NEONATAL HSV INFECTION

KEY POINTS

- Neonatal HSV infection is a rare, but potentially fatal, disease of babies, occurring within the first 4-6 weeks of life. Symptoms are non-specific and a high index of suspicion is required.
- Most neonatal HSV infections are acquired at birth, generally from mothers with an unrecognised genital herpes infection acquired during pregnancy.
- Any baby developing skin vesicles or atypical bullous, pustular skin lesions, particularly on the scalp or face (vaginal deliveries) or over the buttocks (breech presentation) must be referred immediately to a paediatrician.
- Specialist obstetric and paediatric advice on management and anticipatory guidance should be sought for a woman with a history of genital herpes and active lesions at term and especially in the high-risk situation of a first episode within 6 weeks of delivery.

Neonatal HSV infection rates vary from country to country, with national surveys reporting a wide range in annual incidence. The number of cases per 100,000 live births in Western Europe (France 1.15, United Kingdom 1.65, and the Netherlands 3.2)[70-72] is lower than reported for Scandinavia (Sweden 6.5)[73] and North America (USA 9.6 and Canada 5.9).[74,75] Marked differences in incidence can also exist within countries.[46]

The differences in reported rates is likely multifactorial, including differences in case definition and study design as well as differences in rates of HSV acquisition amongst maternal populations. Reliable New Zealand data are lacking but a prospective national active surveillance in Australia from 1997 to 2011 found an incidence of 3.7 per 100,000 live births.[76,77] This incidence was stable over this time period but noted a significant increase in the cases of HSV-1 infections compared to HSV-2 (OR, 1.10 95% CI, 1.00–1.21). This study also found a decrease in mortality in the later part of the study. Prospective longitudinal data of this nature are helpful in providing accurate incidence and epidemiological data to help guide effective education and prevention strategies.[78]

Transmission to the Fetus and Newborn

HSV-1 and HSV-2 can be transmitted to the fetus or newborn infant at one of three times: intrauterine, perinatally and postnatally.[46] However, the majority of cases of neonatal HSV result from women who acquire genital HSV-1 or HSV-2 infection at or near term.

Intrauterine infection

Intrauterine infection causes approximately 5% of neonatal HSV infection. It results from either transplacental HSV transmission or an ascending HSV infection from the cervix.

Perinatal infection

The main risk of transmission to the neonate is at delivery, where contact with HSV-infected secretions in the birth canal accounts for most neonatal HSV infection.[46] The site of entry is usually the eye, nasopharynx or an abrasion secondary to scalp electrodes or forceps. Roughly 60–80% of infants with neonatal HSV disease are born to women with unrecognised infection.[79,80]

Several factors influence the risk of the newborn acquiring HSV infection, the most important of which is whether the mother has newly acquired or recurrent genital disease.[42,43] **The risk is greatest when a previously seronegative woman acquires genital herpes (HSV-1 or HSV-2) near the time of delivery.** Under such circumstances the risk of neonatal HSV infection is 50%, while vertical transmission rates of 25% are found in those with a non-primary first episode (infection with one virus type, e.g. HSV-2, in the presence of antibodies to the other virus type e.g. HSV-1).

In contrast, the transmission rates are lowest for women who acquire herpes before pregnancy, with the risk being about 0.05% for such women who have no signs or symptoms of an outbreak at delivery.[42,45] If lesions are present at delivery, there is a small but still significant risk of transmission of 0.25–3%.[43] High maternal titres of type-specific neutralising antibody are associated with a substantially lower risk and severity of neonatal infection; risk factors include invasive obstetric procedures, such as fetal scalp electrodes, method of delivery, and prolonged rupture of membranes.[43] Recent studies report an increasing proportion of genital and neonatal herpes infection from HSV-1 strains.[74,76]

Postnatal infection

Postnatal infection accounts for approximately 10% of cases. Sources of postnatal HSV infection include maternal breast milk, skin and oral lesions, and HSV lesions on caregivers, other family members and medical staff, having close contact with the newborn.

Disease Classification

Intrauterine HSV infection

This is rare and usually occurs after primary herpes infection in pregnancy. Transplacental transmission before the 20th week of pregnancy may cause spontaneous abortion in as many as 25% of cases. In contrast to neonatal herpes infection, the signs of intrauterine HSV infection are present at delivery and may include intrauterine growth retardation, hydranencephaly, chorioretinitis and skin scarring. The long-term outlook for these infants is very poor. A minority with intrauterine HSV infection will present at delivery with skin or eye lesions. There is frequently a history of prolonged rupture of membranes, often as long as 2 weeks. The prognosis for successful anti-viral therapy in these infants is better than that for newborns with more long-standing intrauterine infection and complications such as hydranencephaly, but a small group will have severe, disseminated disease or fatal pneumonitis.[38]

Neonatal HSV infection

There is no clear pattern of signs and symptoms that identifies babies with neonatal HSV disease, meaning a high index of suspicion is required.

Presenting symptoms of neonatal HSV infection include fever, lethargy, seizures and respiratory distress. Vesicles may be present in only 40% at presentation and some infants will have no vesicles at any time during the course of their illness.[81,82] Fever may be absent initially.[79] Mortality is highest in those with an altered conscious state, seizures, disseminated intravascular coagulation, and prematurity.[38,68]

The usual age for onset of symptoms in neonatal HSV infection is between 5 and 21 days of life, but there may be a delay in presentation if the significance of the symptoms is not initially recognised. Physicians caring for sick infants in the first 6 weeks of life should always be aware that neonatal HSV infection remains a possibility, even when no parental history of herpes infection is given.[74]

Presentation is divided into three categories (Table 2), each of which has different clinical symptoms and outcomes. There is overlap within these categories and patients can progress from one category to another if not treated early.

Table 2: Classification of Neonatal HSV Infection[46]

Type (% of Total)	Mortality		Mean Age at Presentation	Normal Outcome	
	Untreated	Treated		Untreated	Treated
SEM (45%)	< 1% (70% progress)	0%	10–11 days	62%	98%
CNS (30%)	50%	6%	16–19 days	33%	31%
DIS (25%)	90%	30%	9–11 days	50%	83%

SEM = Skin, Eyes and/or Mouth; CNS = Central Nervous System; DIS = Disseminated

Skin, eyes and/or mouth (SEM) infection[79]

Nearly half of neonates with HSV infection will present with lesions confined to the skin, eyes or mucous membranes. This is the most readily recognised form of the disease, with most babies having vesicular skin lesions at sites of trauma, such as over the presenting body part, fetal scalp electrode sites and eyelid margins. Lesions usually appear between one and two weeks of age but are sometimes evident shortly after birth when prolonged rupture of membranes has been present. Typically, vesicles overlie an erythematous base and contain clear or slightly cloudy fluid. Need to look carefully for eye involvement as this can initially be asymptomatic with early ophthalmologic review if symptoms appear.

Although rarely fatal if lesions are confined to skin and mucosal sites, without antiviral treatment many neonates progress to either the disseminated or CNS forms of the disease. In addition, more than one-third of those with untreated localised SEM lesions develop signs of major neurological impairment such as microcephaly, spastic quadriplegia or sensory loss by 12 months of age. A study of infants with presumed SEM disease reported that 24% had HSV DNA detected in their CSF by PCR testing, suggesting that HSV can infect the CNS without overt neurological symptoms.[83]

There are data to suggest that three or more recurrences of cutaneous vesicles in the first 6 months of life are predictive of poor neurological outcome.[84] Specifically the likelihood of developing normally is nearly 100% when there are fewer than three recurrences within the first 6 months of life compared with only 79% when three or more recurrences occur during this period. At the time of such episodes PCR detection of HSV-DNA in the CSF may explain the emergence of new neurological deficits.[85]

Central nervous system (CNS) disease

Almost one-third of neonates with HSV infection will have only encephalitis. Infants usually present between 10 days and 4 weeks of age with symptoms of fever or temperature instability, lethargy, poor feeding and irritability, followed by seizures, a bulging

fontanelle and focal neurological signs. Cerebrospinal fluid (CSF) findings typically include 50–100 white blood cells x 106 per litre, predominantly mononuclear cells, normal to low glucose and elevated protein concentrations, both of which increase over the first few days. At presentation many are devoid of skin lesions but overall 60–70% will have skin vesicles at some point during the disease course.[79]

Untreated, the mortality rate approaches 50% with most survivors suffering severe neurological impairment. Morbidity is higher among infants with HSV-2 infection than among those with HSV-1 infection.[46] Even with the use of high dose aciclovir, morbidity has shown little improvement. Relapses may occur.

Disseminated disease (DIS)

Disseminated disease develops in about one-quarter of neonates with HSV infection. It is more common in preterm infants and carries the worst prognosis. Symptoms generally develop in the first 14 days of life. Clinical findings include a sepsis-like presentation with respiratory distress, haemodynamic instability, jaundice, hepatomegaly, elevated liver enzymes, bleeding with associated coagulopathy, and seizures with signs of meningitis, encephalitis or respiratory failure. Vesicular skin lesions may not be present in up to 50% of cases. Mortality in untreated patients is approximately 90% and even with antiviral therapy, may still be as high as 20–30%.

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. Other infectious agents that might be considered are toxoplasmosis, rubella and syphilis. Finally, non-infectious cutaneous disorders that could be confused with neonatal HSV infection include erythema toxicum, neonatal pustular melanosis, acropustulosis and incontinentia pigmenti.

Management of Neonatal HSV Infection

Evaluation

The poor prognosis associated with untreated neonatal HSV infection means that every effort should be made to obtain a diagnosis as early as possible. This includes prompt communication with the mother's lead maternity caregiver. Many cases present with a sepsis-like clinical picture without identifiable risk factors; many with disseminated or CNS disease will initially lack skin lesions to assist in a timely diagnosis. A high level of suspicion is required.

Management of suspected neonatal HSV infection

Successful management relies on a high index of suspicion of HSV infection and early institution of therapy. Only about 40% of affected neonates will initially have skin lesions and most lack a parental history of genital herpes.[46,81,82]

Consequently, physicians should consider neonatal HSV infection when confronted with an infant younger than 6 weeks of age who has vesicular or atypical bullous, pustular skin lesions or a progressive febrile illness without a bacterial cause. 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, pneumonitis, thrombocytopaenia, 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.[80]

Skin and oral lesions must be carefully looked for on a daily basis, particularly on the scalp and face (vaginal deliveries) or over the buttocks (breech presentation) as these may develop later in the course of disseminated and CNS disease. The index of suspicion is heightened by progressive abnormalities of liver function, particularly during the first week of life. When neonatal HSV infection is considered likely, undertake diagnostic tests and administer aciclovir immediately, before the results of definitive investigations are available.[86] GRADE A Aciclovir should be considered for an unwell infant without clinical improvement and negative bacterial cultures at 48–72 hours.[87]

Diagnosis

In the presence of vesicular lesions, the base of the lesion should be scraped and sent for PCR; it requires operator expertise in obtaining an adequate specimen and a negative result should be interpreted with caution.

As neonatal HSV infection may occur in the absence of skin lesions, other diagnostic specimens are required. In addition to testing any cutaneous lesions, swabs of the nasopharynx/mouth, conjunctiva, umbilicus, rectum **plus** urine should be performed. Swabs are best deferred until >24 hours of age. This delay is to avoid possible contamination by maternal cervico-vaginal secretions, positive results after 24 hours should reflect viral replication.

CSF should be taken for HSV PCR testing as well as usual parameters of cell count, protein and glucose. Whole blood PCR should also be performed to assist with diagnosis of neonatal HSV infection.

PCR is a rapid, highly sensitive and specific technique, which detects minute quantities of viral DNA. It is more reliable than viral

culture for CNS infections. However, although the presence of a positive PCR is highly predictive of infection, a negative result does not eliminate the possibility of disease.[88] A negative CSF PCR should be evaluated in conjunction with the entire clinical picture including other diagnostic modalities, and should not be used on its own to exclude CNS herpes disease. Grade A

Liver function tests, including serum transaminases may indicate HSV hepatitis and a CXR may diagnose pneumonitis.[83,89] These tests are performed on **all** infants suspected of neonatal HSV infection. Grade A

Neurological imaging – CT or MRI brain scan and EEG should all be considered as an important adjunct to diagnosis. MRI and CT scan can be normal early in the disease course and do not rule out HSV CNS disease.

An ophthalmology consultation should be sought in suspected or confirmed cases of neonatal HSV infection, to help identify and monitor ocular complications that may arise during the illness. Grade C

In addition, a sexual history from the parents is taken. The mother's lead maternity caregiver is asked to obtain HSV PCR of maternal genital secretions and to perform type-specific HSV serology. This is important, even when the presentation is weeks after the delivery.

Treatment

Intravenous aciclovir (20mg/kg every 8 hours) decreases the mortality and morbidity of neonatal HSV infections (see Table 2 on page 26).[83,86,90] Early therapy improves neurological outcome. The treatment duration is 14 days for SEM disease and a minimum of 21 days for CNS and disseminated infections.[90] The recommendation for the longer course of aciclovir also includes those infants with SEM disease with abnormal CSF parameters, including HSV DNA detected by PCR. Grade A & B

For neonates with ocular involvement topical therapy may be required and an ophthalmologist should be consulted. For pre-emptive therapy in high risk asymptomatic infants without laboratory confirmation 10 days therapy with aciclovir is recommended.[91,92]

All infants with HSV CNS involvement should have a lumbar puncture at the end of aciclovir therapy to determine if the CSF is PCR negative for HSV. For those neonates when end of treatment CSF is still PCR positive the American Academy of Pediatrics recommends repeating CSF a week later and if still positive a further week later and if persistently positive discuss with an infectious disease specialist.[93] Others have suggested that neonates with PCR positive should continue receiving intravenous aciclovir until viral DNA in the CSF is no longer detected.[68,83] Grade B Aciclovir-resistant neonatal HSV remains rare.

A double-blind placebo-controlled study found that infants surviving neonatal HSV disease with CNS involvement had improved neurodevelopmental outcomes when they received suppressive therapy with oral aciclovir, 300mg/m2/dose administered 3 times daily for 6 months.[92] Use of oral aciclovir suppressive therapy also reduced skin recurrences in infants. Regular monitoring of neutrophil count needs to occur while on suppressive aciclovir therapy, with 20–25% of study patients developing neutropenia while receiving aciclovir.[94] Oral valaciclovir has not been evaluated for use as suppressive therapy. Grade A

Suppressive therapy can be considered in infants with recurrent SEM disease, but it has not been shown to alter neurological outcome.[92]

General management points

A monocytic leukocytosis in the CSF is suspicious of CNS HSV infection.[95] Treatment with aciclovir should be instituted before HSV PCR results are available. Aciclovir can be discontinued if an alternative diagnosis has been established or the clinical course is no longer compatible with HSV CNS disease, viral PCR testing is negative and a CT or MRI head scan is normal or does not suggest HSV encephalitis. Be aware, however, that a negative initial HSV PCR result does not exclude CNS disease. It is well established that neonatal HSV CNS infection may occur despite the findings of normal CSF counts and biochemistry, and that a negative CSF HSV PCR result may occur, especially if the lumbar puncture was performed early in the course of the illness.[83,96] Consequently, repeat lumbar puncture is recommended when laboratory tests are negative but clinical suspicion remains high. Grade B & C

Empirical treatment with aciclovir is recommended if, an infant remains critically ill despite antibiotic therapy and disseminated HSV cannot be excluded, if bacterial cultures are negative, or there are signs of progressive liver dysfunction with coagulopathy.[97] Grade C

In addition to the administration of aciclovir, other important aspects of the infant's management include:

- Respiratory support.
- Control of circulation.
- Management of seizures.
- Maintenance of fluid and electrolyte balance.
- Correction of coagulopathy.
- Administration of antibiotics for concomitant bacterial infections.

Infants with neonatal HSV disease should be managed by contact precautions throughout the course of their illness.[98] Grade C

Follow-up of neonatal HSV infection

Long-term follow-up in survivors is instituted to monitor for sequelae and should include assessment of hearing, vision and neurodevelopment. Grade C

When a cutaneous recurrence occurs full clinical examination should be performed. If any evidence of systemic involvement is present, e.g. fever and especially irritability, a CSF examination, including HSV DNA PCR, should be performed. A low level of suspicion should be used to initiate parenteral aciclovir therapy. Abnormal result should lead to a further course of intravenous aciclovir being administered, followed by suppressive oral aciclovir until at least 6 months of age. GRADE C

Counselling

Neonatal HSV infection causes considerable stress within the family. The experience of many is that most couples eventually separate.[99] 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.** GRADE C

GUIDELINES FOR TALKING TO PARENTS OF A BABY DIAGNOSED WITH NEONATAL HERPES

Being comfortable with discussing the diagnosis (what, why, how, etc.) is critical to the parents' ability to understand and come to terms with what has happened. The following points are additional to **Key Information for Health Professionals to Give Patients in Counselling** (see page 34).

- Parents are likely to be shocked, and feeling both grief and shame, which may be expressed as anger and/or withdrawal from staff.
- A crisis of this nature may well trigger a relationship crisis and health professionals can act most usefully by listening and not attributing blame to either parent.
- Parents need to know that healthcare providers do not blame them for the baby contracting HSV (attitudes are conveyed verbally and non-verbally).
- Although one or other parent may have had previous knowledge that they have HSV, it is most common for people not to know and be undiagnosed.
- Most neonatal herpes happens when a woman experiences a 'silent' (asymptomatic) primary episode in late pregnancy.
- Many people do not realise that cold sores are caused by HSV and may be passed through oral sex. A primary HSV-1 episode of genital herpes in late pregnancy creates a high risk for neonatal transmission.
- Given the social stigma of STIs, parents may be unable to initiate a conversation with healthcare providers or ask the questions that are worrying them. Health professionals need to take the initiative in addressing possible concerns. An opening line such as, "many parents wonder about… is this a concern for you?" is useful for normalising parental queries.
- Health professionals need to convey that they are comfortable talking about adult sexuality; that intercourse and oral sex are normal practices when a woman is pregnant and that HSV may have been transmitted during sexual activity in pregnancy.
- Health professionals may need to initiate a conversation about sexual transmission, e.g. "would it be helpful if I explained to you how the virus is passed?"
- Advise parents regarding any transmission precautions with regard to other siblings and family members, otherwise parents may initiate precautions they imagine to be necessary.

See page 34 for Key Information for Health Professionals to Give Patients in Counselling and consider referring to the Herpes Helpline tollfree 0508 11 12 13.

Anticipatory Management of Newborn Infant with Known Risk for Neonatal HSV[91,100]

High risk

This category involves a subgroup of infants born to mothers with their first episode of genital herpes during late pregnancy, that is, those women infected near or at term. A paediatrician experienced in identifying the signs of neonatal HSV infection should examine these newborn infants. GRADE C

Women with first episode genital HSV infection associated with either genital lesions or subclinical shedding at delivery have a 25–57% chance of transmitting HSV to their babies if they deliver by the vaginal route.[42] Although not completely protective against neonatal HSV disease, elective caesarean section significantly reduces the risk of transmission and is recommended for pregnant women who have a known or presumed first episode of genital herpes within 6 weeks of delivery, even if receiving suppressive anti-viral therapy.[42] GRADE B

Because of the high risk of infection, an asymptomatic infant inadvertently delivered vaginally from a woman with active first episode genital lesions should be managed as for suspected neonatal HSV infection. This means the immediate collection of specimens, including CSF, for cell count, chemistry and PCR testing, HSV blood PCR, full blood count, liver function tests and surface HSV PCR swabs, ideally at 24 hours but earlier if clinically indicated. Anticipatory aciclovir therapy should be initiated. Duration of aciclovir will depend on surface HSV PCR and CSF results. Also check the mother's total and type-specific HSV serological status, to confirm that this is a first episode of genital herpes and not a recurrence. GRADE C

Similarly, when the woman has active first episode genital lesions and is febrile, or has ruptured membranes for more than 4 hours, or when fetal scalp electrodes or forceps have been used, irrespective of the mode of delivery, the infant should be managed as for suspected neonatal HSV infection. GRADE C

Anticipatory aciclovir therapy can be discontinued if the neonate remains well, HSV PCR and molecular diagnostic testing have not identified HSV, and the CSF studies including PCR results are normal. If the HSV PCR of surface swabs only is positive and the neonate remains clinically well aciclovir treatment should continue for 10 days.[100] Treatment is continued for 14 days when HSV is identified but CSF results are normal, and for 21 days if there is an abnormal CSF finding.[101] GRADE B & C

Low risk

Within this category are most infants born to mothers with their first episode of genital herpes during pregnancy and those with recurrent genital lesions at the time of delivery. A paediatrician experienced in identifying the signs of neonatal HSV infection should examine these newborn infants. GRADE C

Anticipatory guidance including surveillance HSV PCR testing, but no empiric aciclovir, is reserved for well appearing infants without skin or mucosal lesions at birth and born to mothers within the following categories: GRADE B & C

1. First episode genital herpes more than 6 weeks before delivery.
2. First episode genital herpes within 6 weeks of delivery where the mother has delivered by elective caesarean section.
3. Active recurrent genital herpes at delivery.
4. History of recurrent genital herpes during this pregnancy.

The examining paediatrician should undertake the following:

Anticipatory guidance

- Document risk of neonatal HSV infection on infant's chart.
  Notify the infant's lead maternity caregiver and general practitioner of risk.
- Educate parents on risks of HSV and instruct them to report signs of fever, respiratory distress, jaundice, lethargy or irritability, poor feeding, skin, eye or oral mucosal lesions.
- If clinical symptoms, skin, eye or mucosal lesions appear, manage as for suspected neonatal HSV infection.

Surveillance HSV PCR testing

- HSV PCR swabs should be taken at 24–48 hours of age (not at birth or within the first 24 hours of life, because of possible contamination by maternal cervico-vaginal secretions).
- HSV PCR swabs should be obtained from eyes (conjunctiva), mouth, nasopharynx, umbilicus, urine and rectum.
- Further clinical and laboratory evaluation, as for suspected neonatal HSV infection, followed immediately by aciclovir therapy is mandated, if HSV PCR testing is positive.[86] GRADE A

For caregivers who develop lesions after delivery

Advise caregivers about hand washing. For mothers with vesicular breast lesions, caution those not to breastfeed while vesicles are present. Particular care when handling the baby must be taken by those with recently acquired or reactivated oral or other skin lesions. In addition to hand washing, this includes covering skin sites and, for herpes labialis or stomatitis, wearing a surgical mask and not kissing the baby until the lesions have crusted and dried.

Breastfeeding and Use of Oral Aciclovir/Valaciclovir

The American Academy of Pediatrics has approved use of aciclovir for treating first episode or recurrent genital herpes in breastfeeding mothers. Although concentrations are high in breast milk and the baby, toxicity is low.[55] GRADE B