Management of Congenital Cytomegalovirus (CMV)

Guideline Responsibilities and Authorisation

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Guideline Review History

Version	Updated by	Date Updated	Summary of Changes

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Contents

1 Background

Cytomegalovirus (CMV) is a double-stranded DNA virus and is a member of the Herpes viridae family. Infection with CMV is ubiquitous, infecting approximately half the adult population.

Congenital CMV is the most common congenital viral infection and is the leading cause of sensorineural hearing loss (SNHL) and an important cause of neurodevelopmental disabilities.

The risk of intrauterine transmission is highest when primary infection occurs during pregnancy (30%) compared to non-primary infection or re-activation (1%). There is a higher rate of vertical transmission in mothers with older gestational age at infection, while the risk of adverse fetal effects significantly increases if fetal infection occurs during the first half of pregnancy.

Clinical findings of congenitally acquired CMV

Symptomatic

Affecting approximately 10% of congenital CMV cases

- 8-10% of symptomatic congenital CMV have severe, life-threatening disease with up to 30% mortality rate
- Multiple manifestations including: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, haemolytic anaemia, hepatitis (raised transaminases or bilirubin), jaundice at birth, small for gestational age, intrauterine growth retardation, prematurity and pneumonia
- Central nervous system involvement such as microcephaly, radiographic abnormalities consistent with cytomegalovirus central nervous system disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations), abnormal cerebrospinal fluid indices for age, chorioretinitis,, or the detection of cytomegalovirus DNA in cerebrospinal fluid, lethargy and/or hypotonia, poor suck and seizures.
- Sensorineural hearing loss –
  - Occurs in 1/3 to 1/2 of infants with symptomatic disease. May be detected at birth but 18-30% have delayed onset.
  - Up to 71% bilateral hearing loss
  - Often progressive and eventually becomes severe to profound in up to 78% of cases

Asymptomatic

Up to 90% of cases are apparently asymptomatic

- Subtle differences may be present – earlier gestational age, lower birth weight
- 10-15% experience sensorineural hearing loss either congenital or in infancy and early childhood
- Ocular abnormalities including retinal lesions and strabismus occur in 1-2% cases – rarely sight-threatening
- Abnormal brain imaging findings of periventricular leukomalacia, ventriculomegaly and punctate calcifications observed in 5-20% of otherwise asymptomatic cases.

2 Overview

2.1 Purpose

To outline guideline for management of infants with potential risk of developing sequelae from intrauterine transmission of CMV. Infection of the fetus can result in embryonic death, stillbirth, prematurity, intrauterine growth retardation, developmental abnormalities or congenital disease.

2.2 Scope

Te Whatu Ora Waikato staff working in NICU.

2.3 Patient / client group

Babies and infants under Neonatal Service which includes NICU, delivery suite, postnatal ward and community.

2.4 Definitions and acronyms

CMV	Cytomegalovirus
CNS	Clinical Nurse Specialist
DNA	Deoxyribonucleic acid
LFTs	Liver function tests
NICU	Neonatal Intensive Care Unit
NNP	Neonatal Nurse Practitioner
PCR	Polymerase chain reaction
SNHL	Sensorineural hearing loss
SMO	Senior Medical Officer
Ubiquitous	Present, appearing or found everywhere

3 Clinical management

3.1 Competency required

Registered Midwife, Nursing and all Medical Staff.

3.2 Guideline

3.2.1 Investigations – see Appendix A, Algorithm 4.

Newborns with suspected congenital CMV should have:

- Urine CMV PCR (ideally at birth or in first three weeks as virus can shed for up to 3 weeks so if diagnosis is delayed urine can still be collected). Must be performed in the first 3 weeks to confirm congenital infection. Minimum volume 1ml.
- Blood CMV PCR is not routinely required but may be considered if the CMV urine is positive, after discussion with an infectious diseases specialist to assess response to anti-viral treatment.
- Option to review the Metabolic Screening Card for CMV – can be requested retrospectively – needs specific request and parental consent

If Urine or PCR positive to have;

- LFTs (elevated transaminases and SBR)
- FBC (thrombocytopenia)
- Newborn hearing screen
- Ophthalmology assessment for chorioretinitis
- Head ultrasound (infants may require an MRI head, please consult the paediatric infectious disease team)
- Long term: serial audiology and developmental assessment, head circumference, ophthalmology.

Note: all congenital CMV infections must be reported to the New Zealand Paediatric Surveillance Unit (NZPSU) https://www.otago.ac.nz/nzpsu/index.html

3.2.2 Breastfeeding when Mother has CMV Infection

- Term babies may breastfeed.
- Premature babies <32 weeks and low birth weight babies (<2000g) - freeze the expressed breast milk for 24 hours. This reduces the CMV titre.

NOTE: Must put the date and time on the container when it goes into the freezer.

- Staff that are pregnant must not care for CMV positive babies.

3.3 Potential Complications

Approximately 70-80% of cases symptomatic at birth, develop late complications that may include :

- Hearing loss (50 to 58 percent)
- Intellectual disability (intelligence quotient <70; 47-55%)
- Microcephaly (37%)
- Strabismus (25-30%)
- Dental disease (27%)
- Seizures (23%)
- Cortical visual impairment (14-22%)
- Chorioretinitis (20%)
- Cerebral palsy (13-27%)
- Death after the newborn period (1.7-5.8%)

3.4 Long Term Follow-up

1. Paediatrician developmental review at 1 year of age. Additional assessment if severely affected. Consider the following during these and subsequent appointments
    - Regular growth and development monitoring
    - Central nervous system manifestations (intellectual disability, cerebral palsy and seizures) may require special education services and speech, language, occupational and/or physical therapy.
    - Behavioural and developmental disorders i.e. autism spectrum disorder, attention deficit and hyperactivity.
2. Refer to audiology with recommendations to monitor hearing loss as congenital CMV is progressive over the course of a lifetime - every 3-6 months until age 3 years and then annually until age 6 years.
3. Refer to ophthalmology for management of potential chorioretinitis, retinopathy, optic atrophy and strabismus. Recommended annual examination until 5 years of age.

If required, consider referral to other services for:

4. Dental disease as congenital CMV is associated with hypoplasia and hypocalcification of tooth enamel.
5. Liver disease as a result of congenital CMV is relatively uncommon but will need monitoring if still evident after 6 months of age.

3.5 Treatment

The recommendations for treatment of congenital CMV are evolving - please consult the Paediatric Infectious Disease team in Auckland

Treatment is recommended (ganciclovir or valganciclovir) for severely affected infants as follows:

- > 32 weeks
- < 1 month age
- Pulmonary oedema
- Very low platelet counts
- Eye problems that may lead to vision loss
- 6 -12 months treatment has been shown to be more beneficial than 6 weeks for long-term hearing and neurodevelopmental outcomes.

Treatment is not recommended for asymptomatic newborns.

Treatment options include ganciclovir (IV) and valganciclovir (oral) – this will require a NAPPA application – please contact the pharmacist for this

4 Parent information

- See 3.4 and 3.5.
- https://www.healthnavigator.org.nz/health-a-z/c/cytomegalovirus-cmv/
- https://cmvaction.org.uk/download/375/

5 Audit

5.1 Indicators

- Timely peer review of protocol
- Appropriate documented follow-up.

5.2 Tools

Refer Appendix A – Cytomegalovirus Algorithm 3 and 4

6 Evidence base

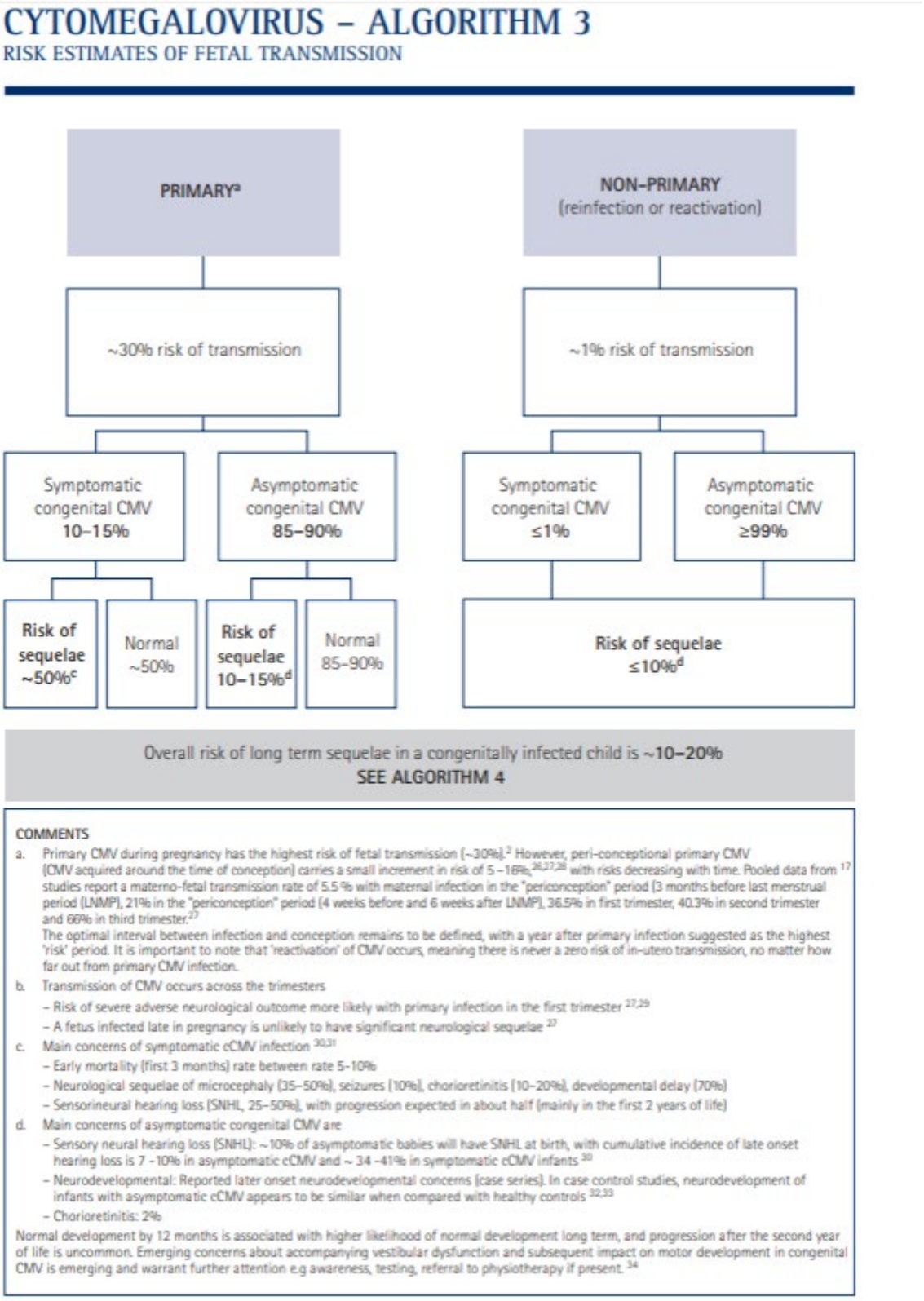
6.1 Summary of Evidence, Review and Recommendations

- Congenital CMV is common worldwide. It is the leading cause of non-hereditary sensorineural hearing loss and can cause other long-term neurodevelopmental disabilities.
- Most infected infants are asymptomatic however they can still develop delayed sensorineural hearing loss.

6.2 Bibliography

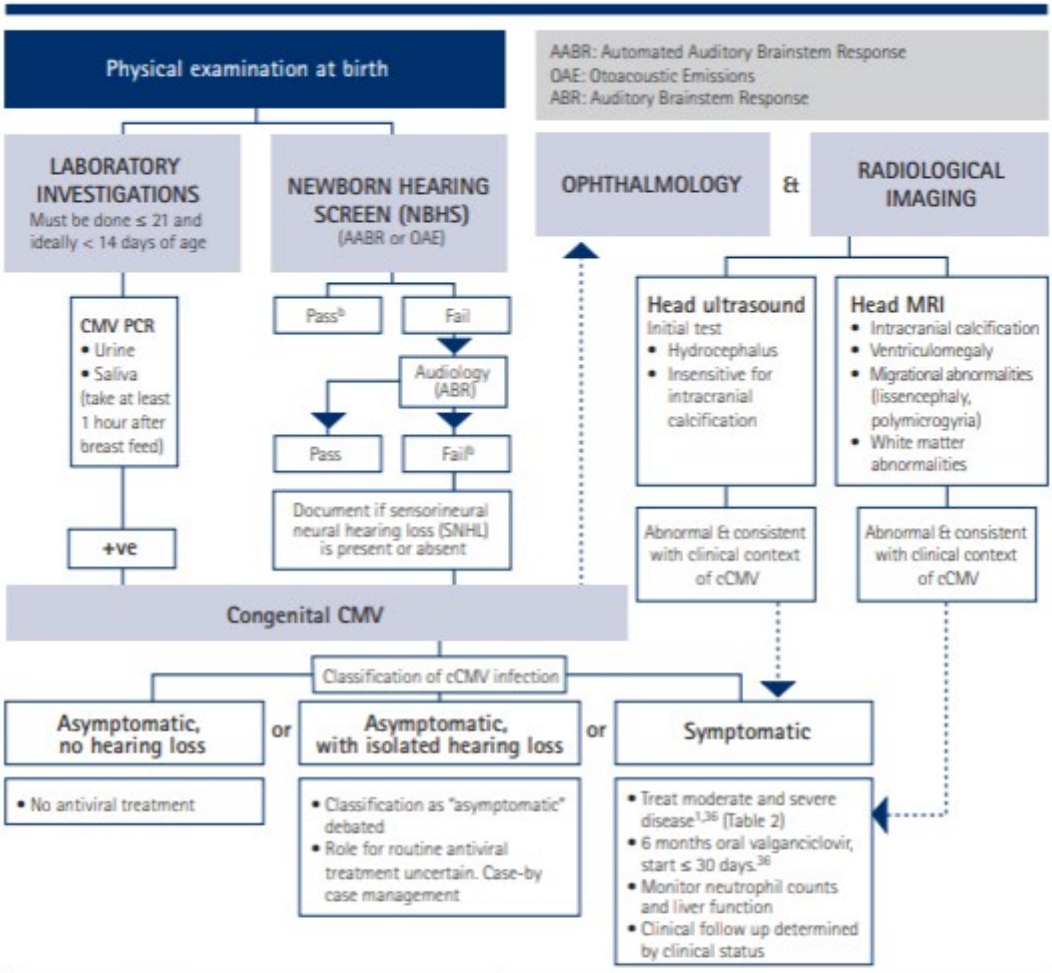
- Congenital cytomegalovirus infection: Clinical features and diagnosis. Retrieved April 2023 from: https://www.uptodate.com/contents/congenital-cytomegalovirus-infection-clinical-features-anddiagnosis?search=congenital%20cmv&source=search_result&selectedTitle=1~62&usage_type=default&display_rank=1
- Congenital cytomegalovirus infection: Management and outcome. Retrieved April 2023 from https://www.uptodate.com/contents/congenital-cytomegalovirus-infection-management-and-outcome#references
- Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Retrieved April 2023 from https://pubmed.ncbi.nlm.nih.gov/28291720/
- Congenital Cytomegalovirus Infection: Update on Diagnosis and Treatment. Retrieved April 2023 from: *Microorganisms* 2020, *8*(10), 1516; https://doi.org/10.3390/microorganisms8101516
- Cytomegalovirus (CMV): Retrieved April 2023 from https://www.healthnavigator.org.nz/health-a-z/c/cytomegalovirus-cmv/
- Ganciclovir. Retrieved April 2023 from https://www.starship.org.nz/guidelines/ganciclovir/
- Medsafe. Ganciclovir. Retrieved April 2023 from https://www.medsafe.govt.nz/profs/Datasheet/c/Cymeveneinj.pdf or
- Management of Perinatal Infections. Funded by ASID. Third Edition. November 2022; Management of Perinatal Infections
- Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease. Retrieved November 2022 from: https://pubmed.ncbi.nlm.nih.gov/25738669/

Appendix A – Cytomegalovirus Algorithms



CYTOMEGALOVIRUS – ALGORITHM 4

NEONATAL DIAGNOSIS AND MANAGEMENT[1,35]



Suggested clinical follow-up:

- Audiological assessments (6 monthly year till age 2 years then annually till age 6)
- Ophthalmology: Annual review till age 6 years
- Paediatric review: 3 – 6 monthly, first 2 years then annually till age 6
- Assessments to include neurological status, head circumferences & neurodevelopmental assessments

COMMENTS

a. Other tests at birth: CMV IgM may be helpful if positive but generally not done (low sensitivity test). The standard test is the urine CMV PCR +/- saliva CMV PCR FBE & differential, LFT if there are clinical concerns

b. In about half of cCMV infections, SNHL will not be identified at birth, but the infant is at risk of later onset SNHL

c. cCMV infected babies are high CMV shedders (urine), particularly in the first year of life

Table 2 : Symptoms associated with congenital CMV [1,35,36]

Moderately to severely symptomatic congenital CMV disease

- Multiple manifestations attributable to congenital CMV infection: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis (raised transaminases or bilirubin), or
- Central nervous system involvement such as microcephaly, radiographic abnormalities consistent with CMV central nervous system disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations), abnormal cerebrospinal fluid indices for age, chorioretinitis, sensorineural hearing loss, or the detection of CMV DNA in cerebrospinal fluid

Mildly symptomatic congenital CMV disease

- Might occur with one or two isolated manifestations of congenital CMV infection that are mild and transient (eg, mild hepatomegaly or a single measurement of low platelet count or raised levels of alanine aminotransferase). These might overlap with more severe manifestations. However, the difference is that they occur in isolation

Asymptomatic congenital CMV infection with isolated sensorineural hearing loss

- No apparent abnormalities to suggest congenital CMV disease, but sensorineural hearing loss (≥21 decibels)

Asymptomatic congenital CMV infection

- No apparent abnormalities to suggest congenital CMV disease, and normal hearing