Management of Neonatal Herpes Simplex Infection- Leicester Neonatal Service

NHS University Hospitals of Leicester NHS Trust

Trust ref:C48/2020

Contents

1. Introduction and Who Guideline applies to

This guideline is aimed at all Health care professionals involved in the care of infants within the Leicester Neonatal Service. This guideline is for Clinicians and Health Professionals assessing and managing babies up to 6 weeks of age with suspected or proven Herpes Simplex Virus (HSV) Infection. For management in pregnancy and for infants admitted to the Children's Hospital please refer to;

- **Genital Herpes in Pregnancy UHL Obstetric Guideline (Trust ref: C11/2013)**
- **Neonatal Herpes Simplex UHL Childrens Medical Guideline (Trust ref: C1/2014)**

Key Points

1. The pregnant woman or person, 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 HSV to their newborn.
2. Untreated neonatal HSV infection is associated with only a 40% survival rate.
3. Most neonatal infections result from exposure to HSV during delivery (perinatal acquisition).
4. The clinical presentation 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
   - Disseminated disease.

2. Guideline Standards and Procedures

Current estimates place the incidence of neonatal HSV infection between 1 in 3200 and 1 in 10,000 births. It causes significant mortality and morbidity, which can be greatly improved with early treatment with aciclovir.

Neonatal HSV has three distinct periods of acquisition: intrauterine, perinatal, and postnatal.

- Intrauterine (5%) – Intrauterine HSV occurs rarely (estimated incidence of 1 in 250,000 deliveries).

- Perinatal (85%) – HSV is acquired perinatally when HSV infection, which may be asymptomatic, is present in the genital tract at the time of delivery. Perinatal transmission is more likely in primary infection, prolonged rupture of membranes, where a fetal scalp electrode has been used and in vaginal vs caesarean delivery. **However, most neonates with HSV disease are born to mothers without a history of HSV infection or other identifiable risk factor.**

- Postnatal (10%) – Postnatal acquisition of neonatal HSV occurs when a caretaker with active HSV infection, such as herpes labialis, has close contact with the newborn infant.

3. 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 live births. 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 typed10. 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.

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.

Outcome of neonatal herpes infection

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*

4. Clinical presentations

Neonatal HSV may be classified into three main categories for therapeutic and prognostic considerations: localized skin, eye, and mouth (SEM); central nervous system (CNS); and disseminated disease. There is some overlap in these categories. Both HSV-1 and HSV-2 may cause SEM, CNS, or disseminated disease.

- **SEM** disease (45%) is characterised by coalescing or clustering vesicular lesions of the skin with erythematous base; excessive tearing, eye pain, conjunctival oedema; and/or localized ulcerative lesions of the mouth, palate, and tongue. Neonates with evidence of SEM disease should undergo evaluation for CNS and disseminated disease.

- **CNS** disease (30%) features include seizures (focal or generalized), lethargy, irritability, tremors, poor feeding, temperature instability (fever or hypothermia), and full anterior fontanelle.

- **Disseminated disease** (25%) involves multiple organs. Neonates with disseminated HSV often present in the first week of life with nonspecific signs and symptoms of neonatal sepsis (e.g., temperature instability, apnoea, irritability, lethargy, respiratory distress, hepatomegaly, abdominal distension, and ascites). Other clinical features include necrotising enterocolitis, acute

kidney injury, disseminated intravascular coagulation, liver failure, pneumonia, pleural effusion, meningoencephalitis, myocarditis, and skin and mucous membrane lesions. Laboratory abnormalities seen in disseminated HSV disease are thrombocytopenia, neutropenia, coagulopathy, transaminitis and direct hyperbilirubinemia.

In summary, features of neonatal HSV may be very non-specific and subtle. It can mimic bacterial and other viral illness such as enterovirus infection. Always think of HSV infection in neonates with mucocutaneous lesions, CNS abnormalities or sepsis-like picture. If left untreated, mortality rate of disseminated disease and CNS disease are 85% and 50% respectively. SEM disease which is not treated early with acyclovir has 50% risk of progressing to CNS or disseminated disease.

5. Investigations

Table 3: Essential diagnostic virology investigations

Type of investigation	Site	Specimen container
PCR	Skin vesicle base, if open vesicle scrub the base	Green top viral transport medium (VTM) container
PCR	Eyes, Mouth, Nasopharyngeal aspirates (NPA's)	Green top viral transport medium (VTM) container
PCR	Blood	EDTA bottle
PCR	CSF	Clear CSF universal container

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

*A Nervecentre request order set for a neonatal herpes screen is currently being constructed; In the meantime, these requests should be handwritten on a virology request form. Each swab should be clearly labelled to allow the laboratory staff to determine the site the swab was taken from.'

6. Management

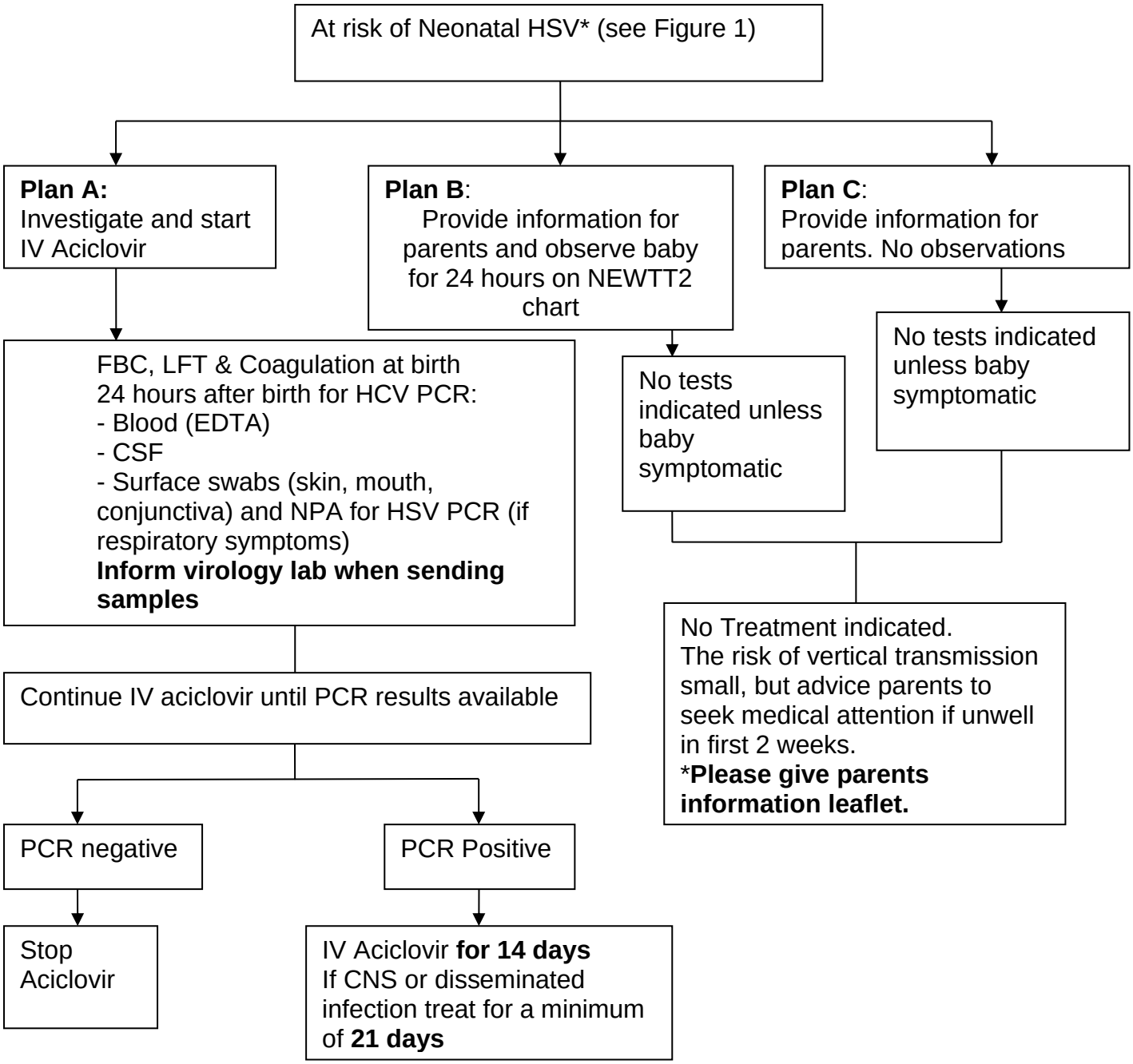
6.1 Management options

See flowcharts below detailing options for observation vs treatment for those babies with risk factors for HSV infection and then separately those who are symptomatic at the time of presentation regardless of whether there are risk factors present or not.

Figure 1: Babies born with risk factors for HSV infection but asymptomatic

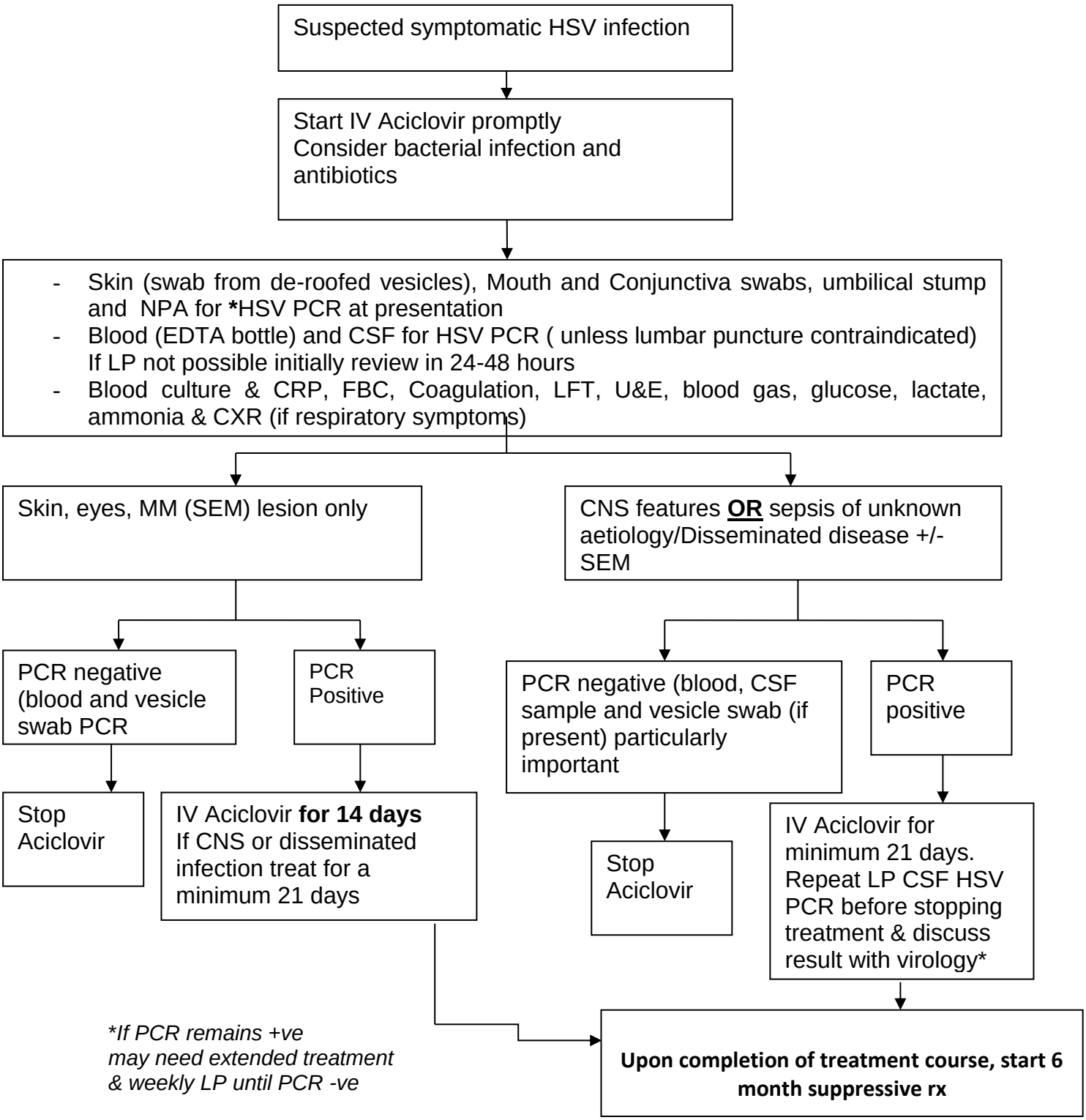
Risk group	Timing of maternal HSV	Maternal HSV Symptoms in Pregnancy	Gestation at birth	Mode of Delivery	Maternal Aciclovir from 36 weeks	Neonatal Plan
R1	Pre pregnancy genital HSV	No symptoms	Any	Any	N/A	Plan C (do nothing)
R2	Recurrent infection in pregnancy	Recurrent genital herpes with **NO** active lesions at the onset of labour	Any	El LSCS No SROM We would aim for normal birth here as the risk to the baby is very low	Yes	Plan C (do nothing)
					No	Plan B (observe)
				Other	Yes	Plan C (do nothing)
					No	Plan A (treat)
R3		Recurrent genital herpes **WITH** active lesions at the onset of labour	Any	EL CS No SROM	Yes	Plan B (observe)
					No	Plan A (treat)
				Other	N/A	Plan A (treat)
R4	Primary infection in pregnancy	1st episode >6 weeks before delivery with **NO** active lesions by the onset of labour	Any	Any	Yes	Plan C (do nothing)
					No	Plan A (treat)
R5		1st episode <6 weeks before delivery	Any	EL CS No SROM	Yes	Plan B (observe)
					No	Plan A (treat)
				others	N/A	Plan A (treat)

Figure 2: Asymptomatic baby exposed to HSV (use in conjunction with Figure 1)



- If mother develops a cold sore on PNW – observe baby and counsel family on preventing transmission (see 6.4). Treatment is not beneficial.

Figure 3: Symptomatic Neonatal HSV



**Standard PCR panel includes HSV 1/2, VZV, EV (enterovirus), PeV (parechovirus) – depending on the presentation; you may also include PCR testing for these other viruses if needed (e.g. perinatal EV/PeV infection)

6.2 Pharmacological management:

Aciclovir monograph in the neonatal formulary provides information of dosing and frequency of the medication. Intravenous aciclovir treatment should be continued for a minimum 21 days in disseminated and CNS disease and for 14 days in infants with HSV infection limited to the skin and mucous membranes. Repeat CSF HSV PCR near to day 21 of completion of IV aciclovir.

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. During aciclovir treatment, maintain adequate hydration, monitor neutrophil count, renal function and infusion site.

6.3 Long Term Suppressive Treatment

Recent studies have shown that long term suppressive therapy may improve neurological outcomes. Upon completion of acute treatment course for any HSV disease, start 6 months suppressive treatment with oral Aciclovir (300mg/m2 TDS). These babies will need regular FBC and LFTs at 2 and 4 weeks and then monthly during treatment.

6.4 Prevention:

Infants may acquire HSV infection postnatally from contact with active HSV6 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.

F) For parent information go to:
Https://www.nhs.uk/conditions/neonatal - herpes

7. Follow Up

In the era of antiviral therapy, one-year mortality rate for disseminated HSV disease is reduced to 29% but almost 20% of survivors have neurodevelopmental abnormalities. One-year mortality rate is 4% among those treated for CNS disease with aciclovir. 70% of those who survived CNS disease suffer from neurodevelopmental complications. Mortality is rare in isolated SEM disease and less than 2% have developmental delay after recovery. However, those with ocular involvement are at risk of long-term visual complication.

Babies, especially those with CNS disease, require close developmental follow up and appropriate referral to the wider MDT if necessary. All babies should undergo a

hearing test. Those with HSV disease of the eye require long term follow up with ophthalmologist.

8. Education and Training

None

9. 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

10. Supporting References

1. American Academy of Pediatrics. Herpes simplex. In: Red Book: 2018-2021 Report of the Committee on Infectious Diseases, 31st ed, Kimberlin DW (Ed), American Academy of Pediatrics, Elk Grove Village, IL 2018. p.437.

2. Pinninti SG, Kimberlin DW. Management of neonatal herpes simplex virus infection and exposure. Arch Dis Child Fetal Neonatal Ed. 2014 May;99(3):F240-4.

3. Guidance on Management of Asymptomatic Neonates Born to Women With Active Genital Herpes Lesions. David W. Kimberlin, Jill Baley, Committee On Infectious Diseases, Committee On Fetus And Newborn. Pediatrics Feb 2013, 131 (2) e635-e646

4. Nottingham Neonatal Service Clinical Guidelines: Management of Neonatal Herpes. Dushyant Batra et all. Review date September 2022.

5. Management of genital Herpes in Pregnancy/RCOG 2014 replaced by : https://www.bashh.org/resources/24/herpes_in_pregnancy_2014/

6. RCT Oral Aciclovir Suppression and Neurodevelopment after Neonatal Herpes - PMC (nih.gov)

Evidence Criteria

Evidence according to RCPCH

Grade A	At least 1 randomised controlled trial addressing specific recommendation
Grade B	Well conducted clinical trials but no randomised trial on specific topic
Grade C	Expert committee report or opinions

11. Key Words

Aciclovir, Antiviral therapy, CNS disease, Disseminated disease, Genital herpes, SEM disease

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

Contact and review details			
Guideline Lead (Name and Title) **Authors:** Ramune Snuggs - SpR Jane Gill – Consultant **Contact:** S Mittal Consultant – clinical guidelines lead			**Executive Lead** Chief Medical Officer
Details of Changes made during review:			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
August 2021	**2**	**J Gill**	Added, Ammonia, Lactate, Glucose to routine blood investigations. Mode of delivery in risk group R2 amended to elscs No SROM, We would aim for normal birth here as the risk to the baby is very low Clarified the type and duration of neonatal observations required If PCR +ve IV Aciclovir for 14 days, if symptomatic Repeat LP before stopping treatment & discuss result with virology* If PCR remains +ve may need extended treatment & weekly LP until PCR -ve If CNS or disseminated infection treat with aciclovir for a minimum of 21 days in both symptomatic & asymptomatic infants
May 2022	**2.1**	**O Toovey – Str Microbiology**	Added Repeat CSF HSV PCR near to day 21 of completion of IV aciclovir
July 2024		**O Toovey – Consultaant Virilogist**	**Upon completion of treatment course, start 6 month suppressive rx**