Neonatal herpes simplex virus infections

Swetha G. Pinninti, MD[^a], and David W. Kimberlin, MD[^b,⁎]

[^a]: Department of Pediatrics, University of Nebraska Medical Center, 982167 Nebraska Medical Center, Omaha, NE 68198
[^b]: Division of Pediatric Infectious Diseases, The University of Alabama at Birmingham, 1600 Seventh Avenue South, CHB 303, Birmingham, AL 35233

**Abstract**

Neonatal herpes simplex virus (HSV) is an uncommon but devastating infection in the newborn, associated with significant morbidity and mortality. The use of PCR for identification of infected infants and acyclovir for treatment has significantly improved the prognosis for affected infants. The subsequent use of suppressive therapy with oral acyclovir following completion of parenteral treatment of acute disease has further enhanced the long-term prognosis for these infants. This review article will discuss the epidemiology, risk factors and routes of acquisition, clinical presentation, and evaluation of an infant suspected to have the infection, and treatment of proven neonatal HSV disease.

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**Viral structure**

Herpes simplex viruses (HSV-1 and HSV-2) are large, enveloped virions with a double-stranded DNA core. HSV-1 and HSV-2 glycoproteins are responsible for attachment to and penetration into cells besides evoking host immune responses. Despite considerable cross-reactivity between HSV-1 and HSV-2, antibody responses to glycoprotein G allow for serologic distinction between the two strains.

**Maternal genital herpes**

Seroprevalence rates of HSV-1 and -2 vary significantly depending on age, sex, race, and geographic distribution. HSV-2 prevalence has been reported to be highest in areas of Africa, followed by decreasing incidences in North America, northern Europe and western and southern Europe, with the least incidence reported from Asia. HSV-2 reactivates more in the genital tract than HSV-1, thus increasing the chances of transmission to the neonate. HSV-2 seroprevalence among pregnant women is estimated to be 20–30%, and approximately 10% of HSV-2 seronegative women have a seropositive partner and hence are at risk for acquisition of genital HSV-2 infection during pregnancy. Among discordant couples, women seronegative for both HSV-1 and HSV-2 have an estimated 3.7% chance for seroconversion, while the risk for women already seropositive for HSV-1 to seroconvert to HSV-2 is estimated to be 1.7%.

A majority of genital infections caused by HSV-1 or -2 are asymptomatic (clinically inapparent), with two-thirds of women who acquire genital HSV infection during pregnancy being either asymptomatic or having non-specific symptoms. Among women with prior history of genital herpes, 75% will have at least one recurrence during pregnancy and 14% will have repeat events during subsequent pregnancies, increasing the risk for transmission to the neonate. In contrast, HSV-2 has a more frequent pattern of clinical presentation, with recurrent episodes occurring weeks to months after primary infection. HSV-2 has a higher rate of central nervous system involvement, which can lead to severe complications such as encephalitis and meningitis. The clinical presentation of neonatal herpes is often characterized by skin lesions, jaundice, fever, and neurological symptoms.

**Keywords:** Neonatal HSV, Acyclovir, PCR

[^*: Corresponding author. Tel.: +1 205 934 5316; fax: +1 205 975 9972. E-mail address: dtkimberlin@peds.uab.edu (D.W. Kimberlin).]
have prodromal symptoms or lesions at the time of delivery.\textsuperscript{10,11} For peripartum neonatal transmission to occur, women must be shedding the virus in their genital tracts symptomatically or asymptptomatically around the time of delivery. Between 0.2% and 0.39%\textsuperscript{12} of all pregnant women shed HSV in the genital tract around the time of delivery irrespective of prior history of HSV, and shedding increases to 0.77–1.4% among women with prior history of recurrent genital herpes.\textsuperscript{13,14}

The risk of transmission of HSV to the neonate remains significantly higher with primary maternal infections acquired closer to the time of delivery compared with recurrent infections (50–60% with primary infections vs <3% for recurrent infections), most likely due to lack of transplacentally acquired antibodies in the neonate of women with primary infection as well as exposure in the birth canal of those women to larger quantities of virus for longer durations of time.\textsuperscript{15} Fortunately, most genital herpes infections during pregnancy are recurrent and therefore are associated with lower risk of transmission to the neonate.

### Neonatal HSV

Herpes simplex virus (HSV) infection of the neonate is uncommon with varying rates across the world due to differing birth rates and HSV seroprevalence. Both HSV-1 and HSV-2 have been recognized to cause neonatal herpes infection. Studies have reported rates of 1.65 per 100,000, 1.6 per 100,000, 3.2 per 100,000 and 8.4 per 100,000 live births in the British Isles, Switzerland, the Netherlands, and Israel, respectively.\textsuperscript{16–19} In the United States, the incidence rates are reported to be higher with 5–33 per 100,000 live births, resulting in an estimated 1500 cases annually throughout the country.\textsuperscript{20,21} Though neonatal HSV remains an uncommon infection and does not require mandatory reporting, the incidence is higher than currently reportable congenital infections like syphilis, toxoplasmosis, and rubella,\textsuperscript{22} and may be increasing.\textsuperscript{23} The overall global rate of neonatal HSV, based on seroprevalence, birth rates and infections in pregnancy is estimated to be 10 per 100,000 live births, with a best estimate of 14,000 cases annually.\textsuperscript{24} This study marks the first attempt to quantify the global burden of neonatal HSV.\textsuperscript{25}

#### Risk factors for transmission of HSV to neonate

When an individual with no HSV-1 or HSV-2 antibody acquires either virus in the genital tract, a first-episode primary infection results (Table 1). If a person with preexisting HSV-1 antibody acquires HSV-2 genital infection (or vice versa), a first-episode non-primary infection ensues. Viral reactivation from latency produces a recurrent infection.

The risk of neonatal acquisition of HSV is significantly higher with first-episode primary and first-episode non-primary maternal infections compared with recurrent genital infections. In a large study, the risk of neonatal transmission was estimated as 57% with first-episode primary infection compared with 25% with first-episode non-primary infection and 2% with recurrent genital HSV infections.\textsuperscript{21} Other statistically significant risk factors for transmission of HSV to the neonate were isolation of HSV-1 from genital lesions versus HSV-2\textsuperscript{21} and use of invasive monitoring techniques such as fetal scalp electrodes.

Even though cesarean delivery has been proven to be effective in preventing the transmission of HSV to the neonate,\textsuperscript{26} neonatal HSV cases have occurred despite cesarean delivery prior to rupture of membranes.\textsuperscript{8} The American College of Obstetricians and Gynecologists (ACOG) currently recommends cesarean section in the presence of lesions suggestive of herpes at the time of delivery, while the Royal College of Obstetricians and Gynecologists (RCOG) recommends cesarean delivery only with primary genital herpes infections with lesions within 6 weeks of estimated delivery.\textsuperscript{27} Evidence also exists for prolonged rupture of membranes\textsuperscript{28} and disruption of mucocutaneous barrier by the use of fetal scalp electrodes and other instrumentation to increase the chances of acquisition of neonatal HSV disease.\textsuperscript{21,29}

While it has been shown that the chances of acquisition of HSV-1 are decreased in women seropositive for HSV-2, transmission of HSV-1 to the neonate has been documented to be high irrespective of primary or recurrent infection.\textsuperscript{21}

#### Clinical presentation

Neonatal HSV can be acquired in-utero (5%), in the peripartum period (85%), or in the postnatal period (10%). For the latter two modes of acquisition, extent of disease can be classified into the following categories:

1. SEM disease (skin, eye, and/or mouth)
2. CNS disease (central nervous system)
3. Disseminated disease

This classification is predictive of morbidity and mortality associated with this neonatal HSV.\textsuperscript{30–34}

#### SEM disease

In infants with SEM disease, infection is confined to the skin, eye, and/or mouth of newborns without any involvement of CNS or visceral organs. Infants with SEM disease historically accounted for 20% of cases of neonatal herpes disease but have increased to 45% with the introduction of antiviral therapy, as fewer babies progress from an SEM to a

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**Table 1 – Risk factors for HSV transmission to neonate.**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td>1. Type of maternal infection (first-episode primary &gt; first-episode non-primary &gt; recurrent)</td>
<td></td>
</tr>
<tr>
<td>2. Maternal HSV serostatus</td>
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<tr>
<td>3. Mode of delivery (vaginal &gt; C-section)</td>
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<tr>
<td>4. Duration of rupture of membranes</td>
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<tr>
<td>5. Disruption of cutaneous barrier (use of fetal scalp electrodes and other instrumentation)</td>
<td></td>
</tr>
<tr>
<td>6. HSV serotype (HSV-1 &gt; HSV-2)</td>
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disseminated extent of involvement.\textsuperscript{8} Infants with SEM disease present at 10–12 days of life and 80% of these infants have a vesicular rash on physical examination.\textsuperscript{34}

**CNS disease**

Almost one-third of cases of neonatal herpes disease present as encephalitis and are categorized as CNS disease, with or without skin involvement.\textsuperscript{3} Neonates usually present at 16–19 days of life, although it is possible to have disease manifestations start anytime within the first month of life.\textsuperscript{34} Infants present with focal/generalized seizures, lethargy, irritability, poor feeding, temperature instability, and bulging fontanel. In all, 60–70% of these infants have skin lesions at some point during the course of the illness.\textsuperscript{34}

**Disseminated disease**

In the era of effective antiviral therapy directed against HSV, disseminated disease accounts for ~25% of all neonatal herpes infections.\textsuperscript{8} Affected infants present around days 10–12 of life. Newborns with disseminated disease present with respiratory and hepatic failure with disseminated intravascular coagulation (DIC). Disease involves multiple organs, including CNS, lungs, liver, adrenal, skin, eye, and/or mouth. Two-thirds of infants have concurrent encephalitis and ~40% of infants never develop a vesicular rash during the entire illness.\textsuperscript{3,34} Death from disseminated disease is usually due to severe coagulopathy and extensive hepatic and pulmonary involvement.

**Evaluation of the neonate with suspected HSV infection**

The approach to an infant with suspected neonatal HSV infection is outlined in the Figure.

**Serologic testing**

Serologic diagnosis of neonatal HSV is not helpful and is not usually recommended for diagnostic purposes.

**Viral culture**

The definitive method of diagnosing neonatal HSV is by isolation of HSV in tissue culture. Surface culture swabs (swabs from conjunctivae, nasopharynx, mouth, and anus), cerebrospinal fluid (CSF), or blood from affected newborns are inoculated into cell culture systems and monitored for cytopathic effect.\textsuperscript{55}

**Polymerase chain reaction**

The application of PCR to CSF samples has revolutionized the diagnosis of CNS neonatal herpes disease.\textsuperscript{36–39} The overall sensitivities of CSF PCR in neonatal HSV disease have ranged from 75% to 100%, with overall specificities ranging from 71% to 100%.\textsuperscript{37,38} A negative PCR result from the CSF does not in and of itself rule out neonatal HSV CNS disease, as the test may be negative in very early stages of the infection. In comparison, blood PCR in neonatal HSV has been evaluated to a lesser extent and in smaller cohorts, but appears to be a powerful tool in the diagnosis of neonatal HSV infections.\textsuperscript{38–40}

**Specimens to obtain from newborn before initiating antiviral therapy**

Prior to initiation of empiric parenteral antiviral therapy, the following specimens should be collected to aid in the diagnosis of neonatal HSV disease or to determine if antiviral therapy may be discontinued if HSV has been excluded:

1. Swab for viral culture from the base of vesicles, suspicious areas, and mucous membrane lesions for viral culture (if available) or PCR
2. Swab from mouth, conjunctiva, nasopharynx, and rectum (surface cultures) for viral culture (if available) or PCR
3. CSF for indices, bacterial culture, and HSV DNA PCR
4. Whole blood for HSV DNA PCR
5. Blood to determine Alanine aminotransferase (ALT) level

**Treatment of neonatal HSV**

The earliest antiviral agents effective against HSV included 5′-ido-2′-deoxyuridine and 1-β-D-arabinofuranosylcytosine, but were found to be too toxic for human use. Vidarabine was licensed for use in cases of life-threatening HSV disease in the United States in 1977. In the 1980s, lower dose acyclovir (30 mg/kg/day administered three times a day for 10 days) was found to be efficacious for neonatal herpes disease\textsuperscript{31} and was soon the treatment of choice due to its safety profile and ease of administration. Subsequently, a higher dose of acyclovir (60 mg/kg/day divided in three doses for 14–21 days) was demonstrated to improve mortality and morbidity associated with neonatal HSV disease.\textsuperscript{33}

The current recommendations are to treat all neonates with HSV disease parenterally with acyclovir given at 60 mg/kg/day divided every 8 hours.\textsuperscript{35} Duration of treatment is 14 days for infants with SEM disease and 21 days for CNS and disseminated disease presentations.\textsuperscript{35} All neonates with CNS involvement should have repeat CSF PCR near the end of 21 days of treatment to document a negative CSF PCR result and for CSF indices. HSV DNA detected in CSF at or after completion of acyclovir therapy has been associated with poorer outcomes.\textsuperscript{37} In those rare neonates with positive CSF
PCR at the end of therapy, antiviral therapy should be continued until PCR negativity is achieved. Since the significance of blood DNA PCR positivity on disease outcomes remains largely unknown, serial measurement of blood DNA PCR for assessing response to therapy is not recommended at this time.

Adverse effects of high-dose acyclovir treatment include neutropenia, thrombocytopenia, and in elevated creatinine levels. There were no reported cases of renal failure and most cases of neutropenia resolved without intervention or dose reduction. Serial absolute neutrophil count (ANC) determination should be made at least twice weekly while on high-dose acyclovir therapy. Decreasing the acyclovir dosage or administering granulocyte colony-stimulating factor should be considered for persistent neutropenia.

**Prognosis**

In the pre-antiviral era, 85% of neonates with disseminated disease and 50% of neonates with CNS disease died by 1 year of age, while 50% of survivors with disseminated disease and 33% of neonates with CNS disease developed normally at 12 months of age. Altered mental status, DIC, prematurity, and pneumonitis in infants with disseminated disease were associated with increased mortality, whereas increased rates of morbidity were associated with encephalitis, DIC, seizures, and infection with HSV-2. Currently, with the utilization of the higher dose of acyclovir (60 mg/kg/day divided in three doses for 21 days), 1 year mortality has been reduced to 29% for disseminated disease and 4% for CNS disease, while 83% of neonates with disseminated disease and 31% with CNS disease develop normally at 12 months of age. Seizures prior to or at the time of initiation of antiviral therapy has been associated with increased risk of morbidity in neonates with disseminated and CNS disease. None of the infants with SEM disease in the high-dose acyclovir study developed developmental disabilities at 12 months age.

**Antiviral suppressive therapy after treatment**

The outcome of neonatal herpes disease depends on the extent of disease. Approximately 20% of survivors with disseminated disease have been shown to have neurologic sequelae compared with 70% of neonates with CNS disease. A phase III, placebo-controlled trial performed by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) documented that use of oral acyclovir suppressive therapy for 6 months after completion of parenteral acyclovir therapy for neonatal HSV disease improves outcomes. Infants with CNS disease
It is acceptable to discharge infants who continue to be neurodevelopmental outcomes and to have fewer cutaneous recurrences compared to placebo group, and infants with SEM disease were found to have less frequent recurrence of skin lesions while receiving suppressive therapy.\(^5\) The current recommendation is to treat with oral acyclovir at 300 mg/m\(^2\)/dose, three times a day for 6 months. Absolute neutrophil counts should be monitored at 2 and 4 weeks and monthly thereafter following initiation of suppressive therapy.\(^4\) Infection with acyclovir resistant strains or development of resistance after prolonged exposure to acyclovir has been reported,\(^45\) but is rare. Persistence of symptoms despite strict adherence to therapy or clinical worsening while on appropriate therapy should alert the clinician to consider infection with a resistant strain or development of resistance during treatment.

**Approach to infants exposed at delivery to active HSV lesions during maternal primary or recurrent genital HSV infection**

The most recent guidance endorsed by the American Academy of Pediatrics (AAP) provides evidence-based recommendations on the management of neonates born to women with active genital herpetic lesions.\(^6\) The recommendations take into consideration the maternal serological status, presence of genital lesions at the time of delivery, and the route of delivery. The recommendations are applicable only to institutions that have access to PCR facilities with a quick turnaround time, and only to infants exposed to HSV from maternal genital lesions present at the time of delivery. They are not applicable to situations with asymptomatic maternal shedding of HSV.

All women with genital lesions characteristic of HSV at the time of delivery should have viral culture and PCR sent off from the lesions. Further characterization of the virus as HSV-1 or HSV-2 is required for correlation with serology to determine status of maternal infection (primary vs recurrent).

**Management of newborns born to women with lesions at delivery and history of genital herpes prior to pregnancy**

- For women with history of genital herpes prior to pregnancy, the likelihood of lesions present at delivery being recurrent are high and therefore the risk of transmission to infant is low (<3%).
- Collect following samples from newborn approximately 24 hours after delivery:
  - (a) surface cultures (conjunctiva, mouth, nasopharynx, rectum, and scalp electrode site when present)
  - (b) blood DNA PCR
- It is acceptable to discharge infants who continue to be clinically well at 48 hours with instructions to caregivers for very close monitoring and immediate medical attention with development of any findings concerning for neonatal HSV.

- If the surface and blood virological studies are negative at 5 days, further evaluation of the infant is recommended only with the development of any signs suggestive of neonatal HSV in the subsequent 6 weeks.
- If the surface and blood virological studies are positive, suggesting HSV infection, a full evaluation (CSF for indices and HSV PCR, serum ALT level) is recommended to determine presence and extent of HSV disease. Therapy with intravenous acyclovir should be initiated in these infants as soon as possible.
  - If the results of this evaluation are negative (normal CSF indices and negative HSV PCR, normal ALT measurement), suggestive of neonatal HSV infection that has not yet progressed to HSV disease, preemptive treatment for 10 days with parenteral acyclovir should be administered to prevent the progression of HSV infection to HSV disease.
  - If this evaluation is suggestive of neonatal HSV disease (abnormal CSF indices with HSV CSF PCR + or elevated serum ALT), treatment with acyclovir should be continued for 21 days for CNS or disseminated neonatal HSV disease or for 14 days for SEM disease, followed by oral suppressive therapy with acyclovir for 6 months.

**Management of newborns born to women with lesions at delivery and no history of genital herpes prior to pregnancy**

- In women without a history of genital herpes prior to pregnancy, the presence of genital lesions during labor could represent primary infection (>50% risk of transmission to neonate), non-primary infection (25% risk of transmission to neonate), or recurrent infection (<3% risk of transmission).
- At approximately 24 hours after birth, the following samples should be collected:
  - (a) surface cultures (eye, mouth, nasopharynx, and rectum)
  - (b) blood for HSV DNA PCR
  - (c) CSF for determination of indices and HSV PCR
  - (d) serum for ALT level
- Due to higher risk, empiric treatment with intravenous acyclovir should be initiated.
- If the maternal serology and virological studies are suggestive of a recurrent infection and the infant remains asymptomatic with no evidence of HSV infection/disease (negative result on surface cultures, blood DNA PCR, and CSF PCR; and normal ALT level), discontinuation of parenteral acyclovir with instructions for close monitoring and re-evaluation with the development of any new signs is recommended.
- If the maternal studies are suggestive of a primary or non-primary genital infection and the neonate remains asymptomatic and lacks evidence of HSV infection/disease, treatment with 10 days of parenteral acyclovir is recommended (preemptive therapy) because the neonate’s risk of developing neonatal HSV disease is so high (25% to >50%).
- In infants with evidence of HSV infection or HSV disease, the approach is similar to those outlined in the approach to
an infant born to a mother with history of genital herpes prior to pregnancy: 10 days of parenteral acyclovir for HSV infection (preemptive therapy), 14 days of parenteral acyclovir for neonatal SEM disease, and 21 days of parenteral acyclovir therapy for CNS or disseminated disease.

### Strategies for prevention of HSV in the newborn

#### Cesarean delivery

Delivery by cesarean section decreases but does not entirely prevent HSV transmission to the neonate. Transmission of HSV has been documented in circumstances where cesarean section was performed prior to rupture of membranes.5,49 This mode of delivery in women with active genital lesions can reduce the infant’s risk of acquiring HSV21,28 and is recommended when genital lesions or prodromal symptoms are present at the time of delivery.49 Cesarean delivery is more likely to be effective if performed prior to rupture of membranes, but in situations where rupture of membranes has occurred and genital lesions are observed on physical examination, cesarean delivery is recommended to minimize exposure of HSV to the neonate.26 This intervention is not recommended for women with a prior history of genital herpes but no active lesions/prodromal symptoms at the time of delivery.26,50

#### Antiviral suppressive therapy during pregnancy

In women with recurrent genital herpes, initiation of antiviral suppressive therapy with acyclovir//valacyclovir at 36 weeks of gestation is associated with decreased likelihood of genital lesions at the time of delivery and decreased viral detection by culture/PCR. This intervention is currently endorsed by ACOG.26 However, subclinical viral shedding is not entirely suppressed and the utility of such a practice in preventing neonatal HSV disease is not well defined. A recent multi-center case series reported eight cases of infants with neonatal HSV disease acquired from mothers despite receiving antiviral suppressive therapies beyond 36 weeks of gestation.51

#### HSV vaccine

Currently, no vaccine has proven to be effective for preventing acquisition of HSV-1 or HSV-2. An HSV-2 gD subunit vaccine, adjuvanted with alum, initially was found to be effective in preventing HSV-1 or HSV-2 genital herpes (~75% vaccine efficacy) and HSV-2 infection, but the efficacy was limited only to women who were HSV-1 and HSV-2 seronegative.52 In a subsequent randomized, double-blind trial evaluating the efficacy of the same HSV-2 gD subunit vaccine in women seronegative for HSV-1 and HSV-2, the vaccine was found to have an efficacy of 58% for preventing HSV-1 genital herpes but lacked efficacy for preventing HSV-2 genital herpes.53

### Prevention of postnatal acquisition

Approximately, 10% of cases are acquired in the postpartum period by exposure to the virus from symptomatic lesions or asymptomatic shedding of care takers, including following Jewish ritual circumcision involving oro-genital contact.44 The recommendation for infected household contacts and family members is to avoid contact with the newborn. The recommendation for infected healthcare personnel with active herpetic whitlow lesions is not to provide direct care for neonates.35

### Conclusion

Neonatal HSV disease is associated with significant morbidity and mortality. Physicians involved in the care of neonates should consider neonatal HSV in the differential for all sick neonates, and initiate an evaluation for HSV as the cause of illness. Appropriate diagnosis and initiation of antiviral therapy followed by long-term suppressive therapy has significantly improved the outcome of these infants.

### Conflict of interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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