LRI Children's Hospital

Neonatal Herpes Simplex Virus Infection

Staff relevant to:	Clinicians and Health Professionals assessing and managing babies up to 6 weeks of age with suspected or proven Herpes Simplex Virus (HSV) Infection.
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Contents

1. Introduction and Who Guideline applies to

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 working within the Paediatric Emergency Department and Children's Hospital.

Related guidelines:

Meningitis UHL Childrens Medical Guideline C22/2014
Sepsis UHL Childrens Hospital Guideline B31/2016
Antibiotics for Neonatal Infection UHL Neonatal Guideline C54/2019
Herpes Simplex UHL Neonatal Guideline C48/2020
Lumbar Puncture UHL Childrens Hospital Guideline C82/2007
Genital Herpes in Pregnancy UHL Obstetric Guideline C11/2013

Background

Current estimates place the incidence of neonatal HSV infection 1.65 per 100,000 live births. It causes significant mortality and morbidity, which can be greatly improved with early treatment with aciclovir.
The incidence is thought to be increasing in the UK and this is under active assessment by the British Paediatric Surveillance Unit team from the Royal College of Paediatrics and Child Health.
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 maternal infection, prolonged rupture of membranes, where a fetal scalp electrode has been used and in vaginal vs caesarean delivery.
- Postnatal (10%) – Postnatal acquisition of neonatal HSV occurs when a caretaker with active HSV infection, such as herpes labialis (cold sores), has close contact with the newborn infant.
- **However, most neonates with HSV disease are born to mothers without a history of HSV infection or other identifiable risk factor.**

2. Clinical Manifestations

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. **Babies may only have a single sign or symptom at presentation**

- **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, ascites). Other clinical features include necrotising enterocolitis, acute kidney injury, disseminated intravascular coagulation, liver failure, pneumonia, pleural effusion, meningoencephalitis, myocarditis, skin and mucous membrane lesions. Laboratory abnormalities seen in disseminated HSV disease are thrombocytopaenia, neutropaenia, coagulopathy, transaminitis and direct hyperbilirubinemia.

Features of neonatal HSV may be very non-specific and subtle. It can mimic bacterial and 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 aciclovir has 50% risk of progressing to CNS or disseminated disease.

2.1 Assessment

- Use Neonatal Life Support (age ≤28 days) and Advanced Paediatric Life Support (age >28 days) structured approach.

- Involve PICU if GCS<8 or A**V**PU, status epilepticus, raised intracranial pressure, evidence of shock, in need of respiratory support and/or otherwise indicated.

2.2 Investigations

All babies with any form of suspected HSV infection should undergo investigation for disseminated and CNS disease.

Bloods	FBC and Clotting U&E CRP LFT and Conjugated Bilirubin (ALT >2x upper limit of normal value is suggestive of disseminated disease) Ammonia Glucose Lactate Capillary or venous blood gas Blood Culture HSV PCR (*EDTA tube*) Please use a hand-written request form; the correct request is not available on ICE.
CSF	Microscopy, Gram stain and Bacterial Culture HSV PCR (Appears as CSF panel 1 virology screen on ICE) Glucose and Protein
Surface swabs for HSV PCR	Swab any suspicious skin lesions **AND** conjunctiva, mouth, nasopharynx, rectum and scalp electrode placement site (*use viral swab*)
EEG and MRI/CT head	Indicated in CNS disease
CXR and abdominal US	Consider in the presence of lung and liver involvement

2.3 Empirical Treatment

Prompt anti-viral treatment improves outcome. **Indications for starting IV aciclovir** include:

1. Clinically suspected HSV disease (signs and symptoms suspicious of SEM, CNS and/or disseminated disease as mentioned in section 2.) while awaiting viral studies (Algorithm 1)

2. Virologically proven HSV disease (Algorithm 1)

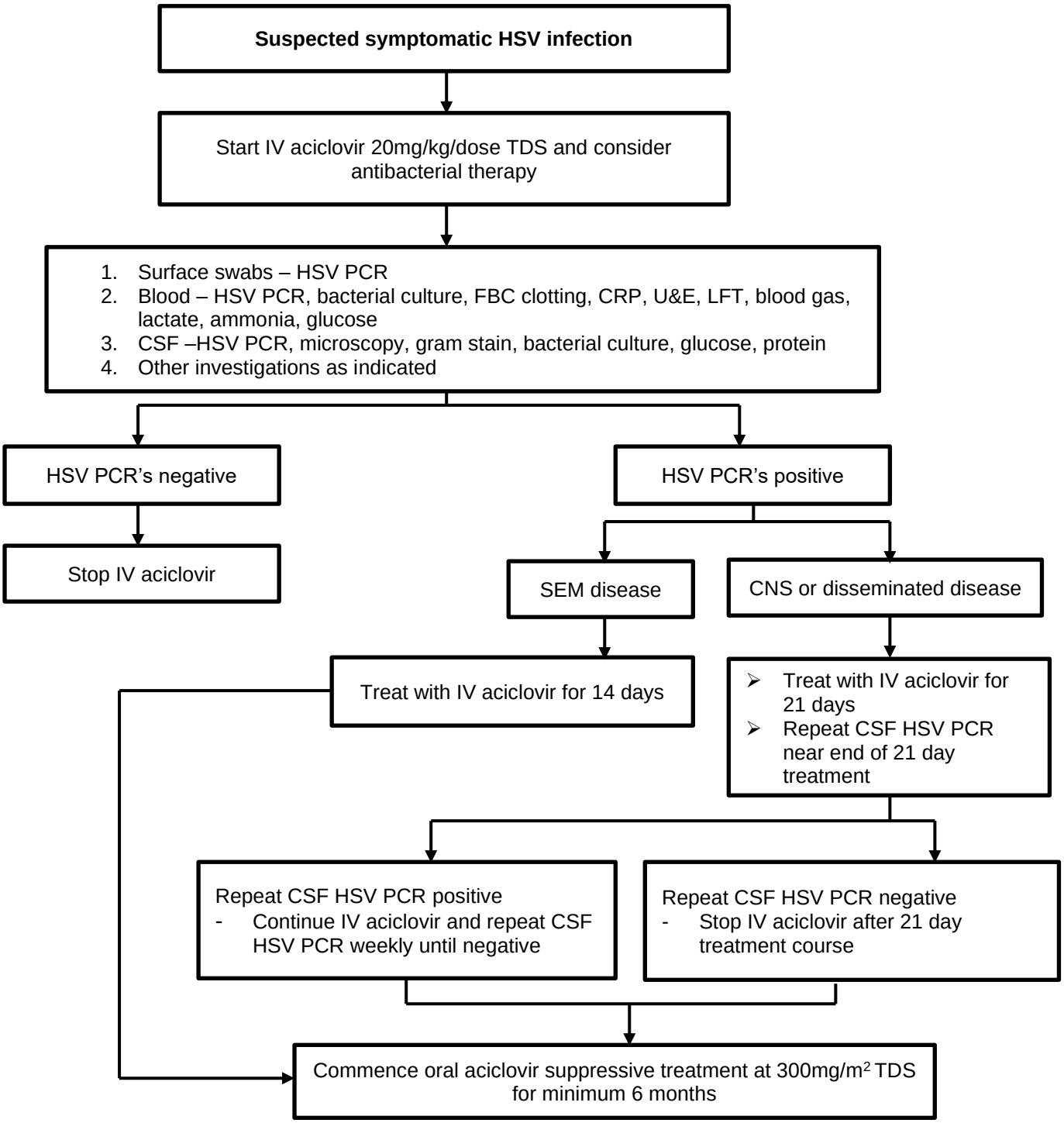
3. For asymptomatic neonates at risk due to exposure to maternal active genital lesions at birth, consult the NNU Herpes Simplex UHL Neonatal Guideline. This provides recommendations on which groups would require empirical aciclovir (refer to NNU Herpes Simplex UHL Neonatal Guideline)

In cases of suspected CNS or disseminated disease empirical treatment for bacterial meningitis and sepsis should be given concurrently. Please see Meningitis Meningitis UHL Childrens Medical Guideline and Sepsis guidelines in children Sepsis UHL Childrens Hospital Guideline.
An LP is essential for diagnosis of HSV infection and should only be delayed if contraindicated. Please see the paediatric Lumbar Puncture guideline Lumbar Puncture UHL Childrens Hospital Guideline for contraindications and document clearly the reasons if an LP is not performed on presentation. Normal CSF indices are shown in Appendix 1.

Please note that CSF studies may be normal and CSF HSV PCR may be negative early in the disease. If there is on-going clinical suspicion, continue IV aciclovir treatment if there is still clinical concern pending additional, repeat sampling and testing. Consider obtaining a repeat CSF sample within the first week.

It is imperative that HSV PCRs are sent when IV aciclovir is started so that decision can be made subsequently whether to continue or to stop antiviral therapy.

Algorithm 1. <u>Management of suspected HSV disease in a symptomatic infant.</u>



If the baby presents with any additional symptoms/signs/lab abnormalities over and above skin and mucous membrane lesions, they should be managed as disseminated disease. Even if there is a potential alternative explanation for those abnormalities, they should be assumed to be due to the neonatal herpes unless clear proof otherwise.

2.4 On-going Management

Aciclovir

Intravenous access

A long line should be sited to minimise cannulation episodes.

IV Aciclovir must be used for initial treatment phase

- The oral bioavailability of aciclovir and valaciclovir is unpredictable and there is no place for using these agents in this initial phase of treatment.
- **IV aciclovir therapy should be used for all categories of HSV infection i.e. SEM, CNS and disseminated disease.**
- During aciclovir treatment, maintain adequate hydration, monitor neutrophil count, renal function and infusion site.

Oral aciclovir suppressive therapy

- Oral aciclovir 300mg/m^2 TDS for 6 months after initial parenteral aciclovir reduces the risk of skin recurrences in all children with neonatal HSV disease (regardless of categories of disease) and improves neurodevelopmental outcomes in those with CNS disease.
- Duration of aciclovir suppressive therapy may be extended to 12 months among those with HSV eye disease and at risk of impaired vision with reactivation.
- Neutrophil counts should be checked at 2 and 4 weeks and then monthly during treatment.

2.5 Supportive Treatment

Includes careful fluid balance and monitoring for and treatment of seizures, coagulopathies, shock and respiratory compromise. Babies may require PICU care.

2.6 Specialist Opinions

Neurology – CNS disease
Hepatology – liver dysfunction (transplantation has occasionally been required)
Haematology – Coagulopathy
Opthalmology – Eye disease

2.7 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.

3. Education and Training

None

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Correct investigations completed in cases of Encephalitis	Retrospective notes audit	R. Radcliffe	3 yearly	Presentation at departmental audit meeting
Correct length of treatment course in HSV Encephalitis	Retrospective notes audit	R. Radcliffe	3 yearly	Presentation at departmental audit meeting

5. 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. Meningitis UHL Childrens Medical Guideline C22/2014

5. Sepsis UHL Childrens Hospital Guideline B31/2016

6. Antibiotics for Neonatal Infection UHL Neonatal Guideline C54/2019

7. Herpes Simplex UHL Neonatal Guideline C48/2020

8. Lumbar Puncture UHL Childrens Hospital Guideline C82/2007

9. Genital Herpes in Pregnancy UHL Obstetric Guideline C11/2013

6. Key Words

Aciclovir, Genital, Herpes Simplex Virus (HSV), Infection, Lesions

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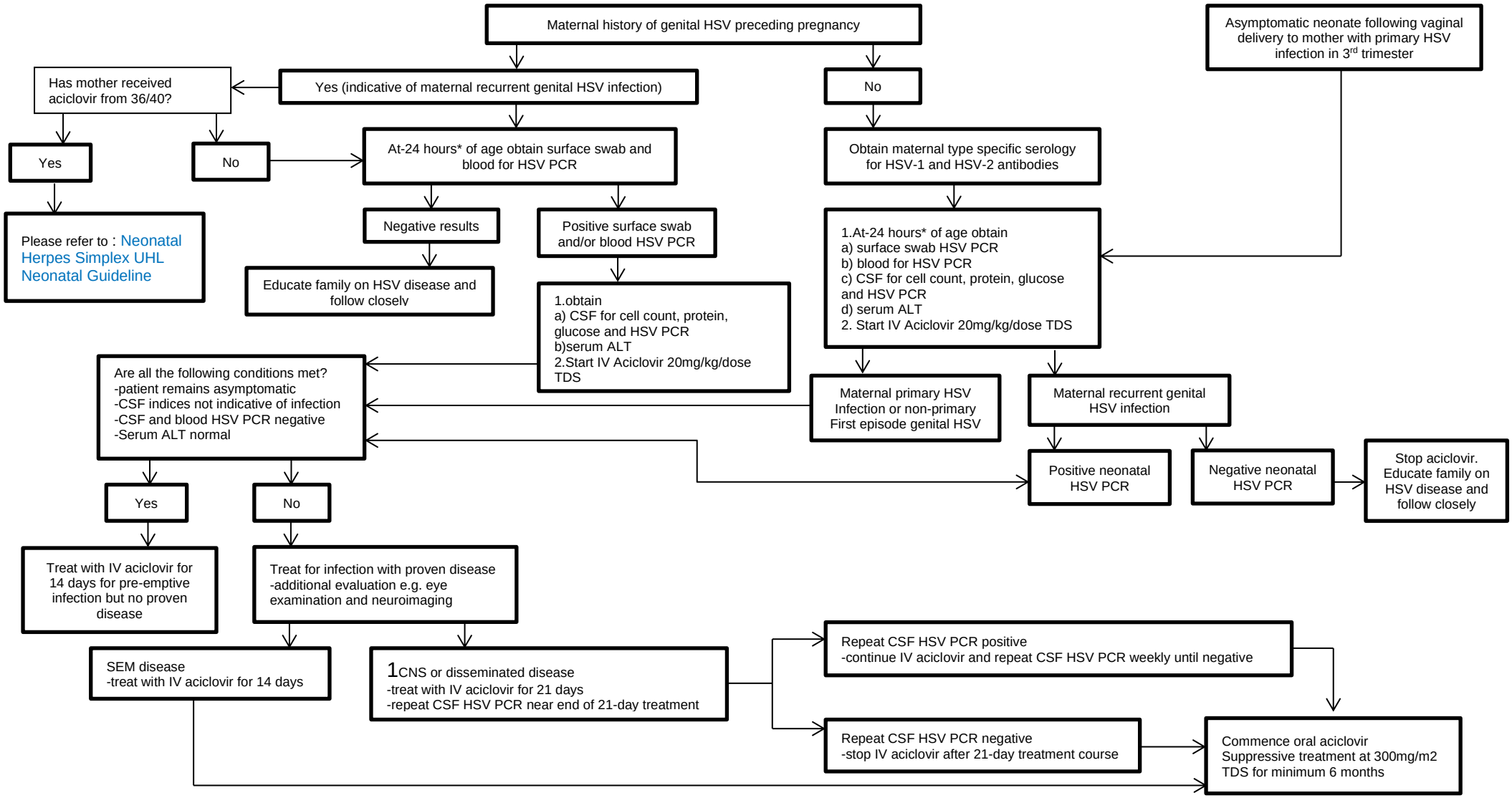
The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality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

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Ruth Radcliffe - Consultant	**Executive Lead** Chief Nurse
Details of Changes made during review: • Highlighted that Babies may only have a single sign or symptom at presentation • When requesting HSV PCR (*EDTA tube*) need to use a hand-written request form; the correct request is not available on ICE.	

Appendix 1: CSF Normal results

Age of Child	RBC/mm3	WBC/mm3	Protein (g/l)	Gluc (mmol/l)
<28 days	<10	<20	0.15 – 1	>50% blood gluc
>28 days	<10	<5	0.15 -0. 45	>50% blood gluc

Appendix 2 Algorithm 2. Management of asymptomatic infant born to mother with active genital HSV lesions.



*Immediate evaluation and treatment should be considered if the infant is symptomatic of HSV disease, premature (<37 weeks of gestation) or if there is prolonged rupture of membrane >4-6 hours.