Clinical Guideline: Guideline for the Management of Neonatal Herpes Simplex Virus Infection

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For use in: EoE Neonatal Units
Guidance specific to the care of neonatal patients.

Used by: All neonatal/paediatric medical & nursing staff

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Neonatal Clinical Oversight Group	
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Ratified by ODN Board:

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Audit Standards:

1. **All neonates with a maternal history of genital herpes are risk assessed so that a neonatal plan can be made**
2. **Investigations and treatment are followed as per algorithm following risk assessment**
3. **All neonates with suspected symptomatic HSV infection start IV Aciclovir promptly**

KEY POINTS:

1. **Most neonatal HSV infections are acquired at birth, generally from mothers with an unrecognised genital herpes infection acquired during pregnancy.**
2. **There is no clear pattern of signs and symptoms that identifies babies with neonatal HSV disease, meaning a high index of suspicion is required.**
3. **All neonates 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.**
4. **The risk of perinatal transmission is increased by late pregnancy primary infection, rupture of membranes > 4 hours, invasive fetal monitoring.**
5. **In view of high mortality and morbidity along with rising incidence of neonatal herpes infections, early administration of Aciclovir and timely investigations may help to avert adverse outcome.**

Introduction

Herpes simplex virus (HSV) is a member of the *Herpes viridae* family of viruses. It enters human host through inoculation of oral, genital or conjunctival mucosa or breaks in skin. It infects the sensory nerve endings and transports via retrograde axonal flow, to dorsal root ganglia where it remains for the life of the host, thus establishing 'latent' or silent infection and reactivating in the presence of humoral and cell-mediated immune responses. The latent virus is not susceptible to antiviral drugs.

Historically, HSV-2 was the cause of most genital herpes and was almost always sexually transmitted while HSV-1 was 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.

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. In the majority of cases of neonatal herpes disease, there is no antenatal history of herpes. In approximately one third of cases, there will be a pre-pregnancy history of herpes, if this is pursued.

The highest incidence of HSV infections is in women of reproductive age and hence the risk of maternal transmission of the virus to the foetus or neonate is a major health concern. Recent findings reveal that first-time infection of the mother is the most important factor for the transmission of genital herpes from mother to foetus or 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.

Epidemiology

Neonatal (HSV) herpes disease is rare but can result in devastating outcomes, including mortality and significant morbidity. 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. It is estimated that up to 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.

Risks of transmission from mother to baby is around **60% for first episode primary infection, 25% for first episode non primary infection (infection with one virus type, e.g. HSV-2, in the presence of antibodies to the other virus type e.g. HSV-1) and fall to 2% following recurrent infection**. Risk of transmission varies with serotype, mode of delivery, invasive obstetric procedures such as scalp electrodes, prolonged rupture of membranes (ROM), extent of viral shedding and prematurity.

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[1]. In England, first-episode genital herpes has increased by 89% between 2003 and 2012. Neonatal HSV infection rates vary from country to country, with national surveys reporting a wide range in annual incidence. Marked differences in incidence can also exist within countries. In USA the incidence of neonatal HSV infection is 33 per 100,000 live births.

Clinical Presentation

Congenital HSV infection accounts for around 5% of all cases of neonatal herpes. In contrast to neonatal herpes infection, the signs of intrauterine HSV infection are present at delivery. The infected babies are usually profoundly damaged with microcephaly, hydrocephalus, chorio-retinitis and skin lesions with ulceration and scarring.

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.

Perinatal acquisition results from exposure to HSV during delivery and accounts for most neonatal infections.

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 disease (skin, eyes and mucosa)**
2. **CNS disease**
3. **Disseminated disease**

Categories of clinical presentation

SEM disease – Cutaneous (45%)	CNS HSV infection (30%)	Disseminated HSV infection (25%)
Typically lesions develop by **end of first week** or into second week but may present **at birth**.	It usually presents in **first 2 -3 weeks** of life.	Typically present in the **first week**
Infection is confined to the skin, eyes and mucosa. **Disease elsewhere (disseminated and CNS) must be excluded.**	Encephalitis, mainly affecting temporal lobes and territory surrounding the middle cerebral artery.	Mimics bacterial sepsis like illness involving multiple organs **(liver, lungs, adrenals, brain) and is indistinguishable from bacterial sepsis.**
May be a single vesicle or group of 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. The eye or mouth initially may be asymptomatic but can develop conjunctival erythema, periorbital vesicles, excessive watering and localised ulcerative lesions of mouth, palate and tongue **High risk of progression to CNS or disseminated disease if left untreated.** With high dose IV acyclovir, long term outcome is good. May have recurrent outbreaks of cutaneous herpes during early childhood.	Associated with lethargy, poor feeding and seizures; can manifest as a multifocal stroke; cutaneous lesions may or may not be present. **Pleocytosis** 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. Prompt initiation of therapy with Aciclovir can improve outcome and survival. Higher morbidity with CNS HSV-2 infection than HSV-1. **Mortality 50% in untreated and 6% in treated CNS HSV infection.** Long term morbidities - developmental delay, epilepsy and blindness. Relapses of CNS infection may occur, further increasing morbidity. Long term suppressive therapy may have a role in reducing morbidity.	**Signs and symptoms of** • **Apnoea** • **Temperature instability** • **Irritability/ Seizures** • **Lethargy** • **Respiratory distress** • **Abdominal distension** • **Unexplained bleeding** Vesicles maybe absent in up to 50% of cases. Need to ensure blood and CSF sent for HSV PCR. Clues in lab tests include **elevated liver transaminases (ALT), coagulopathy, neutropenia, thrombocytopenia** If a baby continues to be unwell despite treatment with antibiotics in the first 2 weeks of life, consider herpes presenting as disseminated disease often as hepatitis. **Mortality > 80% in untreated and 30% in treated disseminated HSV infection.** Long term suppressive therapy may have a role in reducing morbidity.

Differential diagnosis for Neonatal HSV

Bacterial pathogens responsible for neonatal sepsis, sometimes with skin lesions that may be mistaken for disseminated or CNS HSV infection, include Group B Streptococcus, Listeria monocytogenes and gram-negative bacilli.
Cutaneous infections resulting in vesicular lesions similar to neonatal HSV are bullous impetigo, Varicella zoster, enteroviruses and disseminated CMV infection.
Non-infectious cutaneous disorders that could be confused with neonatal HSV infection include erythema toxicum, neonatal pustular melanosis, acropustulosis and incontinentia pigmenti.

Investigations

- Routine blood investigations – Blood culture, CRP, Full blood count, Liver function tests, split bilirubin, coagulation profile, Urea & electrolytes
    - **Note: Serum hepatic transaminase (ALT) should be measured to provide supporting evidence of disseminated HSV infection**
- CXR, if respiratory symptoms
- CSF cell count, glucose, protein and HSV DNA PCR for suspected CNS/ disseminated disease
- Neuroimaging with MRI/CT regardless of disease classification[2]
- In SEM, seek ophthalmologic opinion early. In all other cases dilated ophthalmologic examination to assess chorioretinitis during the first week and at 6 months
- EEG if suspected to have CNS involvement, especially if seizures observed
    - CFM may be considered to assess seizures
    - EEG typically shows characteristic temperoparietal high-voltage low-frequency activity

Type of investigation	Site	Specimen container
Herpes PCR	Skin vesicle base, de-roof and scrub the base	Discuss with local laboratory
Herpes PCR	Eyes, Mouth, NPA aspirates	Discuss with local laboratory
Herpes PCR	Blood	EDTA sample
Herpes PCR	CSF	Clear CSF bottle

Management

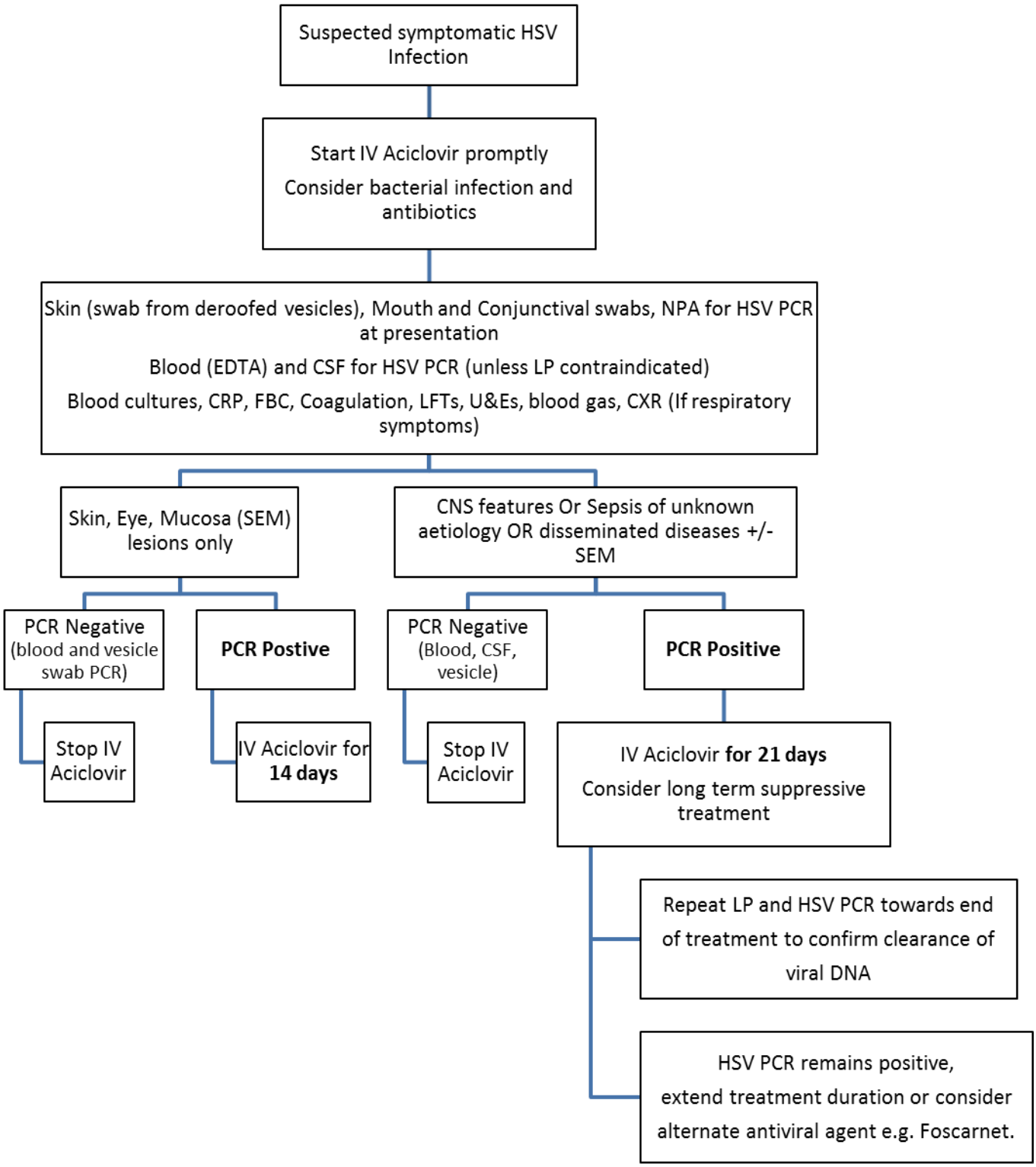
Obstetric

Please refer to the joint Royal College of Obstetricians and Gynaecologists and British Association for Sexual Health and HIV (BASHH) guideline on Management of Genital Herpes in Pregnancy[3].

Neonatal

- Symptomatic Neonatal HSV – Algorithm 1
- Asymptomatic baby exposed to HSV – Algorithm 2
- Neonates treated for suspected bacterial sepsis with antibiotics and who do not improve rapidly and have negative bacterial cultures at 24-36 h incubation – consider neonatal HSV infection and treat pending laboratory confirmation.
- Particular alerting symptoms are a progressive febrile illness without a confirmed bacterial cause, which is unresponsive to antibiotics and associated with *one or more* of the following: skin vesicles, hepatomegaly, liver dysfunction/hepatitis, pneumonitis, thrombocytopenia, coagulopathy, or seizures. Other factors *recently* suggested to be of diagnostic importance in a neonate without a rash are maternal fever, respiratory distress requiring mechanical ventilation and CSF pleocytosis.
- Neonates started on intravenous (IV) antibiotics for suspected sepsis that are found to have unexplained hepatitis - consider neonatal HSV infection and treat pending laboratory confirmation
- A sexual history from the parents should be taken.

Algorithm 1: Symptomatic Neonatal HSV[2,4]



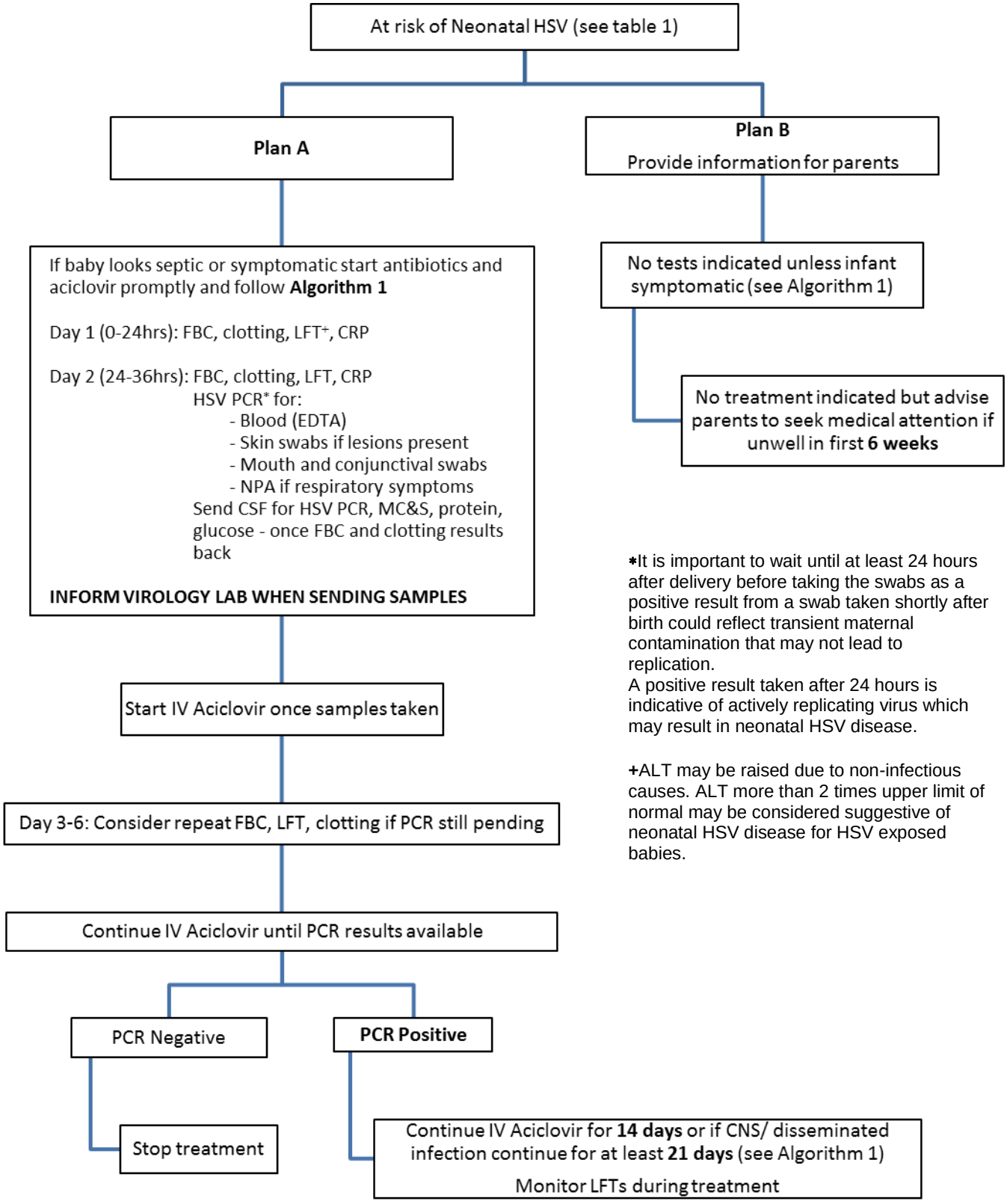
Negative PCR results should be evaluated in conjunction with the entire clinical scenario, including the results of other tests, and should not be used on their own to exclude invasive herpes disease

Table 1: Assessment of Risk of Neonatal Herpes Infection and Neonatal Plan[2,4]

Timing of Maternal HSV	Maternal HSV Symptoms in Pregnancy	Gestation at Birth	Mode of Delivery	Neonatal Plan
Pre pregnancy genital HSV	No symptoms	Any	Any	Plan B
Recurrent infection	Recurrent genital herpes with NO active lesions at the onset of labour	Any	Any	Plan B
	Recurrent genital herpes WITH active lesions at the onset of labour	Any	Elective LSCS	Plan B
			Other	**Plan A**
Primary infection	1st episode more than 6 weeks before delivery	Any	Any	Plan B
	1st episode less than 6 weeks before delivery	Any	Elective 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 fetal blood sampling, any LSCS with ROM greater than 4 hours.

Algorithm 2: Asymptomatic baby exposed to HSV[2,4]



*It is important to wait until at least 24 hours after delivery before taking the swabs as a positive result from a swab taken shortly after birth could reflect transient maternal contamination that may not lead to replication.
A positive result taken after 24 hours is indicative of actively replicating virus which may result in neonatal HSV disease.

+ALT may be raised due to non-infectious causes. ALT more than 2 times upper limit of normal may be considered suggestive of neonatal HSV disease for HSV exposed babies.

Provide information for parents – http://www.nhs.uk/conditions/neonatal-herpes[5]
Advise parents to seek medical attention if unwell in first 6 weeks

Pharmacological management

- Early therapy with IV Aciclovir improves the prognosis **for all three presentations** of Neonatal HSV. Therefore, neonates should be started on IV Aciclovir before laboratory confirmation of HSV, as soon as the infection is suspected clinically
- IV Aciclovir treatment at a dose of 60mg/kg/day in three divided dosed should be continued for 21 days in disseminated and CNS disease and for 14 days in infants with HSV infection limited to the skin and mucous membranes
- For neonates with CNS disease, CSF should be sampled near the end of a 21-day course of therapy. If the PCR remains positive, treatment should be extended with weekly CSF sampling and Aciclovir stopped when a negative result is obtained[6]. Alternative antiviral medication such as foscarnet should be considered
- All neonates suspected of symptomatic Herpes infections must be treated with intravenous Aciclovir, not oral Aciclovir. Levels of oral Aciclovir are only high enough for suppressive therapy
- 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. 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, 1month, 3months and 6months).

Counselling & Referral

Neonatal HSV infection may cause considerable stress within the family. This is because of concern over a critically ill infant, exacerbated by guilt over transmission of the virus and the demands of the long term care of an often severely impaired child. Because of this, expert education and counselling is required by making a referral to GU Medicine.

Prevention

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

- Family members and healthcare workers should be aware of the risk of neonatal transmission from active HSV lesions, including oro-labial herpes. Avoid direct contact between active lesions and neonate. Topical Aciclovir should be used by staff members for cold sores.
- Avoid direct contact between lesions and the neonate, e.g. no kissing if labial/oral herpes, and covering of lesions if possible
- Use strict hand washing techniques
- Breastfeeding is only contraindicated in the event of a herpetic lesion on the breast.

References

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4. Batra D et al. Guideline for management of neonatal herpes infection. Nottingham Neonatal Service – Clinical Guidelines. Review date September 2022.
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6. Kimberlin, David W., et al. "Natural history of neonatal herpes simplex virus infections in the acyclovir era." Pediatrics 108.2 (2001): 223-229.

Exceptional Circumstances Form

Form to be completed in the **exceptional** circumstances that the Trust is not able to follow ODN approved guidelines.

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