MCN for Neonatology

West of Scotland

Neonatal Guideline

Herpes Simplex infection

Management of infants born to mothers with genital herpes

This guideline is applicable to all medical staff caring for neonates in the West of Scotland. Users should also refer to the appropriate drug monographs

Introduction

Neonatal Herpes Simplex Infection has an incidence of 1.65/100000 live births in the UK. As such it is an uncommon disease, but due to a high mortality and severe long term morbidity is a devastating one when contracted:

Category of infection	Proportion	Mortality*	Morbidity (neurologically impaired)*
Disseminated	40%	90%	≥95%
CNS infection (encephalitis)	40%	75%	49-67%
Skin, eye and mouth	20%	Uncommon	30%

*(In untreated infection)

Aciclovir is active against the Herpes Simplex virus but is only effective if started early in the disease, which often has an insidious onset and no pathognomonic features. Therefore where there is a known risk of disease we should act to ensure that appropriate action is taken.

Contents:

Symptomatic infection

Clinical assessment

Successful management of neonatal herpes relies on a ***high index of suspicion*** of herpes simplex virus (HSV) infection and early instigation of therapy. It should be borne in mind that the majority of infants with neonatal herpes simplex infection are borne to mothers *without* a clear history of genital herpes. The extent of disease can be assessed using physical evaluation, biochemical tests along with cultures or polymerase chain reaction (PCR) to detect HSV. Thus, an understanding of the presentations of the different categories of neonatal disease can help in management. The symptoms of infection that should alert the physician to neonatal HSV infection include:

- a progressive febrile illness without bacterial cause, associated with one or more of the following:
    - liver dysfunction
    - skin vesicles
    - seizures
    - coagulopathy
    - pneumonitis unresponsive to antibiotics.

Skin, eye and mouth disease

Skin lesions should be carefully sought and examined. However, only approximately one third of neonates present with cutaneous lesions, whereas one-third develop cutaneous disease later in life and one-third never develop lesions. Moreover, in central nervous system (CNS) disease, 55–60% of cases are devoid of skin lesions at presentation. Even when cutaneous manifestations are present, they may be difficult to detect without careful examination. Thus, diagnostic methods are required.

CNS disease

Infants with CNS disease usually present with fever and changes in consciousness, ranging from lethargy to coma. These changes in sensorium may be followed by focal or generalized seizures that are difficult to control. Where disease involves only the CNS and is not disseminated, neonatal transmission of HSV to the CNS tends to result in unitemporal involvement with subsequent bitemporal illness as disease progresses.
Typical findings in the cerebrospinal fluid (CSF) include 50–100 white blood cells/mm3 that are predominantly mononuclear, and an elevated protein concentration (>900mg/l or as per local lab), though viral detection by PCR is the most useful measure. If CSF cannot be obtained MRI and EEG may be of use if CNS disease is suspected.

Disseminated disease

The clinical findings in neonates with disseminated disease include jaundice, bleeding with associated coagulopathy, haemorrhagic pneumonitis, vascular instability, hepatomegaly, hepatitis and neurological deterioration with signs or symptoms of meningitis or encephalitis. Liver enzymes should be assessed and if they are progressively abnormal, the index of suspicion for disseminated neonatal herpes is increased, especially in the first week of life.

Management of the symptomatic baby

Any baby with suspected HSV infection should be isolated until results are available.

Samples required (contact virology on 50080 and discuss with consultant virologist, but do not delay sampling and treatment):

Swabs: Swabs sent in viral PCR solution (***not*** charcoal swabs), asking for HSV PCR from:

- o any lesions seen
- o throat
- o nose
- o conjunctiva
- o rectum

Swabs should be swirled in the viral PCR solution then discarded and the PCR solution sent.

Urine Urine in plain universal container asking for HSV PCR (do not delay treatment by waiting for urine- it can be taken and sent after acyclovir has been commenced)

Blood HSV PCR (1ml EDTA)
LFTs and FBC
Coagulation screen

CSF Asking for urgent HSV PCR as well as viral culture/isolation C&S, protein and glucose

Other investigations as dictated by the child's clinical condition (chest X rays etc).

Please also ensure that swabs have been sent from the mother if not already done, by asking the obstetric team.

Treatment

- Aciclovir 20mg/kg three times daily pending results
- Supportive treatment as dictated by baby's clinical state
- Ophthalmology review if eye involvement

Assessment of risk in asymptomatic babies born to mothers with genital HSV

Where woman has a history of genital herpes it is prudent to act to prevent transmission to her child. To do this in a rational way we look at the degree of risk.

The risk of infection in the neonate is related to the following:

- Presence of active lesions at the time of delivery
- Primary (first) or secondary (recurrent) infection

Highest Risk

First Episode with active lesions, any mode of delivery.

In this scenario there is a risk of direct inoculation of virus onto the child at delivery, with no passive maternal immunity to confer protection. The risk of infection in this group is estimated at 39% [6]. Delivery by section is felt to be of benefit but does not confer sufficient protection to avoid the need for intervention.

Lower Risk

Recurrent infection at the time of delivery, any mode of delivery.

In recurrent infection although there is direct inoculation of virus at delivery, a degree of protection is conferred by passive maternal antibody. The risk of infection around 2% in this group[6].

Lowest Risk

A history of previous herpes infection with ***no active lesions at the time of delivery***.

In this scenario there should not be any direct inoculation of virus onto the baby at birth so the risk of transmission is thought to be minimal.

Risk based management of the asymptomatic baby born to a mother with HSV (6)

This approach is summarised in a flow diagram at the end of the document (link)

Highest Risk

First Episode with active lesions, any mode of delivery.

Due to the high risk of infection and the devastating nature of this disease all infants should be investigated and treatment commenced, even if initially asymptomatic. A clinical assessment should be made as soon as possible after birth to look for signs of disease. It should be born in mind that the presentation can be non-specific and skin lesions are *not necessarily* present.

Infants should be isolated pending results of testing.

Samples required – (inform consultant virologist, but do not delay samples and commencing treatment): Regional virology lab 0141 201 8722 or 38722 (short code within Glasgow)

Sampling:

Swabs, blood and urine should be obtained and sent for urgent processing as described earlier and in the appendix at the end of this document

CSF

There has been a degree of controversy over if and when to obtain CSF in this group, both due to the invasiveness of the investigation in a well child, and the fact that the CSF is likely to be negative in the early stages as inoculation, invasion, spread and replication will take some time to occur. The American Academy or Paediatrics however has issued guidance that all infants in this group should have a lumbar puncture performed at the assessment stage.

There may be circumstances where CSF is not obtainable or when obtained the result is negative but there are clinical concerns that CNS disease was present. In these circumstances repeat CSF sampling, MRI scanning and EEG may be of use in determining whether there is any evidence of CNS involvement.

Treatment

Treatment should be commenced immediately after samples have been obtained as aciclovir, 20mg/kg/dose I/V 3 times daily (see monograph)

The ***length of treatment course*** depends on whether there is disseminated or CNS disease. Standard treatment courses are 14 or 21 days dependent on whether there is local or disseminated/CNS disease.

If all investigations are negative, a course of treatment is still recommended by the AAP(6), though this is slightly shortened to 10 days:

All investigations negative, asymptomatic

- 10 days IV aciclovir at 20mg/kg three times daily

SEM disease only

- 14 days IV aciclovir at 20mg/kg three times daily

Disseminated or CNS disease (or no CSF obtainable in infant with

lesions/symptoms/positive swabs)

- 21 days IV aciclovir at 20mg/kg three times daily
- Send repeat blood and CSF (where previously positive) on day 17-19 for HSV PCR to ensure eradication of the virus prior to stopping treatment.
- Following this, if there has been CNS involvement or disseminated disease, oral aciclovir should be commenced at 300mg/m^2 three times daily, and continued for 6 months (see **long term suppressive aciclovir therapy**, below). Prophylaxis may be considered in infants with SEM disease to reduce risk of cutaeneous recurrence - see below.

Lower Risk

Recurrent infection at the time of delivery, any mode of delivery.

Infants who develop ***lesions, signs or symptoms*** should be investigated and treated in the manner described above for symptomatic infants.

Management of asymptomatic infants born in this group is more controversial, largely due to the lack of information about the scale of risk to these infants. There is no evidence that prophylactic/empiric aciclovir is of benefit, and the potential for adverse effects and the need of IV administration (given low oral bio-availability) mean that it is not routinely recommended.

In order to catch those that are most at risk within this group swabbing and obtaining blood for PCR is advocated to establish if there virus present. If positive results are obtained, then the infant should be assessed for signs of infection (rather than colonisation). To avoid detecting superficial virus picked up on transit through the birth canal, and to avoid delay in diagnosis, swabbing should be optimally timed to achieve a balance.

To achieve this balance the swabs should be taken first thing on the morning after the baby has turned *at least* 24 hours old and has been bathed.

Samples:

Blood for HSV PCR

Swabs as detailed in final appendix

It is not necessary to isolate these infants unless positive results are obtained.

Interpretation of results

Negative swabs and blood PCR:

If all of the above are negative and the baby remains well, then no further action is required other than counselling the parents that medical attention should be sought if the baby becomes unwell. Babies presenting early with recurrences should be carefully assessed for possible CNS occurrence/recurrence.

Positive swabs and/or blood PCR:

Positive swabs or blood PCR taken on the second day of life or later should be regarded as representing infection until proven otherwise.

As such any infants with a positive swab result should be investigated with repeat swabs, bloods and CSF obtained as described in the red box high risk group above. Aciclovir should be commenced at 20mg/kg three times as day whilst results of these investigations are awaited.

If all subsequent investigations are normal then a 10 day treatment course is recommended, otherwise treatment durations should be as for the red box babies ie 14 days for those who are surface swab positive but blood/CSF negative and 21 days with a retest at 17-19 days for those who are CSF/blood positive.

Lowest Risk

A history of previous herpes infection with ***no active lesions at the time of delivery***.

No action is required in this scenario other than counselling the family to seek prompt medical advice in the event of their child becoming unwell.

Long term suppressive acyclovir therapy

Unfortunately a proportion of babies with neonatal HSV infection either cutaneous or CNS most commonly will go on to have recurrence of the infection despite a course of IV aciclovir,.

Recent research (5) has given us guidance on this topic where previously there had been a great deal of debate:

CNS disease (alone, or with disseminated disease):

Long term suppressive aciclovir suppressive therapy has now been shown to improve neurodevelopmental outcome at 1 year of age (Adjusted Bailey Mental development score 88.24 (treatment) v 68.12 (placebo), p 0.046). The treatment schedule was 300mg/m^2 aciclovir three times daily for 6 months, with an incremental benefit seen dependent on the duration of suppressive therapy. No significant adverse effects were seen in the treatment group, though there was a trend to higher rates of neutropenia in the treatment group (5).

SEM disease:

The evidence to support longer term suppressive therapy is less clear in this group. Cutaneous recurrences as a whole were reduced if the CNS and SEM groups were combined, but this did not remain significant if the SEM patients were analysed alone. As such routine long term treatment in this group would not be recommended, but may be considered in those with early or frequent recurrences.

Non genital postnatal acquisition

"Cold sores" (herpes labialis) and herpetic whitlows pose a potential threat to the newborn, though the risk is low if basic infection control measures are used.

Family members

No restriction to contact with infant as long as thorough hand washing is adhered to. Family members should be advised not to kiss or nuzzle their baby until oral lesions have crusted and to avoid touching the lesions. Where possible lesions should be covered with an adhesive dressing.

Staff

Cold sores - strict hand washing and avoidance of touching the lesions should be practised. As there remains a small risk of passing on infection, staff with active lesions should avoid working in NICU.

Herpetic whitlow- It is not practicable to continue to work with a whitlow and avoid direct contact. Thus staff with an active herpetic whitlow should avoid direct contact with neonates.

References:

1. British Paediatric Surveillance Unit, Neonatal Herpes 1 Link
2. International Herpes management forum, Herpesvirus Infections in Pregnancy Link
3. Royal College of Obstetricians and Gynaecologists guideline number 30: Link
4. Tiffany KF et al, Improved Neurodevelopmental Outcomes following Long-Term High-Dose Oral Acyclovir Therapy in Infants with Central Nervous System and Disseminated Herpes Simplex Disease, Journal of Perinatology 2005; 25:156–161
5. Kimberlin D et al Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes, N Engl J Med 2011; 365:1284-1292 October 6, 2011
6. www.pediatrics.org/cgi/doi/10.1542/peds.2012-3216 doi:10.1542/peds.2012-3216

Author
Dr Allan Jackson – Consultant Paediatrician

Other Professionals consulted
Dr Celia Aitken – Consultant virologist
Katie Scott – Neonatal Pharmacist

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WoS_HSV_Neonates

Implementation / Review Dates
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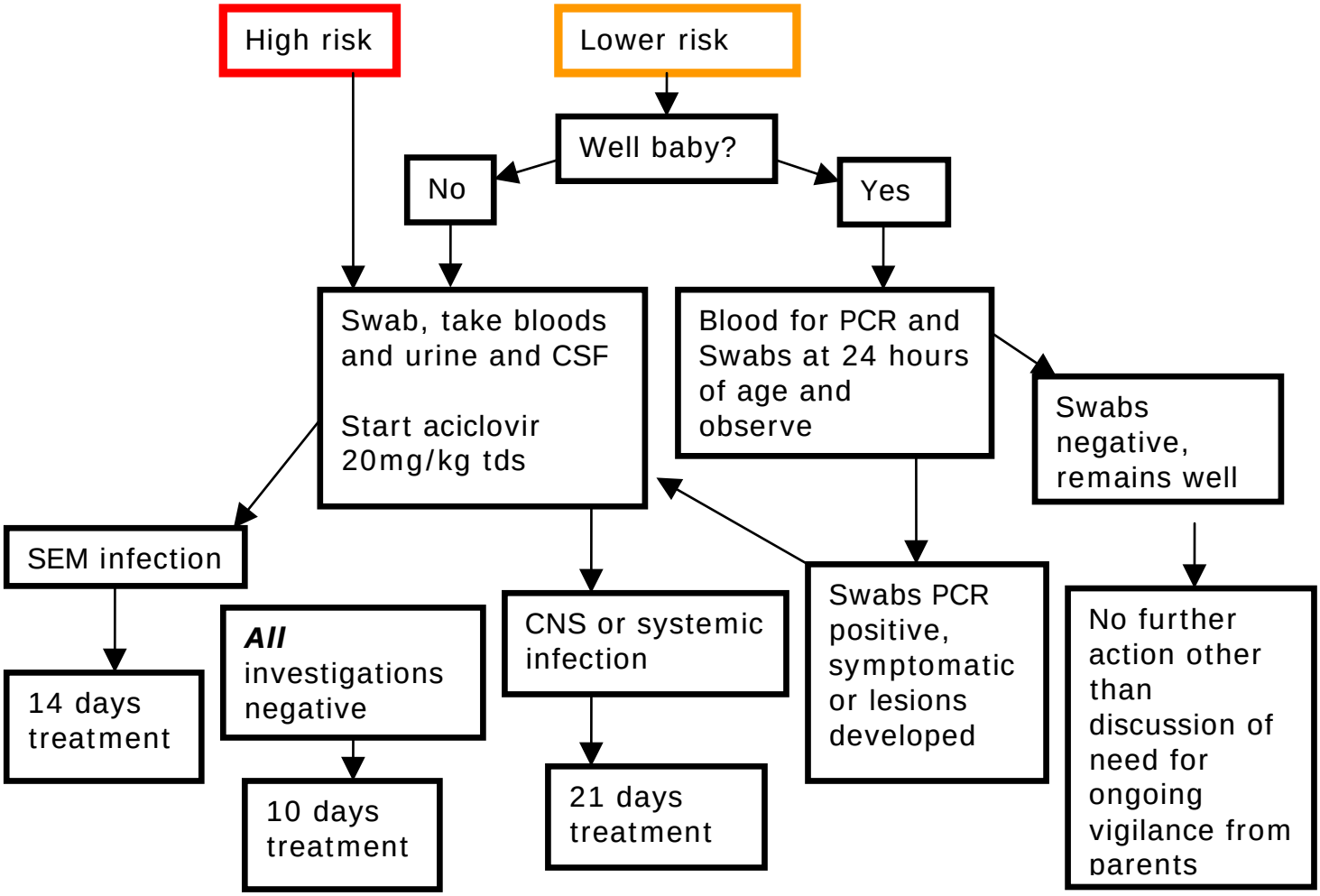
Summary:

Management of the infant born to a mother with genital herpes in pregnancy



Sampling instructions:

In all cases where virological investigations are being sent the consultant virologist should be contacted and the case discussed with them at the first opportunity to ensure prompt processing of specimens and appropriate clinical interpretation of results

All babies being investigated

Swabs: Swabs sent in viral PCR solution (***not*** charcoal swabs), asking for HSV PCR from:

- any lesions seen
- throat
- nose
- conjunctiva
- rectum

Swabs should be swirled in the viral PCR solution then discarded and the PCR solution sent.

Blood : HSV PCR (1ml EDTA)

Please also ensure that swabs have been sent from the mother if not already done.

High risk and symptomatic babies

In ***addition*** to the above:

Urine	Urine in plain universal container asking for HSV PCR (do not delay treatment by waiting for urine- it can be taken and sent after acyclovir has been commenced)
Blood	LFTs and FBC, Coagulation screen
CSF	Asking for urgent HSV PCR, viral culture/isolation, C&S, protein and glucose

Other investigations as dictated by the child's clinical condition (chest X rays etc).