# Management of Babies born to Mothers with Herpes Simplex Virus (HSV) Infection in Pregnancy - Paediatric Full Clinical Guideline

Reference: NIC IN 06

**Introduction:**

Neonatal Herpes Simplex Virus (HSV) infection is a rare but potentially devastating condition that can affect otherwise healthy infants. It is associated with significant morbidity and mortality and if left untreated, the mortality rate is about 60%. Due to the high virulence of HSV and specifically neurovirulence, central nervous system (CNS) and multi-organ involvement is common. Therefore, timely evaluation and early initiation of therapy aims in preventing further disease progression and the long-term sequelae of the infection.

**Aim and purpose:**

To ensure that babies who have acquired or are at risk of acquiring the infection are detected and managed appropriately and timely in the neonatal setting.

**Background and epidemiology:**

The Herpes Simplex viruses (HSV-1 and HSV-2) are double-stranded DNA viruses and are commonly seen as pathogens of sexually transmitted disease worldwide. HSV-2 has predominantly been the cause of genital herpes, however HSV-1 previously associated with orolabial infections is emerging as a cause also for genital infections.

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. In England, first-episode genital herpes has increased by 89% between 2003 and 2012. Neonatal HSV infection rates vary from country to country and within countries with surveys reporting a wide range in annual incidence. An incidence rate of 17.5 per 100,000 live births was reported in a Nottingham tertiary centre retrospective study 2006-13 (1).

**Transmission:**

HSV infection of the newborn infant is acquired during 1 of 3 distinct time periods:

1. Intrauterine transmission via transplacental spread (5%)
2. Intrapartum transmission (85%)
3. Postnatal transmission (10%)

Intrauterine or congenital infections are associated with clinical features usually present at birth. These include CNS pathology (encephalomalacia, hydranencephaly, microcephaly, hydrocephalus, intracranial calcifications), eye disease (chorioretinitis, retinal dysplasia, optic atrophy) and skin abnormalities such as active skin lesions, scarring, hypo/hyperpigmented lesions and cutis aplasia.

Postnatal transmission of the disease is most commonly due to HSV-1 acquired due to contact with family members or hospital personnel who are viral shedding.

The risk of neonatal transmission 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 2% following recurrent infection (2). It is also influenced by the following:

1. Maternal HSV antibody status
2. Mode of delivery (vaginal > C-section)
3. Duration of rupture of membranes
4. HSV serotype (HSV-1 > HSV-2)
5. Disruption of cutaneous barrier (instrumental delivery, use of foetal scalp electrodes)

**Classification and Clinical presentation:**

Neonatal HSV infections acquired either intrapartum or postpartum can be classified into 3 categories according to organ involvement. The classification is also predictive of the associated morbidity and mortality for the affected infant.

- **Skin, eyes and mucosa (SEM disease)- 45%**

  SEM disease is confined to the skin with no involvement of visceral organs or CNS. Therefore, disease elsewhere must be excluded by thorough examination. The lesions typically appear in the second week of life.

  - Skin – crops of vesicles on presenting part with progressive spread
  - Eyes – keratoconjunctivitis / chorioretinitis
  - Mouth – oropharyngeal vesicular lesions

  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. Prolonged suppressive oral antiviral therapy has also been shown to reduce the frequency of recurrences.

- **CNS HSV disease / encephalitis - 30%**

  CNS disease can present without or with SEM involvement. It usually presents around day 16-17 of life if acquired at birth. Signs and symptoms of CNS HSV disease can be very non-specific and include lethargy, poor feeding, irritability, seizures, tremors, bulging fontanelle and pyrexia.

  Pleocytosis is usually present and CSF PCR analysis is the gold standard laboratory test to confirm the diagnosis.

- **Disseminated HSV disease - 25%**

  Disseminated disease often presents in the first week of life. CNS involvement is present in about 60-75% of cases. Usually presents with sepsis-like characteristics and multiorgan involvement. Signs and symptoms include shock, disseminated Intravascular coagulopathy (DIC), jaundice, pneumonitis, and respiratory distress. A vesicular rash is present at about 50-80% of cases.

As symptoms can be indistinguishable from bacterial sepsis, for all neonates with suspicion of sepsis or CNS infection, clinicians should include HSV PCR investigations together with coagulation and LFT studies (raised ALT and coagulopathy can be present) and consider treatment with IV aciclovir especially where no improvement is shown with antibiotic treatment.

If left untreated, mortality rate of disseminated disease and CNS disease are 85% and 50% respectively. SEM disease which is not treated early with aciclovir has 50% risk of progressing to CNS or disseminated disease.

**Investigations:**

**When suspected neonatal HSV (Asymptomatic)**

Specimens should be obtained for HSV PCR including the conjunctivae, mouth, nasopharynx, and rectum taken 24 hours post-delivery (indicates true colonisation rather than surface colonisation).

Swabs from deroofing of the skin lesion will yield best results. Viral swabs if not found in the wards can be obtained from pathology lab.

**When clinical features of HSV infection present (Symptomatic)**

- Viral cultures as above
- FBC, CRP and coagulation screen
- LFT & UE
- EDTA blood for HSV PCR
- CSF – cell count, glucose, protein, viral PCR
- CXR - if respiratory symptoms
- Ophthalmological examination
- Consider EEG if suspected to have CNS involvement especially if seizures observed.
- Consider Cranial U/S or CT/MRI scan

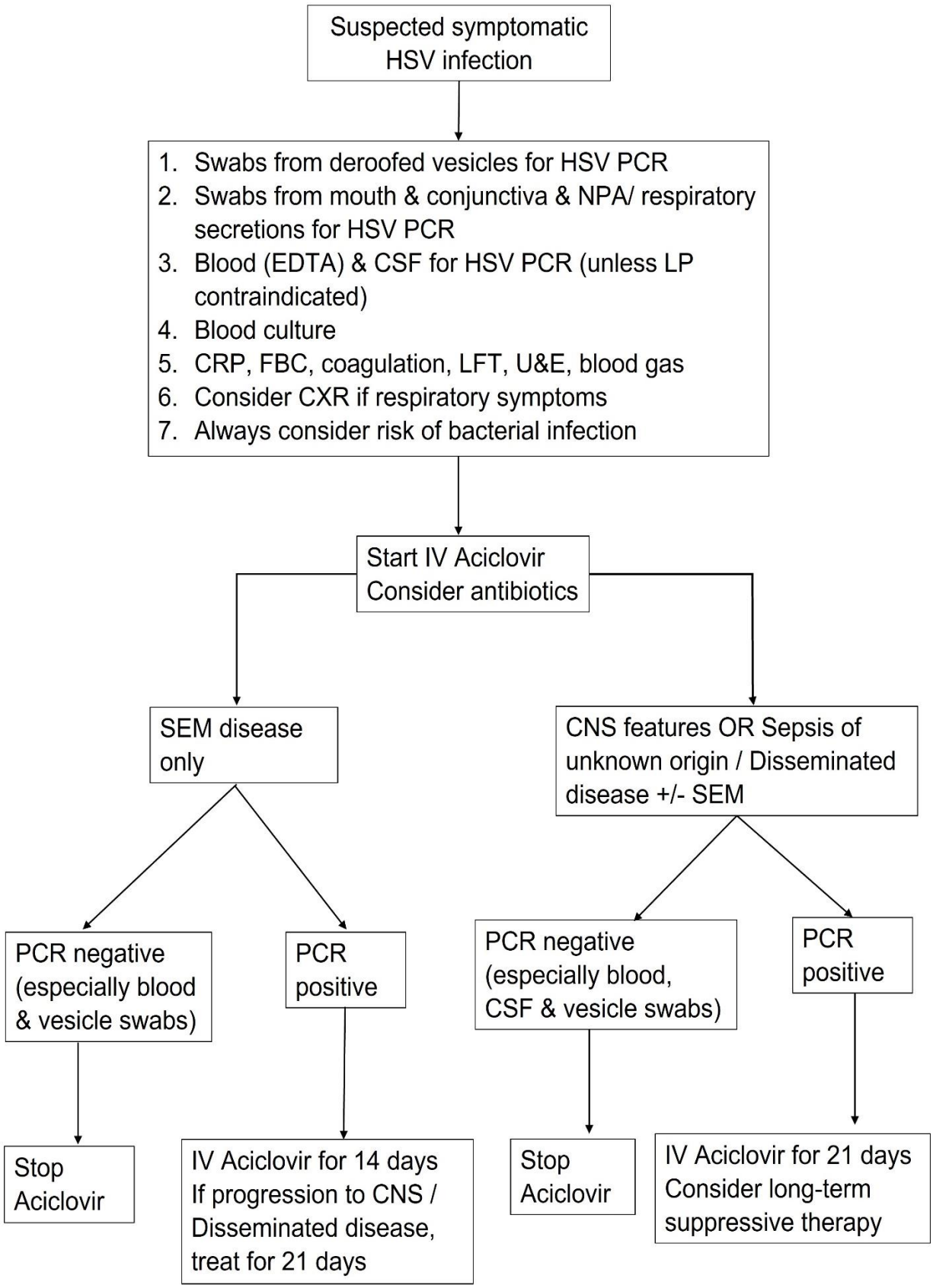
**Management:**

Management is dependent on the clinical status of the infant and the risk factors that the infant has been exposed to. There are two main pathways of action:

1. Infants presenting with symptomatic HSV infection. To note, infants presenting with non-specific infection and CNS or sepsis-like symptoms or infants where initial management with antibiotics has shown no clinical improvement, should also follow this pathway.

2. Clinically well infants who have been exposed to risk factors associated with HSV infection.

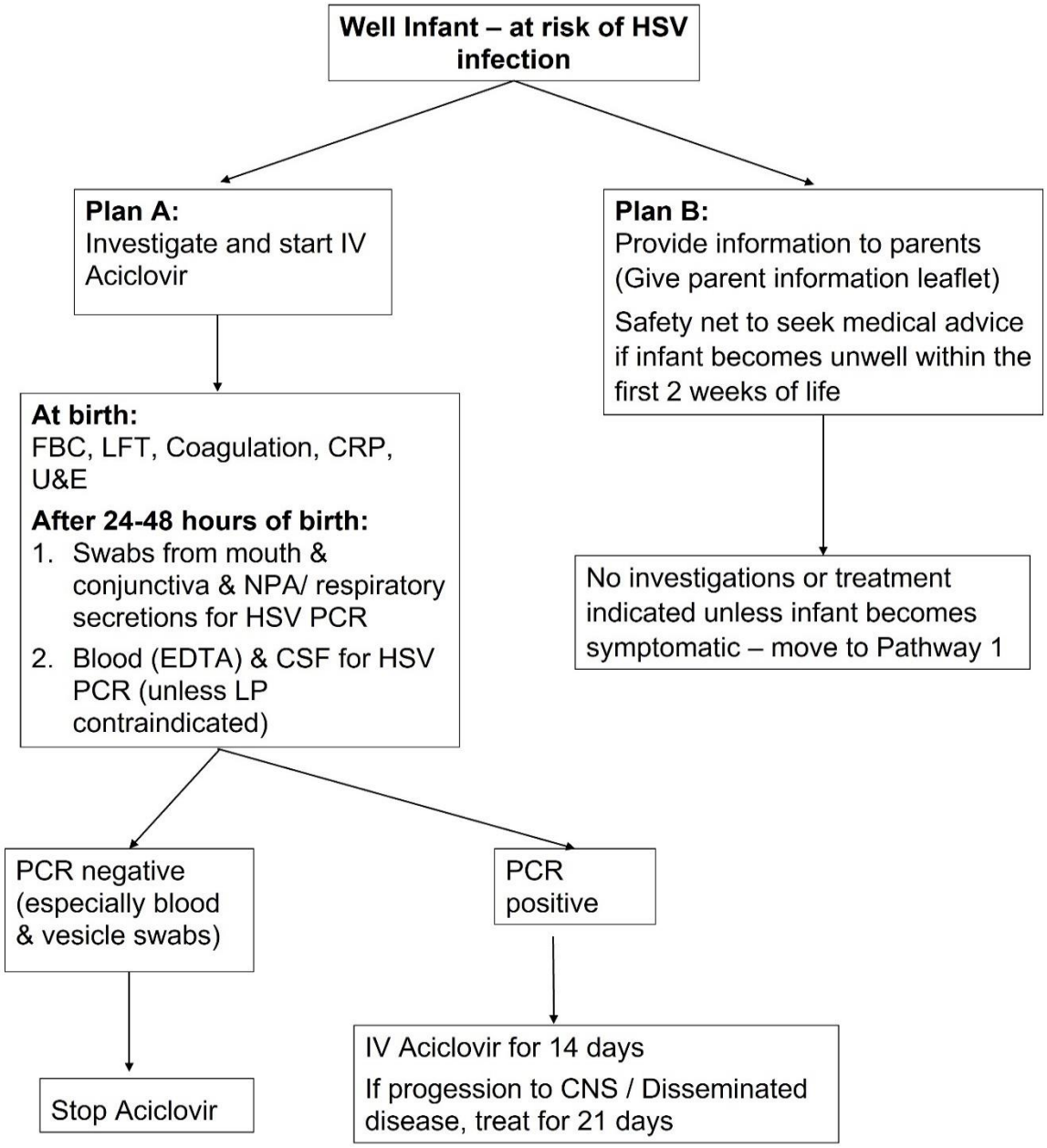
**PATHWAY 1: SYMPTOMATIC INFANT**




Pathway 1: Symptomatic infant.

**PATHWAY 2: WELL INFANT WITH RISK FACTORS FOR ACQUIRING HSV INFECTION:**

**To be used in conjunction with risk assessment (Table 1) below**




Pathway 2: Asymptomatic infant.

**Notes on Pathway:**

- Negative PCR results should not be used in isolation to exclude HSV infection. Consider continuation of therapy even after negative PCR results if the clinical scenario is suggestive of infection.
- Due to the risks of neutropoenia and renal and liver toxicity, FBC, U&E and LFT should be repeated at least weekly whilst on IV therapy.
- If there is CNS involvement, CSF PCR needs to be repeated near the end of the 21 days of treatment. IV aciclovir should continue until the PCR becomes negative.
- Referral for ophthalmology review and ophthalmic examination is necessary for all symptomatic infants.
- Consider Neuroimaging (MRI) for all symptomatic infants.

**Table 1: Assessment of risk of Neonatal HSV infection and Neonatal Plan for management:**

| Time 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 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 >6 weeks before delivery | Any | Any | Plan B |
| | 1st episode <6 weeks before delivery | Any | Elective LSCS | Plan B |
| | | Any | Other | Plan A |

Table 1: Assessment of risk of Neonatal HSV infection and Neonatal Plan for management.

Other: Vaginal delivery, any delivery with instrumentation including Foetal Blood Sampling, any c-section with ROM > 4 hours

**Pharmacological Management:**

IV Aciclovir is the recommended agent for management of symptomatic or asymptomatic infants at high risk of acquiring HSV infection.

The recommended dose and frequency is 20 mg/kg 8 hourly (total of 60ml/kg/day) and the length of treatment is 14 days for SEM disease and 21 days for disseminated and CNS disease (3).

For neonates with CNS disease, CSF should be sampled near the end of a 21-day course of therapy. Treatment should be extended until CSF PCR is negative.

**Long-term suppressive therapy:**

Recent studies have shown the benefit of long-term suppressive therapy in relation to neurodevelopmental outcomes and recurrent skin lesions. Long term treatment with oral Aciclovir (300mg/$m^2$ TDS for 6 months) can be considered in disseminated or CNS disease after completion of acute treatment and in discussion with infectious diseases consultant (virologist) and pharmacist (4,5). It is recommended that FBC, U&E and LFT are repeated at time of discharge, 2 weeks and monthly thereafter.

**Discharge**

Parents should receive safety netting about signs of HSV infection and be advised to seek further medical help if they have any concerns regarding their baby.

Please provide parental information leaflet to parents upon discharge (Appendix A).

**Follow-up:**

Affected infants should be followed up carefully:

- If long-term suppressive therapy is started, then blood tests need to be organised as mentioned above together with follow up in the consultant's clinic in 3 weeks.
- If no long-term suppressive therapy is started, the infants should be followed up in the consultant's clinic in 6-8 weeks.

A structured follow-up programme should be put in place that allows for neurodevelopmental, ophthalmic, and hearing assessments. Infants with CNS involvement will require a close developmental follow-up with appropriate MDT referrals if indicated.

**References:**


1. Batra D., Davies P., Manktelow B.N., Smith C. The incidence and presentation of neonatal herpes in a single UK Tertiary Centre, 2006-2013. Arch Dis Child. 2014;99(10):916–921.
2. Pinninti SG, Kimberlin DW. Preventing herpes simplex virus in the newborn. Clin Perinatol. 2014;41(4):945-55.
3. NICE. (2023).BNFc [online]. Available at: https://bnfc.nice.org.uk/drugs/aciclovir/
4. Kimberlin DW, Whitley RJ, Wan W, Powell DA, Storch G, Ahmed A, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. N Engl J Med. 2011 Oct 6: 1284-92.
5. Tiffany KF, Benjamin DK, Palasanthiran P, O'Donnell K, Gutman LT. improved neurodevelopment outcomes following long-term high-dose oral acyclovir therapy in infants with central nervous system and disseminated herpes simplex disease. J Perinatol. 2005 Mar; 25 (3): 156-61.


**Documentation controls:**

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# Neonatal Herpes Simplex Virus Infection – Parent information leaflet

## What is Neonatal Herpes Simplex Virus infection?

Neonatal herpes infection can affect about 10 babies every 10 000 births. This infection can affect the baby's skin, eyes, brain, and other organs. If left untreated, the baby may become seriously ill or die. Early treatment with drugs targeting the virus may help in preventing or reducing the damage to the baby.

## How can my baby catch the infection?

1. When baby is in the womb: This type of infection is rare but serious.
2. During birth: This is the most common type of infection and occurs through contact with the viral secretions present in the birth canal.
3. Contact with the virus after birth: This infection occurs through direct exposure to an active herpes infection. The infection can be on anyone (mainly through cold active cold sores) who comes into close contact with the baby. This includes family members, caregivers, and healthcare professionals.

## Signs of infection in a baby:

Neonatal HSV infection can present as any other infection in a baby. A rash is not always present, and symptoms can be non-specific. Look for signs of:

- Lethargy /extreme tiredness
- Poor feeding
- Floppiness
- Irritability
- Abnormally high or low temperature
- High-pitched or abnormal cry
- Grunting or difficulty breathing (you may notice the baby 'sucking in' between and underneath their ribs)
- Rash or sores on the skin, eyes or inside the mouth

## What can I do to help?

- Seek medical help if you have any concerns regarding the baby.
- Wash your hands before and after handling / feeding your baby.
- Avoid skin-to-skin contact between your baby and anyone with active herpes simplex infection (cold sores on the mouth or nose, herpetic whitlow on the hands)
- People with oral herpetic lesions (cold sores) should not kiss the baby.
- Breast feeding is only contraindicated if there are herpetic lesions on the breasts.