

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, the United Kingdom 1.65, and the Netherlands 3.2)^{55,74,75} is lower than reported for Scandinavia (Sweden 6.5)⁷⁶ and North America (the United States 4.0, and Canada 5.9).^{77,78}

Marked differences in incidence can also exist within countries. For example, in the United States the incidence of neonatal HSV infection in Seattle is 31-48, in Atlanta 15-20 and in California 12.1 cases per 100,000 live births.^{47,79,80} While reliable New Zealand data are lacking, in Australia the incidence is estimated at 3.2 per 100,000 live births.⁸¹

These differences in rates may be explained, at least in part, by variations in HSV-1 and HSV-2 seroprevalence rates, which influence the risk of acquiring first episode genital infections during pregnancy.^{79,82} Other possible explanations include different sexual practices, maternal age, types of hospitals surveyed and neonatal and paediatric post-mortem rates. It is fortunate that neonatal HSV infection is a rare disease given the potential for exposure as, for example, 20-30% of the childbearing population in the United States is seropositive for HSV-2.⁸³

Current data collection and case definitions are inadequate to provide sufficiently accurate incidence and epidemiological data, yet these are essential to guide effective education and prevention strategies.⁸⁰

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.⁸⁴

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 at least 85% of neonatal HSV infection.⁸⁵ 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.⁸⁴

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.^{46,47} The risk is greatest when a previously seronegative woman has a primary first episode of genital herpes near the time of delivery. Under such circumstances the risk of neonatal HSV infection is 57%, while vertical transmission rates of 25% are found in those with a non-primary first episode (infection with one virus type in the presence of antibodies to the other virus type).

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.^{46,48} If lesions are present at delivery, there is a small but still significant risk of transmission of 0.25-3%.⁴⁷ 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.⁴⁷ Recent studies report an increasing proportion of genital and neonatal herpes infection from HSV-1 strains.⁷⁸

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 fathers, other family members and medical staff.

Disease Classification

Intrauterine HSV infection

This 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 far better than that for newborns with more long-standing intrauterine infection and complications such as hydranencephaly.⁴⁴

Neonatal HSV infection

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.⁷⁸

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.^{50,86} Fever may be absent initially.⁸⁴ Mortality is highest in those with an altered conscious state, seizures, disseminated intravascular coagulation, and if born preterm.^{44,66}

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

Table 2: Classification of neonatal HSV infection^{44,66,87-89}

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

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 and the liver is the most commonly involved organ from primary viraemia. Multiple organs are seeded by a secondary viraemia, particularly the lung and adrenal glands. Focal embolisation of the brain may occur late in the illness. 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 or encephalitis. Vesicular skin lesions may not be present. Mortality in untreated patients is approximately 90% and many untreated survivors are severely impaired.

Central nervous system (CNS) disease

Almost one-third of neonates with HSV infection will have only encephalitis. It is believed that this represents axonal transmission of the virus to the brain. A history of recurrent genital herpes in the mother can act as a warning sign, since maternal transplacental antibodies may prevent disseminated disease, but not the virus spreading to the brain.⁹⁰ Infants usually present between 10 days and 4 weeks of age with symptoms of fever or temperature instability, lethargy 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, and elevated protein concentrations, both of which increase over the first few days. At presentation many are devoid of skin lesions. Untreated, the mortality rate approaches 50% with most survivors suffering severe neurological impairment. Even with the use of high dose aciclovir, morbidity has shown little improvement.

Skin, eyes and/or mouth (SEM) infection

Nearly half of neonates with HSV infection will present with lesions confined to the skin, eyes or mucous membranes. This proportion has increased in recent decades and is attributed to recognising and treating SEM infection before it progresses to more severe manifestations of the disease.^{78,88} 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.

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.⁹¹ It is also likely that a widespread rash represents underlying viraemia and greater risk of insidious reactivation later in infancy.

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.⁹² 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 techniques can detect HSV-DNA in the CSF, which may explain the emergence of new neurological deficits.⁹³

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. Most cases will present without identifiable risk factors and many with disseminated or CNS disease will initially lack skin lesions to assist in a timely diagnosis.

Management of suspected neonatal HSV infection

Successful management relies upon 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.^{50,86}

Consequently, most 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, thrombocytopenia, 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.⁹⁴

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.⁸⁹ **GRADE A** Aciclovir should also be considered for an unwell infant without clinical improvement and negative bacterial cultures at 48-72 hours.⁹⁵

Diagnosis

As neonatal HSV infection may occur in the absence of skin lesions, other diagnostic methods are required. These confirm the diagnosis and determine the extent of disease.⁴⁴ Acquisition of material for viral culture, from sites such as the eyes (conjunctiva), mouth, nasopharynx, urine and rectum, and from skin lesions (when present) is undertaken.

GRADE A

Liver function tests, including serum transaminases, as well as viral culture and PCR of CSF determine the extent of disease.^{91,96} These tests are performed on all infants suspected of neonatal HSV infection. **GRADE A**

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**

PCR

PCR is a rapid, highly sensitive and specific technique that avoids problems that may affect culture results such as inadequate quantity of specimen, bacterial contamination, and inadvertent inactivation of virus by sub-optimal handling and sample transport delays. Stringent quality control is necessary because of potential contamination by 'carryover' DNA from other biological samples.¹⁹ Interpretation and determination of significance of PCR results needs to be correlated with clinical presentation and course.⁹⁷ A negative 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.

Suitable specimens for PCR include:

- CSF
- Peripheral WBC (EDTA or CPD sample – not heparin)
- Vesicle fluid

Culture

Viral culture should provide a result within 2-4 days and is highly sensitive for HSV in mucocutaneous lesions. However, in contrast to PCR, fewer than 20% of neonates with CNS disease have positive CSF cultures.

Suitable specimens for viral culture include:

- CSF
- Blood
- Vesicle fluid
- Throat swab
- Nasopharyngeal aspirate
- Eye (conjunctival) swab
- Stool or rectal swab
- Urine

Direct immunofluorescence

This is the least sensitive diagnostic technique and is no longer recommended.

In addition, a sexual history from the parents is taken. The mother's lead maternity caregiver is asked to obtain cultures or PCR of maternal genital secretions and to perform total and type-specific HSV serology. This is important, even when the presentation is weeks after the delivery. Infant acute and convalescent serum to determine seroconversion may aid long-term evaluation when clinical suspicion is high but cultures or PCR results are negative. However, in general, serology plays no role in the diagnosis of neonatal HSV disease.

Treatment

Intravenous aciclovir (20mg/kg every 8 hours) decreases the mortality and morbidity of neonatal HSV infections.^{89,91,98} Early therapy improves neurological outcome. The treatment duration is 14 days for SEM disease and 21 days for CNS and disseminated infections.⁹⁸ The recommendation for the longer course of aciclovir also includes those infants with SEM disease but who have abnormal CSF parameters, including HSV DNA detected by PCR. **GRADE A & B**

Infants with persistent HSV DNA in the CSF following completion of antiviral therapy are more likely to die or suffer serious neurological impairment than infants whose post-therapy CSF specimens are PCR negative.^{98,99} All infants with HSV CNS involvement therefore should have a lumbar puncture at the end of aciclovir therapy to determine if the CSF is PCR negative for HSV. Those who remain PCR positive should continue receiving intravenous aciclovir until viral DNA in the CSF is no longer detected.^{66,91} **GRADE B**

As a rule neonatal HSV infections are presumed to be susceptible to aciclovir as the frequency of resistant strains is very low in this population. Use of agents such as foscarnet should only be considered if there is a slow response to therapy or if an initial improvement is followed by a subsequent deterioration.¹⁰⁰ **GRADE C**

A role for routine suppressive aciclovir therapy for neonatal HSV infection to prevent cutaneous recurrences and neurological complications once therapeutic courses have been completed has not been established.⁹³ A recent small study of infants with CNS or disseminated disease found no acute neurological deterioration using suppressive aciclovir for 2 years.¹⁰¹ Further studies are required before aciclovir can be recommended routinely for long term suppressive therapy.¹⁰² **GRADE B**

General management points

A monocytic leukocytosis in the CSF is suspicious of CNS HSV infection.⁴⁴ Treatment with aciclovir should be instituted before cultures or PCR results are available. After 5 days, aciclovir can be discontinued if the clinical course is no longer compatible with HSV CNS disease, all cultures (including PCR) are negative and a CT or MRI head scan is normal or does not suggest HSV encephalitis. Be aware however that a negative initial CSF culture or 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.^{91,103} Consequently, perform serial lumbar punctures when microbiological tests are negative, but clinical suspicion remains high. **GRADE B & C**

Empirical treatment with aciclovir of suspected disseminated HSV infection is recommended if after 48 hours the infant is critically ill despite antibiotic therapy, if bacterial cultures are negative, and if there are signs of progressive liver dysfunction with coagulopathy.¹⁰⁴ **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.¹⁰⁵ **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**

Management of cutaneous recurrences is difficult. Recurrences are more commonly associated with HSV-2 infections and a poorer prognosis.^{92,106} The benefit of routine suppressive therapy has not been established. Data from an uncompleted clinical trial indicate that oral aciclovir (300mg/m² three times daily) prevents HSV recurrences after SEM disease, but almost half the infants experienced neutropaenia while on treatment.⁹³ While controversial,¹⁰² it is recommended that if there are two such episodes during the first 6 months of life suppressive oral aciclovir be considered and the white blood cell count monitored.¹⁰⁷ It must be realised however that treatment failures resulting in serious disease have still been reported during aciclovir suppressive therapy.¹⁰⁸ **GRADE B & C**

When a cutaneous recurrence is accompanied by fever and especially irritability, a CSF examination, including HSV DNA PCR, should be performed and if abnormal 3 weeks of intravenous aciclovir 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. Couple separation is not uncommon.¹⁰⁹ 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** (see page 42).

- 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 staff 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 staff 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?"
- It is very important for health professionals to address transmission; how the baby did and did not become infected. Parents may prefer to believe that the baby was infected from contaminated medical equipment or a staff member with a 'cold sore' to mitigate the burden of parental responsibility for the baby's infection.
- 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 42 for Key Information for Health Professionals to Give Patients and consider referring to the NZHF Helpline toll free 0508 11 12 13

Anticipatory Management of Newborn Infant with Known Risk for Neonatal HSV

High risk

This category involves a subgroup of infants born to mothers with their first episode of genital herpes during 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.⁴⁶ Although not completely protective, 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.⁴⁶ **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 culture and PCR testing (see above) and initiation of anticipatory aciclovir therapy. 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 is continued for at least 5 days. It can be discontinued at this time if the neonate remains well, viral cultures and molecular diagnostic testing have not identified HSV, and the CSF studies including PCR results are normal. 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.⁹⁸ **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 cultures, 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.
- Advise mothers about hand washing and caution those with vesicular breast lesions 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.
- 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 cultures

- Cultures should be taken at 48 hours of age (not at birth or within the first 24 hours of life because of possible contamination by maternal cervico-vaginal secretions).
- Cultures should be obtained from eyes (conjunctiva), mouth, nasopharynx, urine and rectum.
- Further clinical and laboratory evaluation, as for suspected neonatal HSV infection, followed immediately by aciclovir therapy is mandated, if cultures are positive.⁸⁹ **GRADE A**

Breastfeeding and use of oral aciclovir

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.⁷⁰ **GRADE B**