Wales Neonatal Network Guideline

Guideline for the Management of Neonatal Herpes Infection

Introduction:
Herpes simplex virus type 1 and 2 are DNA viruses that belong to Alphaherpesviridae, a subfamily of the Herpesviridae family. Both serotypes are transmitted across epithelial mucosal cells as well as through skin interruptions, and then migrate along local sensory nerves, where they persist in a latent stage. Neonatal herpes may be caused by herpes simplex virus type (HSV-1) or herpes simplex virus type 2 (HSV-2); either viral type can cause genital herpes in a mother. In the United States and Canada, HSV-1 is now emerging as the principal cause of genital herpes. 1,2,3. Most people are unaware if they have a herpes infection and in the majority of neonatal herpes disease there is no antenatal history of herpes. 4 Neonatal infection can follow primary or recurrent maternal infection, or be acquired postnatally through direct contact with infected secretions. Trans-placental transmission is unusual (5%) and perinatal infection in usually acquired during vaginal delivery through an infected birth canal. The pregnant woman who acquires genital herpes as a primary infection in the latter half of pregnancy is at the greatest risk of transmitting these viruses to her newborn (25-60% risk). Whereas an infection resulting from reactivation of an infection acquired during the first half of pregnancy or earlier has a <2% risk. 3, 4, 5, 12 It is estimated that 6 weeks may be required for a mother to develop and transfer immunity after a primary episode. If babies are born prematurely, then the transplacental transfer of immunity is reduced. 3

Epidemiology:
Neonatal HSV disease is a rare but potentially devastating condition. Untreated neonatal HSV infection is associated with only a 40% survival rate. Early recognition and the early initiation of high-dose IV acyclovir can significantly improve survival and morbidity rates. The risk of transmission from mother to neonate is higher during the primary episode of infection 57% and falls 2% following recurrent infection. The risk of transmission varies with:
- serotype
- mode of delivery
- rupture of membranes and
- prematurity.

Surveillance of neonatal HSV in the UK was undertaken through the BPSU in 1986-1991. The estimated prevalence of infection was 1.65/100,000. HSV-1 and HSV-2 were reported in equal proportions, but in one third of cases the virus was not typed. 6 However, the incidence of genital herpes has increased by 89% between 2003 and 2012 and in the USA the incidence of neonatal HSV infection is 33 per 100,000 live births. 7

Clinical Presentation:
Congenital HSV infection is rare; it shares features such as microcephaly, hydrocephalus, and chorioretinitis with other congenital infections and is usually manifested by clinical abnormalities at birth. Postnatal acquisition of HSV is almost always due to HSV-1 and is associated with contact with hospital personnel or family members who are shedding HSV-1. 8 Most neonatal infections result from exposure to HSV during delivery, Perinatal acquisition. The clinical presentation of perinatal and postnatal infections has been divided into 3 categories, each of which is associated with different outcomes and clinical manifestations:
1. SEM (skin, eyes and mucosa),
2. CNS disease and
3. Disseminated disease.
### SEM disease - Cutaneous (45%)

- Infection is confined to the skin, eyes and mucosa. **Disease elsewhere (disseminated and CNS) must be excluded.**
- Typically present by 1-2 weeks of life, but may present at birth.
- May be a single vesicle or group of vesicles, often in a linear distribution if affecting the limbs.
- Progression to extensive disease will occur in the absence of treatment. With high dose IV acyclovir, long term outcome is good.
- May have recurrent outbreaks of cutaneous herpes during early childhood.

<table>
<thead>
<tr>
<th>CNS HSV infection (30%)</th>
<th>Disseminated HSV infection (25%)</th>
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</thead>
<tbody>
<tr>
<td>Encephalitis, mainly affecting temporal lobes and territory surrounding the middle cerebral artery.</td>
<td>Highest fatality rate (30-80%), even with antiviral therapy.</td>
</tr>
<tr>
<td>Associated with lethargy, poor feeding and seizures; Can manifest as a multifocal stroke; cutaneous lesions may or may not be present.</td>
<td>Typically present at 5-10 days with sepsis like illness involving multiple organs (liver, lungs and brain).</td>
</tr>
<tr>
<td><strong>Pleocytosis</strong> is usually present; HSV DNA in the CSF is the most sensitive lab test for confirming the diagnosis. Samples of CSF obtained early in the illness may be falsely negative.</td>
<td>Rash is absent in up to 50% of cases.</td>
</tr>
<tr>
<td>Higher morbidity with CNS HSV-2 infection than HSV-1. Long term morbidities - developmental delay, epilepsy and blindness. Relapses of CNS infection may occur – further increasing morbidity.</td>
<td>Need to ensure blood and CSF sent for HSV PCR.</td>
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<td></td>
<td>May be clues in lab tests like a raised ALT and coagulopathy but may not be evident at presentation.</td>
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<tr>
<td></td>
<td>Long term suppressive therapy may have a role in reducing morbidity.</td>
</tr>
</tbody>
</table>

### Investigations:

Essential diagnostic virology investigations

<table>
<thead>
<tr>
<th>Type of investigation</th>
<th>Site</th>
<th>Specimen container</th>
<th>Expected availability or results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes PCR</td>
<td>Skin vesicle base, de-roof and scrub the base</td>
<td>Dry Swab – not in Transport Medium – snap black swab into universal container</td>
<td>Processed in UHW - 24-72hrs</td>
</tr>
<tr>
<td>Herpes PCR</td>
<td>Eyes, Mouth, NPA aspirates</td>
<td>Dry Swab – snap into universal container.</td>
<td>Processed in UHW – 24-72hrs</td>
</tr>
<tr>
<td>Herpes PCR</td>
<td>Blood</td>
<td>EDTA – purple top (send 2mls of blood)</td>
<td>Processed in Manchester – can take up to a week.</td>
</tr>
<tr>
<td>Herpes PCR</td>
<td>CSF</td>
<td>Clear universal container</td>
<td>Processed in UHW – 24-72hrs</td>
</tr>
</tbody>
</table>
1. Routine blood investigations: FBC, U&E, LFT and coagulation, blood culture & CRP
2. CXR if respiratory symptoms. Typical findings of a bilateral diffuse pneumonitis.
3. Neuroimaging with MRI may be beneficial in localising disease.
4. In SEM, seek ophthalmologic opinion early. In all other cases dilated ophthalmologic examination to assess chorioretinitis during the first week and at 6 months. Additional topical agent (trifluridine) is recommended for ocular disease.
5. EEG if suspected to have CNS involvement, especially if seizures observed. Typically shows characteristic temperoparietal high-voltage low-frequency activity

Management:
Please see Table 1 and Algorithm 1 and 2 for full explanation of management pathways.

Please discuss with virology team for specific advice about investigations during working hours and please alert the laboratory before sending specimen asking to be processed urgently.

UHW process HSV PCR tests Monday – Friday only, not over weekends.

For information on chasing results – University Hospital of Wales Cardiff Virology department: 029 2074 2178

Reference Number: 25
Dr J.Evans
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Authors: Dr R.Morris, Dr A.Khandhari, Dr G.Thomas,
Review date: July 2020
Algorithm 1: Symptomatic Neonatal HSV

Suspected symptomatic HSV infection

Start IV Aciclovir promptly
Consider bacterial infection and antibiotics

- Skin, Mouth, Conjunctival swabs & NPA for HSV PCR
- Blood and CSF PCR (unless LP contraindicated)
- Blood culture & CRP, FBC, COAG & LFT, U&E, blood gas, CXR (if respiratory symptoms)
- EEG if suspected CNS involvement

Skin, Eye, MM (SEM) lesions only

PCR Negative
Stop Aciclovir*

PCR Positive
IV Aciclovir – 14 days

CNS features OR sepsis of unknown cause OR Disseminated disease +/- SEM

PCR Negative
Stop Aciclovir*

PCR Positive
IV Aciclovir – 21 days & Consider long term suppressive RX.
If CSF PCR previously positive, then repeat LP on day 19 to ensure negative before stopping RX on day 21.

If PCR remains positive continue RX for a further 7 days and repeat LP again

*Negative PCR results should not be used on their own to exclude invasive herpes disease, but in conjunction with the entire clinical scenario.
Algorithm 2: Asymptomatic baby exposed to HSV\textsuperscript{10,11}

Table 1: Assessment of Risk of Neonatal Herpes Infection, and Neonatal Plan

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Timing of Maternal HSV</th>
<th>Maternal HSV Symptoms in Pregnancy</th>
<th>Mode of Delivery</th>
<th>Neonatal Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>Pre pregnancy genital HSV</td>
<td>No Symptoms</td>
<td>Any</td>
<td>Plan C</td>
</tr>
<tr>
<td>R2</td>
<td>Recurrent Infection</td>
<td>Recurrent genital herpes with NO active lesions at onset of labour</td>
<td>Any</td>
<td>Plan C</td>
</tr>
<tr>
<td>R3</td>
<td>Recurrent Infection</td>
<td>Recurrent genital herpes WITH active lesions at the onset of labour</td>
<td>EL. LSCS with no ROM*</td>
<td>Plan C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
<td>Term baby - Plan B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preterm baby – PlanA</td>
</tr>
<tr>
<td>R4</td>
<td>Primary Infection</td>
<td>1\textsuperscript{st} Episode &gt; 6 weeks before delivery and no active lesions (if lesions present – treat as Risk group 3)</td>
<td>EL. LSCS with no ROM*</td>
<td>Plan C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
<td>Term baby – Plan B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preterm baby – PlanA</td>
</tr>
<tr>
<td>R5</td>
<td>Primary Infection</td>
<td>1\textsuperscript{st} Episode &lt; 6 weeks before delivery</td>
<td>EL. LSCS with no ROM*</td>
<td>Plan C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
<td>Plan A</td>
</tr>
</tbody>
</table>

*Rupture of membranes = > 4 hours before delivery

Plan A:
- Investigate and start IV Aciclovir
- FBC, LFT & COAG at birth
- After 36-48hrs send samples for HSV PCR from blood, CSF, surface swabs (and NPA if respiratory symptoms)
- Continue IV Aciclovir until PCR results available
- PCR negative - stop treatment
- PCR positive – IV Aciclovir 14 days or 21 days if disseminated/CNS infection
- Term babies can remain on the postnatal ward if asymptomatic and clinically well.

Plan B:
- Observe on the postnatal ward for 48hrs.
- After 36-48hrs send samples for HSV PCR from blood and surface swabs. If well at 48hrs parents can be given option to go home to await results with the knowledge they may be required to be readmitted if positive result. **Doctor sending test is responsible for chasing the result**
Plan C:

- Provide information for parents – http://www.nhs.uk/conditions/neonatal-herpes
- No tests indicated, unless infant is symptomatic
- Advise parents to seek medical attention if unwell in first 6 weeks

Pharmacological management:

**Aciclovir dosage**

20mg/kg every 8 hours for 14 days (for at least 21 days if CNS involvement – confirm CSF negative for herpes simplex virus before stopping treatment). Transient neutropenia has been detected in about 20% of infants treated with these high doses of Aciclovir, but it has not been reported to result in clinically significant adverse outcomes.

**Long Term Suppressive Treatment**

Recent studies have shown that long term suppressive therapy may improve neurological outcomes. The long term oral Aciclovir treatment (300mg/m² for six months) should be considered in disseminated and CNS cases after completion of acute treatment. These babies will need regular FBC and LFTs (suggested times at discharge, 1month, 3months and 6months).

**Prevention:**

Infants may acquire HSV infection postnatally from contact with active HSV lesions. Therefore, the following is recommended:

a) Avoid direct contact between active lesions and neonate. Topical Aciclovir should be used by staff and family members for cold sores. Meticulous hand washing precautions.

b) Cover lesions if possible.

c) If baby is not on NICU, the baby should be isolated in a single room with mother so as to isolate from other neonates.

d) Breastfeeding is only contraindicated in the event of a herpetic lesion on the breast.

References:
