/ investigation results consistent with cCMV	Clinical audit	Dr Srini Bandi	5 yearly	CMG audit group
Treatment of cCMV by 28 days old if indicated	Clinical audit	Dr Srini Bandi	5 yearly	CMG audit group

5. Supporting References

With acknowledgements to Stefan Kelf & UHL audiology team for their valuable input in the development of this guidance.

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6. Key Words

Congenital cytomegalovirus, valganciclovir, CMV, screening

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs. As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

Contact & review details				
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New document				