# Treatment of Herpes Simplex Virus in the newborn

## Part 1

### Approval and Authorisation

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Purpose

The purpose of this guideline is to ensure that those at risk of acquiring infection with the Herpes Simplex virus are detected and managed appropriately in the neonatal setting.

Function of the policy

This guideline provides guidance on the detection and management of infants at risk of acquiring the Herpes Simplex Virus. It is for use on the maternity unit of the Royal Berkshire Hospital. It is for the use of all health professionals involved in looking after the newborn infant.

Introduction

Herpes simplex virus (HSV) has been associated with neonatal disease for more than 6 decades. Over the past 20 years, there have been major advances in our knowledge of the epidemiology, pathogenesis and natural history of the disease. In addition, the availability of effective antiviral therapy has resulted in major advances in the management of neonatal HSV infections. Despite these advances, HSV remains a major cause of morbidity and mortality among neonates.

Genital Herpes – Aetiology:

- Herpes simplex virus type 1 HSV-1 the usual cause of oro-labial herpes
  - Or
- Herpes simplex virus type 2HSV-2 historically associated with sexual transmission

Natural History

- Infection may be primary or non-primary. Disease episodes may be initial or recurrent, and be symptomatic or asymptomatic. It is likely that the majority of infections are acquired subclinically as at least 80% of people seropositive for HSV type specific antibodies are unaware that they have been infected.
- Primary genital herpes in the UK is now known to be equally caused by HSV-1 as by HSV-2.
- Following primary infection, the virus becomes latent in local sensory ganglia, periodically reactivating to cause symptomatic lesions or asymptomatic, but infectious viral shedding. The virus can be shed asymptptomatically from the external genitalia, the anorectum, the cervix and urethra.
In HIV positive HSV-2 seropositive individuals, both symptomatic and asymptomatic shedding is increased, especially in those with low CD4 counts and those who are also seropositive to HSV-1.

Management of Herpes in pregnancy

Guidelines for GH in pregnancy are categorised into management of first episodes and recurrent episodes, and its implication to the fetus and the subsequent neonatal outcome. Transmission of infection to the newborn infant is most often related to viral shedding at the time of delivery. However, approximately 60-80% of women, whose infants are infected are asymptomatic during pregnancy and delivery, and have no history of genital herpes in themselves or their partners.

The category of maternal infection at the time of delivery influences the likelihood of neonatal acquisition of HSV. Infants born to mothers who have true primary infections at the time of delivery are at the highest risk of acquiring HSV, with transmission rates of 50% or more.

For infants born to mothers who have new infections that are nonprimary, the transmission rates vary greatly in different studies, but can be as high as 30%. The lowest risk of neonatal transmission occurs in maternal recurrent infections, transplacental neutralizing antibody having a beneficial effect on neonatal infection. Therefore, if a maternal primary infection occurs late in the pregnancy significant amounts of the antibody may not be transferred to the newborn infant.

(In a large prospective study involving 58,000 women in the USA the risk factors for neonatal herpes were first episode genital herpes, HSV-1 isolation, invasive monitoring, and delivery before 38 weeks gestation and maternal age less than 21 years. Meta-analysis of the problem confirms these findings, and also suggests that the duration of ruptured membranes is a contributing factor to the newborn acquiring HSV).

Primary or First episode infections

- First episode genital herpes has been associated with 1st trimester miscarriage; however, there is no conclusive evidence that it causes developmental abnormalities if the pregnancy continues.

- These women are known to be at high risk of transmitting HSV to their newborn infants. Such women may experience benefit from antiviral treatment of primary or first episode infections and suppressive aciclovir therapy starting at 36 weeks gestation.
Primary HSV in third trimester

- Caesarean section should be offered to women who develop primary HSV in the third trimester (after 28 weeks), notably in the setting where the lesions occur within 6 weeks of anticipated delivery, and adequate maternal seroconversion has not yet occurred. These women should be treated by both the Obstetric and Infection Disease Control Teams.

Recurrent Genital Herpes

- Antiviral treatment is rarely indicated for treatment of recurrent episode of genital herpes during pregnancy, as the mother has pre-existing antibodies to the virus type that has been isolated from the genital tract.

- Symptomatic recurrences during the third trimester are likely to be brief, so vaginal delivery is appropriate if no lesions are present at delivery. Procedures that potentially increase the risk of infection should be avoided such as early rupture of membranes, fetal scalp monitoring and scalp sampling.

If there are no genital lesions at delivery, CS to prevent neonatal herpes should not be performed.

Women in Labour

- During labour all women should be asked about recent symptoms and carefully examined for signs of genital HSV

- In the presence HSV lesions in the perineal area CS is recommended. This mode of delivery may reduce the risk of neonatal HSV infection if performed within 4-6 hours of membrane rupture.

- CS should be performed immediately on a woman who presents with ruptured membranes and active lesions at term.

- In the absence of genital lesions a maternal history of HSV is not an indication for CS.

- Procedures that potentially increase the risk of infection should be avoided when possible in women with active genital herpes, or in those women with a
recurrent infection in the 4 weeks prior to delivery. These include early rupture of membranes, fetal scalp electrodes and scalp sampling.

- For women with history of recurrent genital herpes, who would opt for CS if HSV lesions were to be detected at the onset of labour, acyclovir given from 36 weeks of gestation until delivery may be given to reduce the likelihood of HSV lesions at term.

Further note

- Women who report a history of recurrent genital herpes can be reassured that the risk of transmission to the neonate is very small, even if genital lesions are present at birth,
- Recurrences during pregnancy pose no threat to the pregnancy or risks to the fetus.
- Importantly Neonatal herpes may occur as a result of nosocomial or community-acquired infection. Mothers, staff and other relatives/friends with active HSV infection, such as orolabial herpes or herpetic whitlow, should avoid direct contact between lesions and the neonate (see associated guideline RBH. Management of Herpes Simplex Virus Oro-labial - Part 2. July 2010).

Management of the Newborn Infant

The approach to the management of the asymptomatic infants who were exposed to HSV at the time of delivery, takes into account whether the mother has proven or presumed primary infection, known recurrent lesions or unknown current status. Treatment of established or suspected infection is with acyclovir intravenously. All exposed infants should be monitored for clinical evidence of HSV infection (e.g. skin or scalp rashes, conjunctival lesions, irritability, sepsis). The infant’s parents and caregivers should be educated about the signs of neonatal HSV infection. Infants who develop clinical evidence of HSV infection should undergo full clinical and virologic evaluation, and intravenous aciclovir should be administered while results of virologic evaluation are pending.

Infants Born by Caesarean Section – (see Appendix A)
• Infants born by CS with at least 4 - 6 hours of membrane rupture, whose mothers had herpetic lesions should be observed carefully and cultured. **At, 48 hours**, swabs should be obtained from the throat, eye, mouth and nasopharynx, in the appropriate anti-viral medium (obtained from Virology). Antiviral therapy should not routinely be started for such infants who are asymptomatic, but such therapy should be initiated if culture results from the infant are positive for HSV, or HSV infection is strongly suspected on clinical grounds. Do not delay treatment if there are any clinical concerns. A lumbar puncture should be performed and CSF sent for cells, protein, glucose, culture, viral culture and HSV PCR.

**Infants born by Vaginal Delivery – (see Appendix B)**

• All asymptomatic infants who were exposed to HSV at the time of delivery should have cultures taken at **48 hours of age (see above)**.

• There is no firm consensus regarding the antiviral management of asymptomatic infants whose mothers had proven or presumed primary infection at delivery. However, infants born to mothers who have true primary infection at the time of delivery are at the highest risk of acquiring HSV, with transmission rates of 50% or greater. Therefore it is recommended that prophylactic aciclovir is started. However, before the therapy is initiated the infant should undergo a full infection screen. The duration of the therapy is guided by the emerging laboratory results.

• An infant whose mother has known **recurrent**, genital herpes and active genital lesions at delivery, should be observed carefully for evidence of infection, and swabs cultures should be taken at 48 hours of age, and if positive treated with aciclovir. Or if the infant develops signs/symptoms of HSV infection. If these infants have the additional factors that increase the risk of HSV infection e.g. prematurity, scalp electrodes or skin lacerations, they should be monitored very carefully. Do not delay treatment if HSV is suspected.

• An infant, whose mother had recurrent genital herpes during pregnancy but no lesions, at the time of delivery,. Should be observed for signs of infection. Swabs do not need to be taken, unless HSV suspected.

• The length of observation in hospital for infants at increased risk of HSV infection should be individualised, taking into account local resources; adequacy of observation at home, and the nature of follow up care. Once home the caregivers should be vigilant, and rashes and symptoms should be appropriately evaluated.
Further Note

Any symptomatic infant should be evaluated for possible HSV infection, as part of a complete evaluation for sepsis, particularly when this is accompanied by liver dysfunction. In addition HSV should be considered in neonates with fever and irritability and with any abnormal CSF findings, particularly when accompanied by seizures. PCR testing of the CSF for HSV DNA is recommended for all such infants. They should also have swabs sent, from mouth, conjunctiva, nasopharynx and skin lesions (if any).

Infection Control Measures

• Women who have HSV lesions should be managed during labour, delivery and post natally with routine infection control measures. Mothers should have good hand hygiene measures before handling their infants, but do not need to be isolated.

• Breastfeeding to be encouraged unless lesions are present on the breast

• Mothers with oral herpes should follow the guidelines as detailed in the protocol - Herpes simples virus in the newborn – Oro-labial Part 2 - RBH foundation Trust 2010, and abstain from kissing or nuzzling their infant until the lesions have cleared

Treatment of infants with HSV infection:

Aciclovir therapy:

Aciclovir is the antiviral agent of choice for the treatment of HSV infection, and should be administered at the time the diagnosis of HSV is suspected. Recent data support the use of high dose aciclovir (60mg/kg day in 3 divided doses) for the treatment of neonatal HSV. Data from a large collaborative study suggests that mortality and morbidity were lower in infants who were treated with higher doses of aciclovir. Data also supports the use of 21 days duration of therapy for CNS/disseminated disease. Prompt administration improves outcome and survival. Before treatment is initiated the following tests should be performed:

• Complete blood count, including differential and platelet count
• LFT’s
• U & E’s assessing renal function and hydration status
• CSF – cell count, glucose ,protein ,culture, viral culture HSV DN PCR
• Viral culture of blood, urine, tracheal aspirate
• Swabs/ scrapings of skin for viral culture
• Surface cultures from the mouth, nasopharynx, conjunctiva and stool (if possible)
• Chest X Ray

Dose of aciclovir:

60mg/kg/ per day in 3 divided doses intravenously (but adjusted if there is renal failure). Oral aciclovir is not recommended due to poor absorption.

1. The duration of aciclovir therapy for neonatal HSV, depends upon the pattern of illness and response to therapy. Localised skin, eye, and mouth disease should be treated for a minimum of 14 days if disseminated and CNS diseases have been excluded. Disseminated and CNS disease should be treated for a minimum of 21 days, because the persistence of HSV DNA in the CSF is associated with a poorer outcome. A repeat LP towards the end of therapy is recommended to make sure the HSV DNA PCR is negative. Disseminated disease involves multiple organs, notably the liver and lungs. Neonates with localised CNS or disseminated disease do not necessarily have skin lesions.

2. In addition to intravenous aciclovir, if there is ocular involvement due to HSV infection then the infant should receive a topical ophthalmic agent.

3. Adverse effects due to the aciclovir are rare, but close monitoring of the renal function is important. It is essential to maintain hydration, to prevent crystallisation in the renal tubules and can occur if the infant is dehydrated. Also seizures may occur in infants with impaired renal function or failure.

4. There is no data to suggest that immunoglobulin’s are of value in the treatment of HSV infection.

Follow-up

Given the potential for significant neurological sequelae among survivors of neonatal HSV infection, affected infants should be followed carefully. They should have a structured follow-up programme that allows for neurodevelopmental, ophthalmologic and hearing assessments. Recurrent skin lesions in the first 6 months of life can be associated with CNS sequelae, consequently CSF examination and PCR testing along with intravenous aciclovir are recommended, at the time of the recurrent skin lesions, but is at the discretion of the Consultant. In difficult clinical situations discussions with a paediatric infectious disease consultant may be warranted.
Outcome

The outcome of neonatal HSV infection depends upon the clinical pattern, HSV infection is lifelong even with appropriate therapy. Recurrence of mucocutaneous lesion, eye disease and/or CNS disease may occur especially during the 1st year of life. The 1 year mortality rate for CNS/disseminated disease is between 4 – 29%. It is known that the risks increase if there has been acute liver failure, coma or near coma at the time of the presentation of the disease. However, approximately 80% of survivors at 1 year may have a normal neurologic development, if they did not suffer from seizures, at, or before the initiation of antiviral therapy. Severe hepatitis caused by either HSV-1 or 2 may cause potentially fatal acute liver failure.

Mortality is rare in neonatal HSV disease that is localised to the skin, eye and mouth (in whom CNS/disseminated disease have been excluded). The risks of neurodevelopmental abnormalities are increased in infants with >3 recurrences of skin lesions before 6 months of age.

Further research issues

- The optimal management of pregnant women with genital HSV as this relates to the use of aciclovir prior to delivery
- The management of women with known or presumed primary HSV who present with premature rupture of membranes, and also the implication to the fetus
- The pharmacokinetics of aciclovir in very low birth weight infants
- The impact of long term suppressive therapy on the infants 1) neurological status and 2) immune responses
- Future role of combination antiviral therapy with aciclovir plus monoclonal HSV antibodies
- Development of vaccines against HSV
Appendix A

Infants Born by Caesarean Section

- <4-6 hours rupture of membranes
  - Examination at 48 hours
    - No clinical signs of HSV. Exam normal → Home and information
    - Clinical signs of HSV
      - Full infection screen. Treat with IV Aciclovir for total of 14/21 days
        - +ve swabs and/or clinical signs of HSV → Home and follow up.
        - -ve swabs Exam normal → Home and information

- >4-6 hours rupture of membranes
  - Cultures / exam at 48 hours
    - +ve swabs → -ve swabs
    - Exam normal
      - Home and information
Appendix B

Infants Born by Vaginal delivery

Known recurrent HSV + lesions

-ve cultures Normal exam

Home + information

+ve cultures or clinical signs

Full infection screen. Treat with IV Acyclovir for total of 14/21 days

Primary HSV + lesions

Cultures at 48 hours + Exam

-ve cultures Normal exam

Home + information

+ve cultures or clinical signs

Abnormal

Clinical exam

Normal

Recurrent HSV No lesions

Home + follow up

Known recurrent HSV + lesions

Recurrent HSV No lesions

Policy Lead: Urgent Care Group Director

Location: Corporate Governance Shared Drive – GL374
References

1. 2007 National Guidelines for the management of Genital Herpes (clinical effectiveness Group (British Association for sexual health and HIV)


