CYTOMEGALOVIRUS INFECTION

Introduction

- This guideline addresses mainly congenital CMV (CCMV) infection, although some information can be used for the management of symptomatic postnatal CMV infection. Some specific guidance for postnatal CMV infection is also provided.
- Overall birth prevalence of congenital CMV infection is 0.64 % (UK). Of them 0.07 % are symptomatic at birth. This equates to 10 – 15 % of the total number of newborns with congenital CMV. > 70 % of these will develop permanent long-term sequelae.
- About 96% of seropositive mother have localised reactivation of CMV in their breast during lactation. Breastfeeding is the biggest source of postnatal cytomegalovirus infection in preterm infants and may be associated with a symptomatic infection (transmission rate 9 – 55 %, 1.5 – 62 % become symptomatic in varying degrees).

General Considerations

Treatment with Ganciclovir i.v. and Valganciclovir p.o.:

- All newborns qualifying for treatment are started on Ganciclovir i.v.
- Changing to oral treatment can be considered once the viral load starts decreasing and the baby is showing signs of improvement. Change from i.v. to oral treatment, if steady state of concentration achieved.
- Inform Pharmacy at least 1 week in advance about the medication requirement.

Monitoring Levels and Toxicity:

- See checklist for investigations below.
- If renal or liver function deteriorates contact Dr Suzanne Luck, Chief Investigator on 207794 0500 x34941 or page by phoning 07699 119700, quote pager no: SG388, and leave a message.

Labelling and Sending Samples:

- For choice of specimen collectors see table below.
- Specimens used for the study need to be labelled with the prepared labels [found in Baby Pack attached to CRF].
- Urine, blood and CSF viral load samples are sent to our laboratories.
- Salivary swab specimens: available in Baby Pack. [Extra in main CMV VICC Study File in Dr Rabe's office].
- Contact Dr Cubbon about the samples as they will be sent to Dr Luck in batches.
- All the samples need to go to our laboratory to be logged and then they are sent to the reference laboratories. Ganciclovir levels go to the Bristol Lab. They process the samples daily but need to contacted 24 hours in advance. Contact No: 01179 595653 [Between 09.00 – 15.00 hours].

Prevention of postnatal CMV Infection

- Most breast milk becomes CMV positive at 2 weeks, peaking at 4-6 weeks. Colostrum has very low infectivity.
- Freezing (72 h in -20 ºC) expressed human milk from seropositive women before giving it to ELBW infants is an effective and safe way to reduce rate of CMV transmission (CMV infectivity 1 %).

Follow-up:

- Permanent long-term sequelae at follow-up can be cerebral palsy, delayed psychomotor development, mental retardation, expressive language delay and learning disability, epilepsy, optic atrophy and SNHL.
- For timing and investigations of follow-up see table below.

MANAGEMENT OF CONGENITAL CMV INFECTION IN NEWBORNS > 32 WEEKS GESTATION

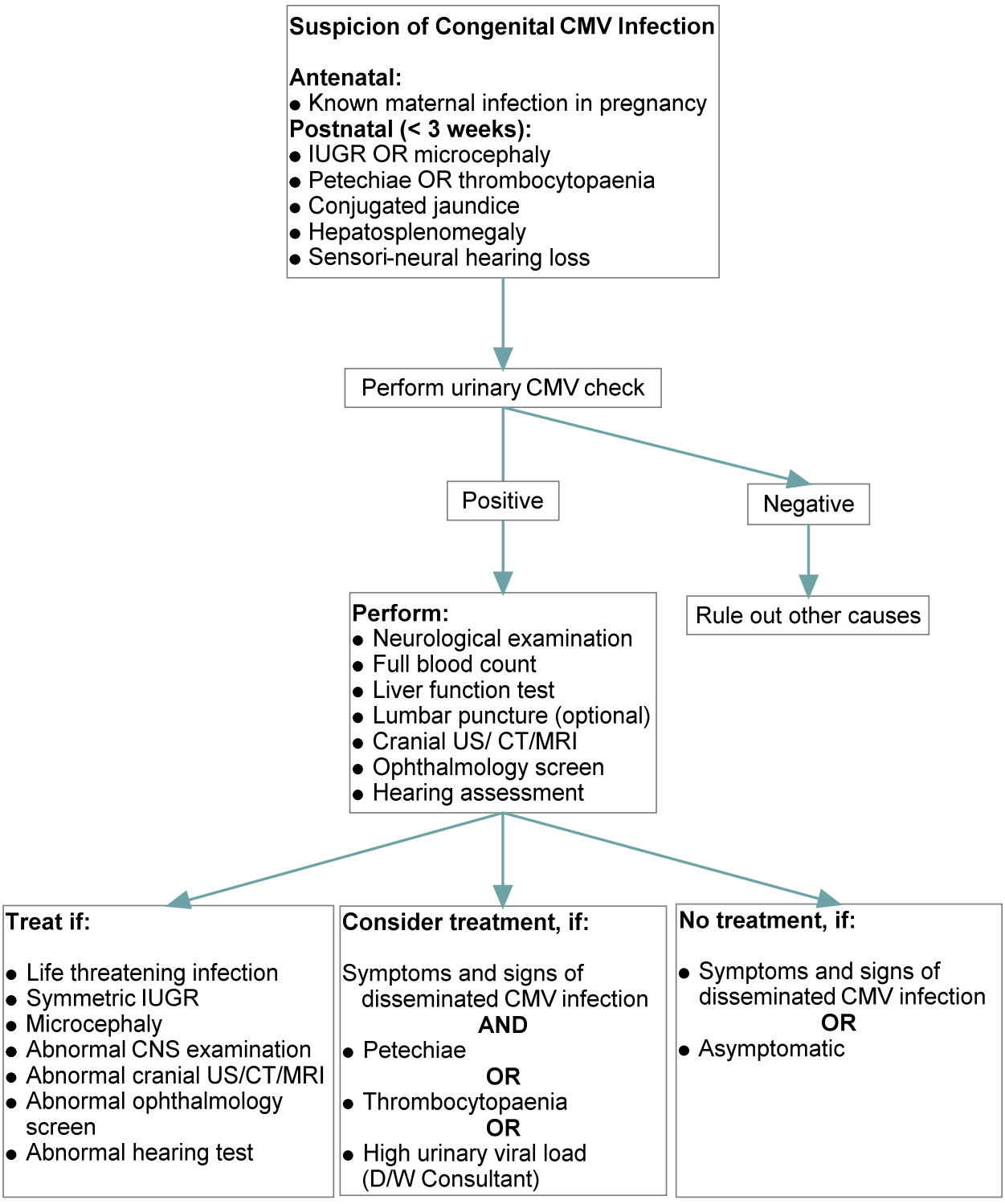

Table for definitions and percentage of occurrence of pathology

Definitions	Percentage of occurrence
Microcephaly: head circumference < 2 SD below the mean for age or < 2nd centile.	37%
Symmetric IUGR: Birth weight and head circumference < 2SD below mean for age.	43%
Thrombocytopenia: <100,000/microliter.	50%
Conjugated hyperbilirubinaemia: > 66 micromol/l (> 3 mg/dl)	50%
Abnormal CSF with high CSF protein: >120mg/dl	*
Abnormal cranial US: moderate to severe ventriculomegaly, and intracerebral calcifications	56%**
Abnormal cranial CT: cortical atrophy, cortical dysgenesis/dysplasia, moderate to severe ventriculomegaly, cerebellar hypoplasia/asymmetry, migration abnormalities and intracranial calcifications.	71%***$
Abnormal ophthalmology screen: Chorioretinitis, retinal detachment, optic atrophy, retinal haemorrhage, retinal scarring or sight threatening infection	14%
Abnormal early hearing assessment:	38%
Abnormal late hearing assessment:	14%

* - Performing lumbar puncture is contentious. There have been no studies to evaluate the correlation of an abnormal CSF result or CSF viral load with long-term outcome.
** - Isolated single ventricular dilatation, subependymal pseudo cyst or lenticulostriatal vasculopathy are not considered pathognomic of CCMV infection.
***- In asymptomatic newborns with unequivocal or normal cranial US findings.
$- MRI scan: No comparison studies performed showing to be superior than CT.

Checklist for investigations (local and VICC study)

Day	Samples required
Day 0:	• Perform Urinary + Blood + Salivary viral load [If performing LP send CSF for viral load]. • Perform U & E, LFT, conjugated bilirubin, ALT + FBC. • Perform cranial USS, ophthalmic screen, AABR hearing test. • In addition take bloods for T-cell immunity and IgG avidity [VICC Study]. • Start Ganciclovir. This can be given via a peripheral line. If treatment is considered to be of longer duration then consider long line insertion.
Day 1:	• After 1 dose of Ganciclovir perform a pre-second dose level and post-dose level 1 hour after completion of infusion.
Day 3:	• Perform Urinary + Blood + Salivary viral load. • Perform U & E, LFT, conjugated bilirubin, ALT + FBC. • Perform random Ganciclovir level + HLA type [VICC study].
Day 7:	• Perform Urinary + Blood + Salivary viral load. • Perform U & E, LFT, conjugated bilirubin, ALT + FBC. • Perform pre-dose level + post-dose level 1 hour after completion of infusion. • Perform Ganciclovir levels if dose adjusted after previous levels [do pre and post dose levels]. • If treatment has been changed to Valganciclovir then levels need to be performed just prior to dose and 2 hours post-dose.
Day 10:	• Perform U & E, LFT, conjugated bilirubin, ALT + FBC
Day 14:	• Perform Urinary + Blood + Salivary viral load. • Perform U & E, LFT, conjugated bilirubin, ALT + FBC. • Perform pre-dose level + post-dose level depending on oral or IV route. • Perform T-cell immunity [VICC Study].
Day 17:	• Perform U & E, LFT, conjugated bilirubin, ALT + FBC.
Day 21:	• Perform Urinary + Blood + Salivary viral load. • Perform U & E, LFT, conjugated bilirubin, ALT + FBC. • Perform pre-dose level + post dose level depending on oral or IV route.
Day 25:	• Perform U & E, LFT, conjugated bilirubin, ALT + FBC.
Day 28:	• Perform Urinary + Blood + Salivary viral load. • Perform U & E, LFT, conjugated bilirubin, ALT + FBC. • Perform pre-dose level + 1 hour post-dose level depending on oral or IV route. • Also perform T-cell immunity [VICC Study].
Day 42	• Perform Urinary + Blood + Salivary Viral Load. • Perform U & E, LFT, conjugated bilirubin, ALT + FBC. • Perform pre-dose level + 1 hour post-dose level depending on oral or IV route.

Table for choice of specimen collectors

Test	Bottle	Amount
Urinary Viral Load	Universal bottle	2 - 3 mls
Blood Viral Load	EDTA bottle	0.5 -1 ml
CSF Viral Load	Universal bottle	0.5 mls
Ganciclovir/ Valganciclovir levels	Li.-Heparin bottle	0.5 -1 ml
FBC	EDTA bottle	0.5 mls
LFT, U & E, ALT, bilirubin	Li.- Heparin bottle	0.5 mls
Salivary swab	Special swab in Baby pack Pre feed: place the end of the swab in baby's mouth for 1 min until it is soaked in the saliva. Label and put in plastic bag and then in Jiffy bag.	
T-cell immunity, HLA type and IgG avidity	EDTA bottle	2 mls

Table for follow-up

Evaluation	Age recommendation
Audiometry	Newborn, 3, 6, 9, 12, 18, 24, 30, 36 months and then annually to school age
Indirect ophthalmoscopy and visual function	Newborn, 12 months, 3 years, and preschool age
Neurological examination and developmental assessment	At each paediatric review