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

- See algorithm below (consider additional tests, e.g. blood viral load)

Diagnostic investigations and treatment with Ganciclovir i.v./Valganciclovir p.o.

- See table below for clinical/diagnostic findings and algorithm for diagnostic decision making
- All newborns qualifying for treatment are started on Ganciclovir i.v. peripherally and continued centrally if i.v. treatment is needed
- 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.
- Discuss treatment with Dr Fidler or Dr Fernandez or Dr Sudarsan and Dr Hassan Ibrahim. Continue treatment for at least 6 weeks and no more than 6 months unless discussed otherwise with Dr. Fidler.
- Inform Pharmacy at least 1 week in advance about the medication requirement.
- Register baby on CMV registry by contacting Dr Fidler or Dr Fernandez or Dr Sudarsan

Monitoring therapeutic response, drug levels and toxicity

- Check urinary and blood viral load after 48 h, then on day 7 and then weekly
- Check U & E, LFT, conjugated bilirubin, ALT + FBC twice weekly
- Perform Ganciclovir pre-dose level + post-dose level 1 hour after completion of infusion after 48 h, then on day 7 and then weekly. If treatment has been changed to Valganciclovir then the post-dose level needs to be performed 2 hours post-dose.
- Perform additional Ganciclovir/Valganciclovir levels if dose is adjusted

Labelling and sending samples (see table below)

- For choice of specimen collectors see table below.
- Urine, blood and CSF viral load as well as drug level samples are sent to our laboratories to be processed or send away. Ganciclovir levels go to the Bristol Lab. Contact 24 hours in advance on 0117 414 6269/6220

Prevention of postnatal CMV Infection

- Colostrum has very low infectivity. Most breast milk becomes CMV positive at 2 weeks, peaking at 4-6 weeks.
- 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.
- Refer early to audiology and check hearing after birth and then at 3, 6, 9, 12, 18, 24, 30, 36 months and then annually to school age
- Refer to ophthalmology and check eyes after birth and then at 12 months, 3 years, and preschool age. Neurological examination and developmental assessment at each paediatric review

### Definitions and percentage of occurrence of pathology

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Occurrence</th>
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<tbody>
<tr>
<td><strong>Microcephaly:</strong> head circumference &lt; 2 SD below the mean for age or &lt; 2(^{nd}) centile.</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Symmetric IUGR:</strong> birth weight and head circumference &lt; 2SD below mean for age.</td>
<td>43%</td>
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<tr>
<td><strong>Thrombocytopenia:</strong> &lt;100,000/microliter.</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Conjugated hyperbilirubinaemia:</strong> &gt; 66 micromol/l (&gt; 3 mg/dl)</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Abnormal CSF with high CSF protein:</strong> &gt;120mg/dl</td>
<td>There have been no studies to evaluate the correlation of an abnormal CSF result or CSF viral load with long-term outcome</td>
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<tr>
<td><strong>Abnormal cranial US:</strong> moderate to severe ventriculomegaly and intracerebral calcifications - isolated single ventricular dilatation, subependymal pseudocyst or lenticulostrialtial vasculopathy are not considered pathognomic</td>
<td>56%</td>
</tr>
<tr>
<td><strong>Abnormal cranial CT:</strong> cortical atrophy, cortical dysgenesis/dysplasia, moderate to severe ventriculomegaly, cerebellar hypoplasia/asymmetry, migration abnormalities and intracranial calcifications</td>
<td>71% (in asymptomatic newborns), MRI not superior</td>
</tr>
<tr>
<td><strong>Abnormal ophthalmology screen:</strong> chorioretinitis, retinal detachment, optic atrophy, retinal haemorrhage, retinal scarring or sight threatening infection</td>
<td>14%</td>
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<td><strong>Abnormal early hearing assessment:</strong></td>
<td>38%</td>
</tr>
<tr>
<td><strong>Abnormal late hearing assessment:</strong></td>
<td>14%</td>
</tr>
</tbody>
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### Choice of specimen collectors

<table>
<thead>
<tr>
<th>Test</th>
<th>Bottle</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Viral Load</td>
<td>Universal bottle</td>
<td>2 - 3 mls</td>
</tr>
<tr>
<td>Blood Viral Load</td>
<td>EDTA bottle</td>
<td>0.5 - 1 ml</td>
</tr>
<tr>
<td>CSF Viral Load</td>
<td>Universal bottle</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>Ganciclovir/ Valganciclovir levels</td>
<td>Li.-Heparin bottle</td>
<td>0.5 - 1 ml</td>
</tr>
<tr>
<td>FBC</td>
<td>EDTA bottle</td>
<td>0.5 mls</td>
</tr>
<tr>
<td>LFT, U &amp; E, ALT, bilirubin</td>
<td>Li.- Heparin bottle</td>
<td>0.5 mls</td>
</tr>
<tr>
<td>T-cell immunity, HLA type and IgG avidity</td>
<td>EDTA bottle</td>
<td>2 mls</td>
</tr>
</tbody>
</table>
Management of Congenital CMV Infection in Newborns > 32 Weeks Gestation

Suspicion of Congenital CMV Infection

Antenatal:
- Known maternal infection in pregnancy

Postnatal (< 3 weeks):
- IUGR OR microcephaly
- Petechiae OR thrombocytopenia
- Conjugated jaundice
- Hepatosplenomegaly
- Sensori-neural hearing loss

Perform urinary CMV check

Positive
- Perform:
  - Neurological examination
  - Full blood count
  - Liver function test
  - Lumbar puncture (optional)
  - Cranial US/CT/MRI
  - Ophthalmology screen
  - Hearing assessment

Negative
- Rule out other causes

Treat if:
- Life threatening infection
- Symmetric IUGR
- Microcephaly
- Abnormal CNS examination
- Abnormal cranial US/CT/MRI
- Abnormal ophthalmology screen
- Abnormal hearing test

Consider treatment, if:

Symptoms and signs of disseminated CMV infection AND
- Petechiae
- Thrombocytopenia
- High urinary viral load (D/W Consultant)

No treatment, if:
- Symptoms and signs of disseminated CMV infection OR
- Asymptomatic