Clinical Guideline

CMV – DIAGNOSIS AND MANAGEMENT OF CONGENITAL AND POSTNATALLY ACQUIRED CYTOMEGALOVIRUS (CMV) INFECTION

SETTING	Paediatric - Bristol Royal Hospital for Children, Neonatal medicine - St Michael's Hospital and Southmead Hospital Bristol – Regional referral centres
FOR STAFF	Doctors, nurses and midwives
PATIENTS	Neonates and Children with suspected CMV infections – congenital or postnatally acquired, including premature babies.

CONGENITAL CMV – see flowchart

Congenital CMV (cCMV) is the commonest infection to be passed from mother to baby during pregnancy in the Western world (6/1000). We know that only 10% of infected babies show signs at birth. Although most infected babies will remain symptom-free and have no further problems, some (around 15% of babies) will develop hearing loss and will have developmental delay or cognitive impairment later in childhood. cCMV is the leading non-genetic cause of sensorineural hearing loss.

An accurate diagnosis has to be made within the first three weeks from birth to distinguish between congenital and acquired CMV, this is important as it changes management.

Acquisition of CMV:

1. Intrauterine (primary infection, reactivation or reinfection) –Primary CMV
2. Intrapartum (vaginal secretions) – Acquired CMV
3. Postnatal (breast milk, blood products, close personal contact) – Acquired CMV

Clinical presentation:
Most commonly CMV infection is asymptomatic (90%). Listed are the most common signs of CMV infection:

- Sensorineural hearing loss (can be present at birth or present later in life)
- Blueberry muffin rash
- Petechiae
- Jaundice
- Intrauterine growth restriction (IUGR)
- Microcephaly
- Hepato-splenomegaly
- Lymphadenopathy

The most common laboratory abnormalities are:
- Conjugated hyperbilirubinaemia,
- Thrombocytopaenia
- Elevated hepatic transaminases

The most common abnormalities on USS are non-specific as present in other congenital infections

- Periventricular calcifications
- Ventriculomegaly

Premature infants appear to have a higher incidence of congenital CMV infection and a lower threshold for CMV testing may is recommended,

Diagnosis:

In pregnancy: If the mother is CMV IgG negative after birth of the baby, congenital infection is excluded.
Primary CMV during pregnancy carries the highest risk for cCMV in the baby. Primary CMV may be diagnosed in the woman if there is evidence of CMV IgG seroconversion, with or without detectable IgM, or the presence of low avidity (less mature) CMV IgG in pregnancy. Amniocentesis may or may not be performed if primary CMV is diagnosed but fetal infection can only be confirmed with a positive amniotic fluid.
Reinfection with another CMV strain or CMV reactivation are also possible in pregnancy and although lower risk, can also lead to cCMV. A positive IgM in the context of high avidity IgG could indicate either reactivation or reinfection although the IgM may also be non-specific (false positive), therefore they are both infections that are hard to diagnose/exclude. **All neonates born to mothers with suspected or confirmed CMV, either clinically or on serology testing should be tested for cCMV at birth.**
Newborn: A diagnosis of congenital CMV infection can be made by testing 2 urine samples for CMV DNA by polymerase chain reaction (PCR) within the first three weeks of life. Whole blood (EDTA/purple top) can also be tested but a negative result may not exclude congenital infection.

If congenital CMV infection is suspected after the first three weeks of life, the Guthrie card should be traced and tested for CMV DNA at the Royal Free Hospital laboratory. Alternatively if any stored urine or blood samples exist from the first three weeks of age, these should be tested.

Other investigations:

- Hearing test needs to be arranged at diagnosis and repeated regularly.
- Ophthalmology investigation should be arranged at diagnosis and repeated yearly
- Brain imaging: Head USS or MRI brain are necessary at diagnosis as any intracranial abnormalities related to cCMV would lead to the neonate being treated as symptomatic. The sensitivity of MRI is higher but often detects subtle abnormalities not linked to the CMV infection, creating diagnostic difficulties and parental anxiety.
- Abdominal USS is necessary if hepatosplenomegaly is detected clinically to confirm CMV infection or rule out other pathology.

Management

Congenital CMV
For babies diagnosed in the neonatal period (<28 days): Valganciclovir orally (16mg/kg BD) for 6 months; Ganciclovir iv (6 mg/kg BD) if the baby is not feeding enterally.
Discuss each case with Paediatric Infectious Disease (PID) team.
As valganciclovir and ganciclovir is potentially teratogenic and mutagenic it is advised to avoid all contact with skin when administering. Use gloves and, if contact with skin does occur, wash immediately. Reconstitution of ganciclovir and valganciclovir is best done in the pharmacy

aseptic/production units as gloves and goggles should be used when reconstituting. Speak to the pharmacy team or on call Pharmacist for more information.

All congenital CMV children will routinely need hearing and ophthalmology assessment. If babies with congenital CMV are from Bristol Children's hospital catchment area refer to the infectious diseases team to ensure appropriate follow up. Babies with congenital CMV in the region can be discussed with the paediatric infectious diseases in Bristol for advice and will be managed locally.

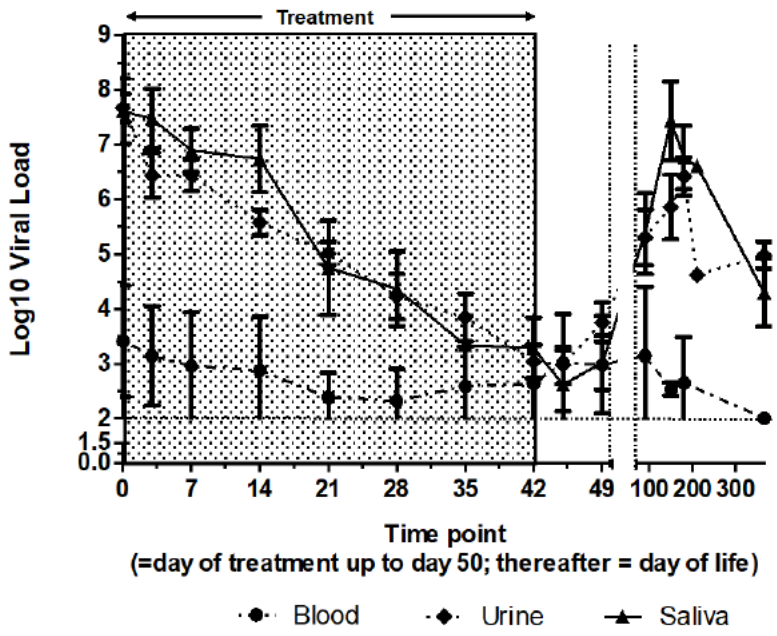
Postnatally Acquired CMV
Discuss with PID, to treat only if the patient is at risk of developing severe complications of CMV (immune suppressed, preterm babies or in rare cases when symptomatic). The treatment choices are as above the duration of treatment is between 2-3 weeks.

Infection control
Babies with congenital or acquired CMV will be shedding the virus in urine and other bodily fluids. They DO NOT have to be isolated but routine infection control precautions need to be followed. In addition, pregnant staff are best not looking after babies with CMV, as a precautionary measure.

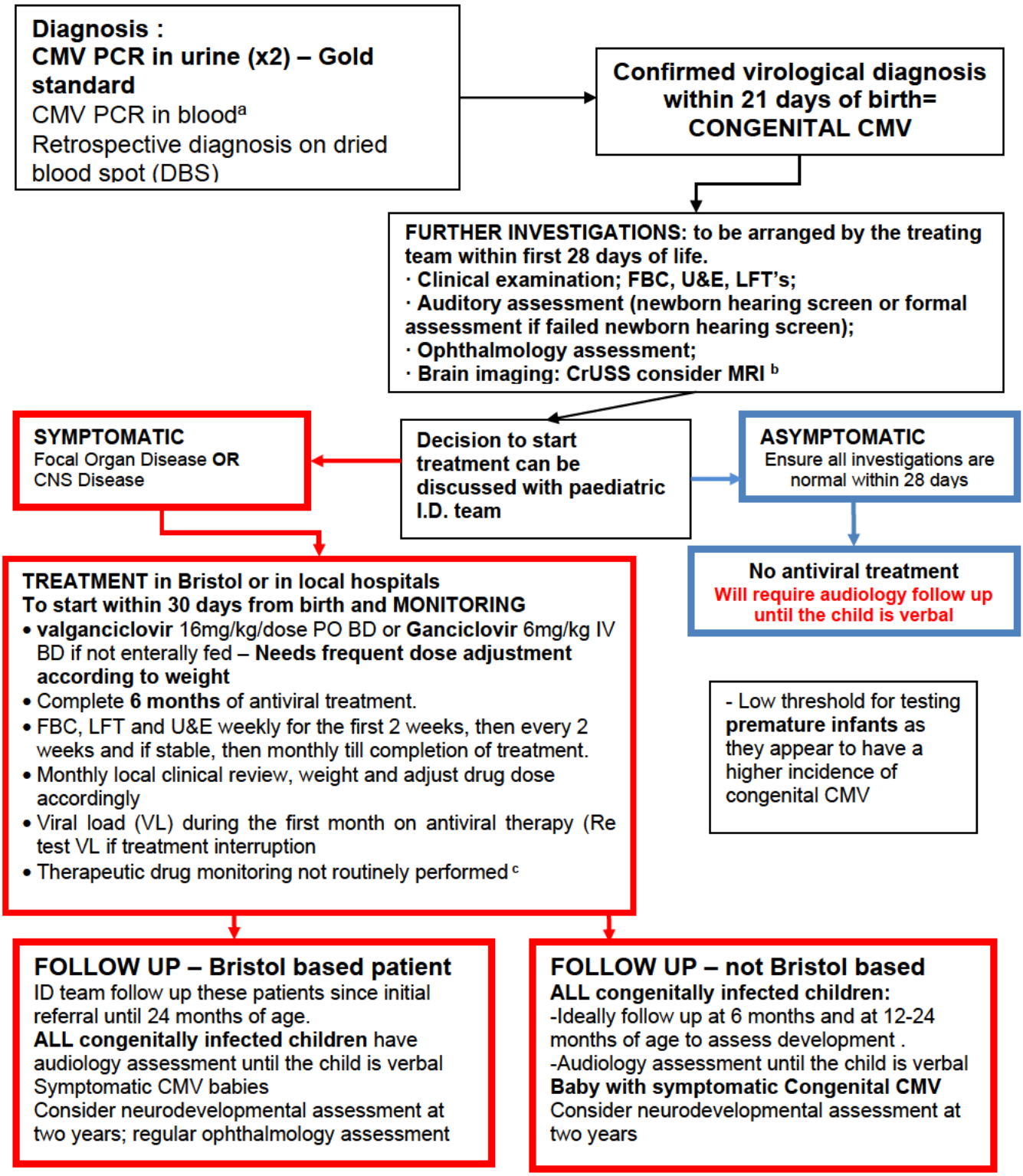
Clinic Follow up
In babies on treatment perform the following:

- If on ganciclovir: FBC, LFT and U&E weekly
- If on valganciclovir: FBC, LFT and U&E weekly for the first 2 weeks, then every 2 weeks and if stable, then monthly till completion of treatment.
- Antiviral dosing needs to be adjusted frequently as the baby weight increases
- Viral load (VL) test during the first month, whilst on antiviral therapy (urine preferably). Re test viral load if there is need for treatment interruptions
- Therapeutic drug monitoring (TDM) if:
    - VL not dropping as in Fig 1(if TDM normal think about resistance)
    - Toxicity is suspected
    - Abnormal renal function or preterm babies (<36 weeks gestation)

Figure 1: Mean viral load over time in different body fluids in 17 babies treated for congenital cytomegalovirus.



CMV viral load was measured in blood, urine and saliva using quantitative real-time PCR.
Treatment was with either ganciclovir or valganciclovir in all babies and for a duration of 42 days +/- 1 day in 16/17 babies.



Flow Chart for the Diagnosis and Management of CONGENITAL CMV infection

Key:

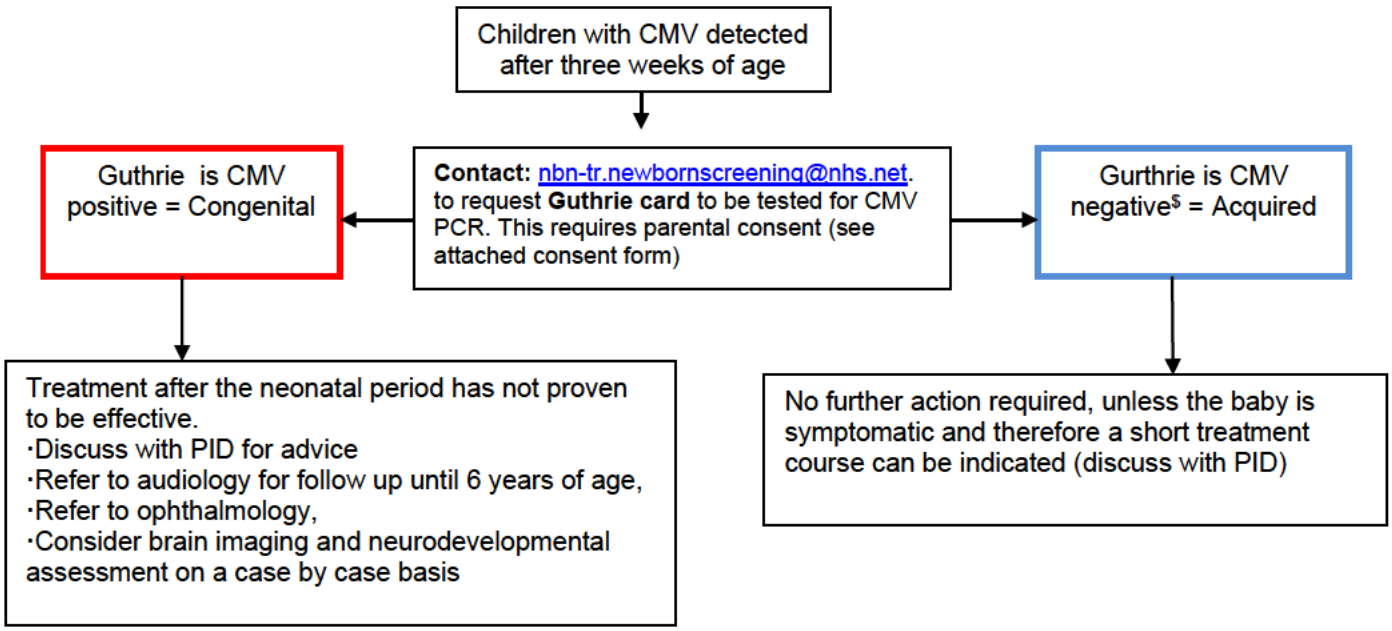
[a] Baseline CMV PCR on blood should be taken as soon as possible after initial diagnosis

[b] Cranial Ultrasound performed in first instance. MRI if clinical concerns

[c] Perform only if toxicity is suspected (more likely if prematurity <36 weeks, abnormal renal function) or if viral loads increasing during treatment

** Children diagnosed in the neonatal unit need to be discussed with the PID team (bleep [redacted] or ext [redacted] for consideration of treatment and the PID nurses need to be notified (ext [redacted] or [redacted] or [redacted] .

Flow Chart for the Diagnosis and Management of children with CMV detected after three weeks



$ Guthrie's Card sensitivity for CMV is variable (45-75%) therefore a negative test does not exclude congenital CMV but for practical purposes this is considered acquired and treatment cannot be reccomended

Website for parents: **cmvaction**.org.uk

Table A

REFERENCES	1. Pediatrics. 2014;134(5):972. 2. Early Human Development 87 (2011) 723–728 3. N Engl J Med. 2015 4. London Congenital CMV guidelines in press
RELATED DOCUMENTS AND PAGES	[redacted]
AUTHORISING BODY	Paediatric Infectious Disease Governance Group
SAFETY	Infection control guidelines recommend that pregnant staff do not look after babies with congenital CMV. As valganciclovir and ganciclovir can be teratogenic and mutagenic it is advised to avoid all contact with skin when administering. Use gloves and if contact with skin does occur wash immediately. Reconstitution of ganciclovir and valganciclovir is best done in the pharmacy aseptic/production units as gloves and goggles should be used when reconstituting. Speak to the pharmacy team or on call Pharmacist for more information.
QUERIES AND CONTACT	During working hours the paediatric infectious diseases service can be contacted on bleep 3997 and the virology department on ext. [redacted]. Out of hours please refer to switchboard for the on call paediatric infectious diseases or virology team.