Nottingham Children's Hospital

Nottingham University Hospitals NHS Trust

Management of Neonatal Herpes

Full Title of Guideline:	**Management of Neonatal Herpes**
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Explicit definition of patient group to which it applies ***(e.g. inclusion and exclusion criteria, diagnosis):***	Neonates on the labour suite, neonatal unit or postnatal ward with risk factors or suspicion of neonatal Herpes
Changes from previous version ***(not applicable if this is a new guideline, enter below if extensive):***	Dates of PCR test updated
Summary of evidence base this guideline has been created from:	Nationally agreed guidance, regional and international cohort studies have been used to develop this guideline.
This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.	

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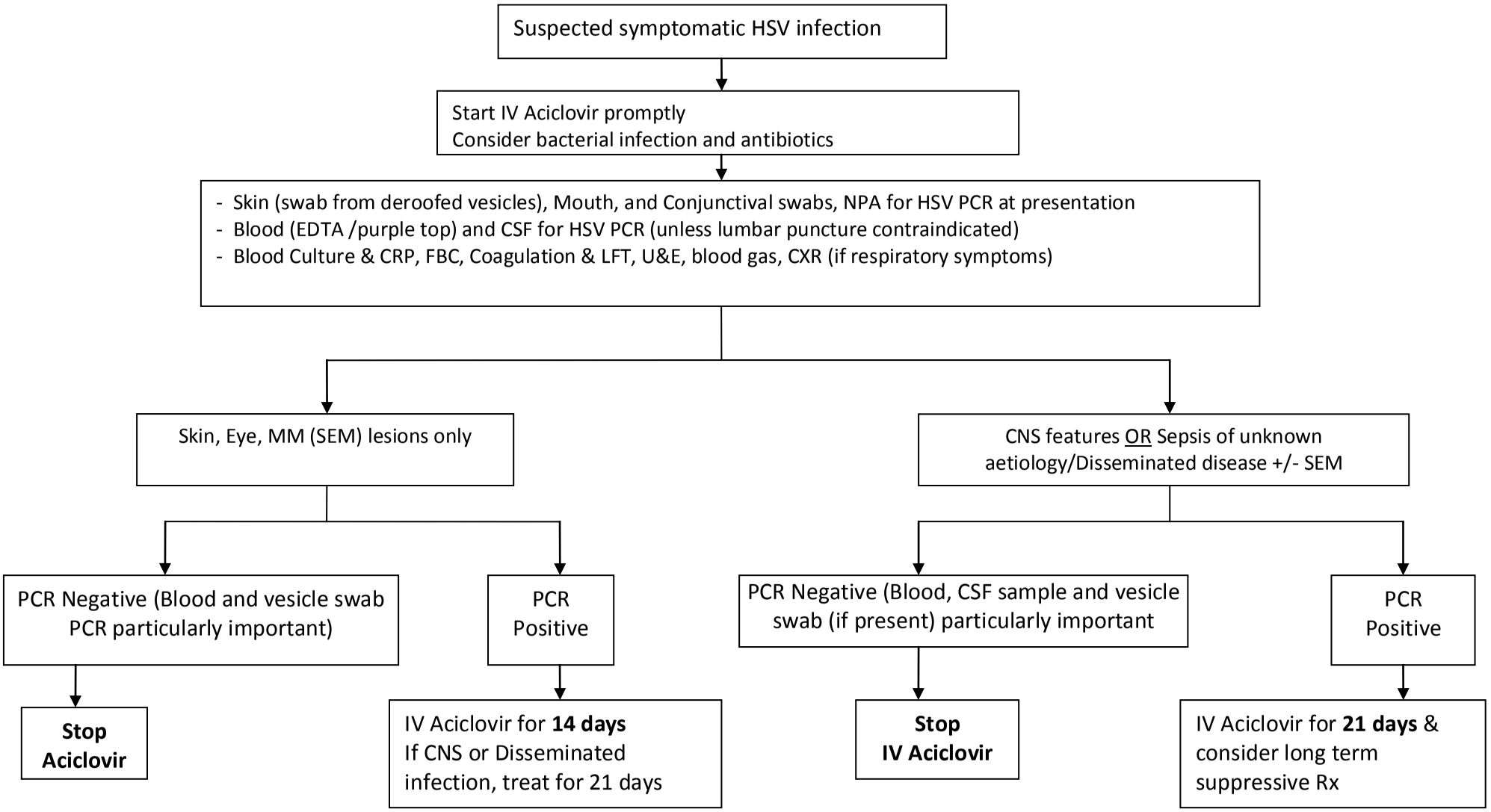
KEY POINTS:

1) **All infants admitted with a maternal history of genital herpes infection during pregnancy need early assessment to make a decision regarding investigations and treatment for possible risk of transmission of infection.**
2) **The risk of perinatal transmission is increased by late pregnancy primary infection, rupture of membranes > 4 hours, invasive fetal monitoring.**
3) **In view of high mortality and morbidity along with rising incidence of neonatal herpes infections, early Aciclovir and timely investigations may help avert adverse outcome.**

Algorithm 1: Symptomatic Neonatal HSV



Negative PCR results should be evaluated in conjunction with the entire clinical scenario, including the results of other tests, and should not be used on their own to exclude invasive herpes disease.

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

Risk group	Timing of Maternal HSV	Maternal HSV Symptoms in Pregnancy	Gestation at birth	Mode of Delivery	Neonatal Plan
R1	Pre pregnancy genital HSV	No Symptoms	Any	Any	Plan B
R2	Recurrent infection	Recurrent genital herpes with NO active lesions at the onset of labour	Any	Any	Plan B
R3	Recurrent infection	Recurrent genital herpes WITH Active lesions at the onset of labour	ANY	EL.LSCS	Plan B
				Other	Plan A
R4	Primary Infection	1st Episode >6 weeks before delivery	Any	Any	Plan B
R5	Primary Infection	1st Episode <6weeks before delivery	Any	EL. LSCS	Plan B
				Other	Plan A

Management **Plan A**= Investigate and start Aciclovir **(See Algorithm 2)**
Management **Plan B**=Provide information to parents **(See Algorithm 2)**
Plan A If maternal Aciclovir was given, the risk of vertical transmission is lower*
Other delivery: Vaginal delivery, any delivery with instrumentation including Foetal Blood Sampling, any C-Section with ROM>4hours
Abbreviations: EL.LSCS= Elective LSCS with no rupture of membranes, HSV= Herpes simplex virus, ROM= Rupture of membranes

Further recommendations:

Obstetric and GUM Advice: Consider maternal Aciclovir for treatment of lesions and advice/Offer maternal Aciclovir (suppressive treatment) from 36/40. Maternal Aciclovir treatment will reduce the viral shedding but would not eliminate the risk of transmission. Follow the recommendation from Table 1 irrespective of the use of maternal Aciclovir.

Non-genital herpes: Meticulous hand washing precautions, avoidance of direct contact of the neonate with active lesions (cover lesions) and prompt treatment of the oral lesions with Aciclovir

Algorithm 2: Asymptomatic baby exposed to HSV
(Use in conjunction with Table 1)

At Risk of Neonatal HSV* (See Table 1)

1. Assess

Plan A:
Investigate and start IV Aciclovir

Plan B:
Provide information for parents

2. Investigate

- FBC, LFT & Coagulation at birth

AFTER 36- 48 hours of birth: Following samples for HSV PCR:

- Blood (EDTA/purple top)
- CSF
- Surface swabs (skin, mouth, conjunctiva) and NPA for HSV PCR (if respiratory symptoms)

INFORM VIROLOGY LAB WHEN SENDING SAMPLES

No tests Indicated, unless infant symptomatic

3. Treat

Continue IV Aciclovir until PCR results available

PCR Negative

Stop treatment

PCR Positive

IV Aciclovir for 14 days
If CNS/ disseminated infection treat for 21 days

No Treatment indicated.
The risk of vertical transmission small, but advise parents to seek medical attention if unwell in first 2 weeks

**** Independently consider risk of bacterial infection (Use this guidance in conjunction with early onset sepsis guideline: Guideline C6)***

2. Herpes Knowledge
2.1 Introduction

Herpes simplex virus (HSV) infection is one of the most commonly acquired sexually transmitted disease (STD) world wide[1, 2]. HSV-1 and HSV-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. Historically, HSV 1 predominates in oro-facial lesions and is latent in the trigeminal ganglia, while HSV 2 is most commonly found in the lumbosacral ganglia. Either of these viruses can infect any region of the body[3].

Historically, HSV-2 is the cause of most genital herpes and is almost always sexually transmitted while HSV-1 is mainly transmitted during childhood via non-sexual contacts. However HSV type 1 is emerging as the principal cause of genital herpes in a few developed countries particularly United States and Canada[2, 4, 5].

The incubation period for infection of HSV-1 or HSV-2 ranges from 2 to 12 days. Most people infected with HSV are unaware they have contracted the virus, and most new infections in pregnant women are asymptomatic[6]. In the majority of cases of neonatal herpes disease, there is no antenatal history of herpes[7]. In approximately one third of cases, there will be a pre-pregnancy history of herpes, if this is pursued.

The greatest incidence of HSV infections occurs in women of reproductive age and hence the risk of maternal transmission of the virus to the fetus or neonate has become a major health concern[1, 3]. Recent findings reveal that first-time infection of the mother is the most important factor for the transmission of genital herpes from mother to fetus/newborn. The pregnant woman who acquires genital herpes as a primary infection in the latter half of pregnancy, rather than prior to pregnancy, is at greatest risk of transmitting these viruses to her newborn[7, 8].

2.2 Epidemiology

Neonatal (HSV) herpes disease is a rare but potentially devastating condition. Untreated neonatal HSV infection is associated with only a 40% survival rate. But early recognition and the early initiation of high-dose intravenous Aciclovir therapy significantly improves survival and morbidity rates.

Neonatal infection can follow primary (first episode primary or first episode non primary) or recurrent maternal infection, or be acquired postnatally through direct contact with infected secretions. Transplacental transmission is unusual (5%), and perinatal infection is usually acquired during vaginal delivery through an infected birth canal.

Risks of transmission are 57% for first episode primary infection, 25% for first episode non primary infection and 2% for recurrent infection. Risk varies with serotype, mode of delivery, rupture of membranes, extent of viral shedding and prematurity.

On the basis of hospital discharge data, the frequency of neonatal HSV infection in the United States is 33 (3-60) per 100,000 livebirths[9]. 1 in 4 adults in the USA have genital herpes. Surveillance of neonatal HSV in the UK was undertaken through the BPSU in 1986-1991 and again in 1994-6. The estimated prevalence of infection, in the first study, was 1.65/100,000 (CI 1.3-2.0/100,000). HSV-1 and HSV-2 were reported in equal proportions, but in one third of cases the virus was not typed[10]. The incidence of reported first episode genital herpes has increased by 89% between 2003 and 2012. The Nottingham incidence of Neonatal Herpes Disease, from a retrospective study 2006-13, is much higher (18 per 100,000 live births) i.e. 2 cases per year[11].

It is estimated that 6 weeks may be required for a mum to develop and transfer immunity after a primary episode. If babies are born prematurely, then the transplacental transfer of immunity is reduced.

Table 2: Outcome of neonatal herpes infection[12, 13]

Site of disease	Death		Normal outcome †	
	No therapy	**IV antiviral therapy**	**No therapy**	**IV antiviral therapy**
Disseminated	85 %	31 %	Rare	83 %
Central nervous system	50 %	6 %	Rare	31 %
Skin Eyes and Mucosa	0 % ‡	0 %	62 %	100 %

† *A normal outcome is defined as the achievement of developmental milestones within 24 months after infection*
‡ *Skin, eye, and mucosal infection will progress to encephalitis or disseminated disease in the absence of antiviral therapy in a high proportion of infants*

2.3 Clinical presentations

Congenital HSV infection is rare; it shares clinical features such as microcephaly, hydrocephalus, and chorio-retinitis 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[14].

Most neonatal infections result from exposure to HSV during delivery (perinatal aquisition). The clinical presentation of these infections and postnatal infections, has been divided into three categories, each of which is associated with different outcomes and clinical manifestations: SEM (skin, eyes and mucosa) disease, CNS disease and Disseminated disease

Cutaneous (45%)
Neonates with infections that are confined to the **skin, eyes and mucosa (SEM Disease)**, account for about 45% of most case series. Disease elsewhere (CNS and other organs) must be excluded.

Herpes simplex lesions may involve the skin, the mouth or the eye and when they do, they provide valuable clues to the possibility of associated disseminated or CNS herpes. Typically the lesions develop by the end of the first week or into the second week of life, if the virus has been acquired at the time of birth. However, there are exceptions and occasionally lesions may be present at birth when, presumably infants would have been exposed to the virus several days prior to delivery.
Skin involvement may vary from a single vesicle to grouped vesicles, often in a linear distribution if affecting the limbs. If the vesicle is eroded, a shallow ulcer with an erythematous base may be noted. There may be associated lesions on the lips, similar to those of the "cold sore" in the adult.

Progression to more extensive disease will occur in the absence of treatment. However, with high-dose intravenous Aciclovir, the long-term developmental outcome of this form of neonatal herpes is good. Children with herpes infection that is confined to the skin, eyes, and mucosa

often have recurrent outbreaks of cutaneous herpes during early childhood. Suppressive antiviral therapy reduces the frequency of these recurrences, but breakthrough infections may still occur.

CNS

CNS HSV infection (30%) is associated with lethargy, poor feeding, and seizures; cutaneous lesions may or may not be present. Pleocytosis is *usually* present; HSV DNA in the cerebrospinal fluid is the most sensitive laboratory test for confirming the diagnosis, and analysis of samples obtained early in the course of the disease may have falsely negative results. Among infants with CNS HSV infection, the morbidity is higher among infants with HSV-2 infection than among those with HSV-1 infection and morbidities may include developmental delay, epilepsy, blindness and cognitive disabilities. Prompt initiation of therapy improves the outcome. Aciclovir therapy has substantially improved survival. However, neonates with CNS HSV-2 infection still have high rates of developmental problems at 1 year, and more than 50% of these children have moderate-to-severe neurologic abnormalities[12, 15]. Moreover, relapses of CNS infection may occur, further increasing morbidity. Long term suppressive therapy may have a role in reducing morbidity.

Disseminated HSV infection (25%): The highest fatality rate associated with neonatal HSV infection is with disseminated infection. Babies typically present at 5-10 days of life with a sepsis like illness involving multiple organs (liver, lungs and brain) and is indistinguishable from bacterial sepsis. The risk of death from disseminated neonatal HSV infection is high (30-80%), even with antiviral therapy[12, 14, 15]. Any vesicular rash in a neonate should be evaluated for HSV infection. Since a rash is absent in up to 50% of cases of neonatal HSV infection, all infants younger than 4 weeks with CNS infection or sepsis syndromes should undergo a laboratory evaluation, with a PCR assay for HSV; the assessment should also include CSF and blood samples for HSV DNA[16, 17]. There may be clues in the laboratory results like **raised ALT and coagulopathy** but they may not be evident at presentation. If a baby becomes unwell despite 3-5 days of antibiotics in the first 10-14days of life, consider herpes presenting as disseminated disease (often as hepatitis). Long term suppressive therapy may have a role in reducing morbidity.

3. Investigations

Table 3: Essential diagnostic virology investigations

Type of investigation	Site	Specimen container	Expected availability of results
PCR	Skin vesicle base , if open vesicle scrub the base	Red top viral transport medium (VTM) container	Performed twice a week (Mon/ Wed/ Fri) 3-5 working days
PCR	Eyes, Mouth, Nasopharyngeal aspirates (NPA's)	Red top viral transport medium (VTM) container	
PCR	Blood (WBC's)	EDTA- purple top bottle	
PCR	CSF	Clear CSF collecting bottle	

Please discuss with virology team for specific advice about investigations during working hours and alert the laboratory before sending specimen (QMC Ext: 63524)

***HSV PCR is run twice a week (Tuesdays and Fridays)**. Discuss all the test requests with consultant virologist at the earliest opportunity to aid the most efficient processing schedule. If results are agreed as urgent then Tuesday/ Wednesday samples can be processed by an external laboratory.*

1. Routine blood investigations – Blood culture & CRP, Full blood count, Liver function tests & Coagulation profile, Urea & electrolytes
2. CXR, if respiratory symptoms
3. Neuroimaging may localise disease but not essential

4. Management

4.1 Management options

1 Investigate and start treatment with intravenous Aciclovir (**Plan A**)

2 Provide parental advice/ information Leaflet (**Plan B**)

3 Investigate and treat for 14 days (SEM disease)

4 Investigate and treat for 21 days and consider long term suppressive therapy (CNS and Disseminated disease)

4.2 Management Scenarios (all patient groups)

Patient Groups

1 Non-specific sepsis and not responding to antibiotics (see infection guideline C6)

2 Suspected Symptomatic HSV infection (see Algorithm 1)

3 At risk of Neonatal Herpes infection from maternal history (see list table 1 /table 4/algorithm 2)

4.3 Pharmacological management:

Aciclovir monograph in the neonatal pharmacopeia provides information of dosing and frequency of the medication. Intravenous Aciclovir treatment should be continued for 21 days in disseminated and CNS disease[16] and for 14 days in infants with HSV infection limited to the skin and mucous membranes.
All neonates suspected of symptomatic Herpes infections must be treated with intravenous Aciclovir, not oral Aciclovir.
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[15].

4.3.1 Long Term Suppressive Treatment

Recent studies have shown that long term suppressive therapy may improve neurological outcomes[19, 20]. The long term oral Aciclovir treatment (300mg/m^2 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, 1mo, 3mo and 6mo).

4.4 Obstetric management:

Please refer to Obstetric guideline for management of genital herpes during pregnancy and RCOG guideline for genital herpes[21].

5. Prevention:

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

A) Family members and healthcare workers should be aware of the risk of neonatal transmission from active HSV lesions, including orolabial herpes. Avoid direct contact between active lesions and neonate. Topical Aciclovir should be used by staff members for cold sores.
B) Avoid direct contact between lesions and the neonate, e.g. no kissing if labial/oral herpes, and
covering of lesions if possible
C) Use strict hand washing techniques
D) If baby is not on NICU, the baby should be isolated in a single room with mother so as to isolate from other neonates.
E) Breastfeeding is only contraindicated in the event of a herpetic lesion on the breast.

6. Audit points:

a) Number of infants treated with Aciclovir and number with positive results

b) Duration of hospital stay for asymptomatic infants where treatment is started

c) HSV PCR sampling: number of samples, results and turnaround time

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