

Management of neonatal herpes simplex virus infection and exposure

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ABSTRACT

Neonatal herpes simplex virus (HSV) infections are rare but are associated with significant morbidity and mortality. Advances in diagnostic modalities to identify these infants, as well as the development of safe and effective antiviral therapy, have revolutionised the management of affected infants. This review will summarise the epidemiology of neonatal HSV infections and discuss the management of infants with HSV exposure and infection.

MATERNAL GENITAL HERPES INFECTIONS

Seroprevalence rates of herpes simplex virus (HSV)-1 and HSV-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.^{1 2} While HSV-2 historically has been the predominant serotype causing genital herpes and neonatal herpes in the USA, HSV-1 increasingly is identified as causing more cases of genital herpes and possibly neonatal herpes in the USA and some European countries.^{2–6} 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.⁷ In the USA, HSV-1 seroprevalence had decreased to 53.9% over the past decade, whereas HSV-2 seroprevalence had not significantly changed from 15.7%.⁸ Secondary analysis of this study population demonstrated that the largest decline in HSV-1 seroprevalence occurred in the 14–19-year-old age group, meaning that an increasing number of adolescents are without protective HSV-1 antibodies at the time of their sexual debut.⁹ This indicates that the incidence of HSV-1 genital disease, and hence neonatal HSV-1 disease, may continue to increase.

The majority of genital infections caused by HSV-1 or HSV-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 prodromal symptoms or lesions at the time of delivery.^{10 11} For peripartum neonatal transmission to occur, women must be shedding the virus in their genital tracts symptomatically or asymptotically around the time of delivery. Between 0.2% and 0.39%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.^{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). Fortunately, most genital herpes infections during pregnancy are recurrent and are therefore associated with lower risk of transmission to the neonate.

NEONATAL HERPES Epidemiology

HSV infection of the neonate is an uncommon occurrence with an estimated incidence 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.^{15–18} In the USA, 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.^{19 20} The reason for the high incidence rates in the USA remains unknown. Both HSV-1 and HSV-2 have been recognised to cause neonatal herpes infection.

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 (box 1). If a person with pre-existing 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.²⁰ Other statistically significant risk factors for transmission of HSV to the neonate were isolation of HSV-1 from genital lesions versus HSV-2 and use of invasive monitoring techniques such as fetal scalp electrodes.

Even though caesarean delivery has been proven to be effective in preventing the transmission of HSV to the neonate,²¹ neonatal HSV cases have occurred despite caesarean delivery prior to rupture of membranes.⁷ The American College of Obstetricians and Gynecologists (ACOG) currently



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Box 1 Risk factors for transmission of herpes simplex virus (HSV) to neonate

1. Type of maternal infection (first-episode primary>first-episode non-primary>recurrent)
2. Maternal HSV antibody status
3. Mode of delivery (vaginal>C-section)
4. Duration of rupture of membranes
5. Integrity of cutaneous barrier (use of fetal scalp electrodes and other instrumentation)
6. Type of HSV (HSV-1>HSV-2)

recommends caesarean section in the presence of lesions suggestive of herpes at the time of delivery while the Royal College of Obstetricians and Gynecologists (RCOG) recommends caesarean delivery only with primary genital herpes infections with lesions within 6 weeks of estimated delivery.²² Evidence also exists for prolonged rupture of membranes²³ 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.²⁰

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.²⁰

Modes of HSV transmission to neonate and 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 groupings, extent of disease can be classified into the following categories:

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

The above classification is also predictive of morbidity and mortality associated with this infection.^{24–28}

Disseminated disease

In the era of effective antiviral therapy directed against HSV, disseminated disease accounts for ~25% of all neonatal herpes infections.⁷ Affected infants present around day 10–12 of life, although disease manifestations can begin earlier. Patients with disseminated neonatal HSV disease present with viral sepsis with respiratory and hepatic failure and 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.^{7 28} Death from disseminated disease is usually due to severe coagulopathy and extensive hepatic and pulmonary involvement.

CNS disease

Almost one-third of cases of neonatal herpes disease present as encephalitis and are categorised as CNS disease, with or without skin involvement.⁷ Babies with CNS neonatal HSV disease present at 16–19 days of life, although it is possible to have disease manifestations start anytime within the first month of life.²⁸ Infants present with focal/generalised seizures, lethargy,

irritability, poor feeding, temperature instability and bulging fontanelle. Sixty to seventy per cent of these infants have skin lesions at some point during the course of the illness.²⁸ Mortality is usually due to devastating brain destruction.

SEM disease

Infants with SEM disease currently account for ~45% of all neonatal herpes disease⁷ and present at 10–12 days of life.²⁸ Infection in affected infants is limited to the skin, eye and/or mouth, and 80% have a vesicular rash on physical examination.

Evaluation of the neonate with suspected HSV infection

The approach to an infant with suspected neonatal HSV infection is outlined in figure 1.

Viral culture

The definitive method of diagnosing neonatal HSV is by isolation of HSV in tissue culture. Swabs from conjunctivae, nasopharynx, mouth and anus (surface cultures) should be obtained and placed in viral transport media for inoculation into cell culture systems and monitoring for cytopathic effect.²⁹ Vesicular lesions should be unroofed and the base of the vesicle swabbed as well for viral culture. Other sites from which HSV can be cultured include cerebrospinal fluid (CSF) and blood, although their yields from these areas are much lower.

Polymerase chain reaction

The application of PCR to CSF samples has revolutionised the diagnosis of CNS neonatal herpes disease.^{30–33} The overall sensitivities of CSF PCR in neonatal HSV disease have ranged from 75% to 100%, with overall specificities ranging from 71% to 100%.^{31 32} 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 due to low viral load or the sensitivity of the test being used. 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.^{32–34} A positive CSF PCR for HSV DNA defines that patient as having CNS involvement (categorised either as CNS disease or as disseminated disease with CNS involvement). However, a positive blood PCR for HSV DNA does not define disease classification since all clinical disease categories (SEM, CNS and disseminated) can have viremia and DNAemia.^{30 32}

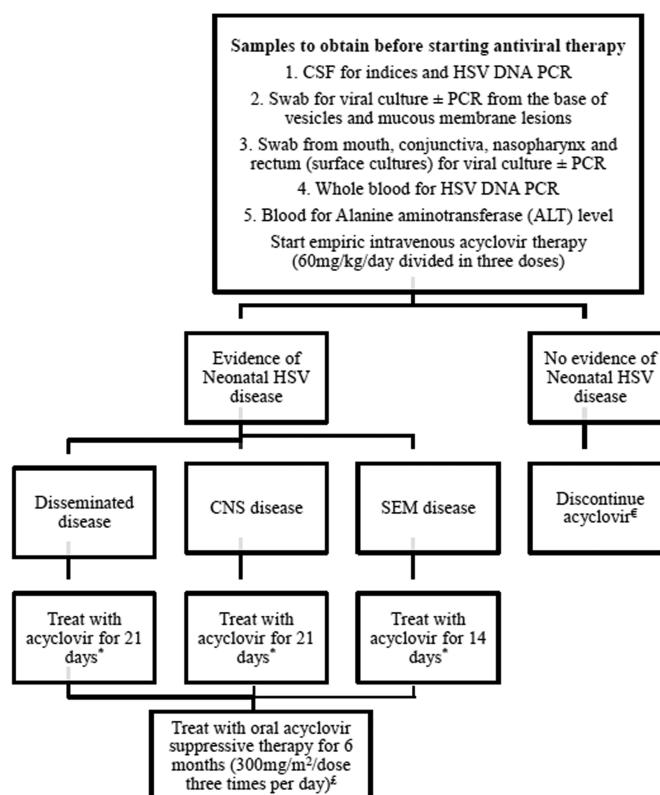
Treatment of neonatal HSV

The earliest antiviral agents effective against HSV included 5-iodo-2'-doxeyuridine 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 USA 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 disease²⁵ 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 into three doses for 14–21 days) was demonstrated to improve mortality and morbidity associated with neonatal HSV disease.²⁷

The current recommendations are to treat all neonates with HSV disease parenterally with acyclovir given at 60 mg/kg/day divided every 8 h.^{27 29} Duration of treatment is 14 days for infants with SEM disease and 21 days for CNS and disseminated disease presentations.²⁹ All neonates with CNS involvement should have repeat CSF PCR to document a negative CSF PCR

Review

Figure 1 Evaluation and management of neonatal herpes simplex virus disease.



[¶] Continue acyclovir and treat as neonatal HSV disease if suspicion remains high

^{*} Monitor with twice weekly CBC while on acyclovir therapy. For babies with CNS disease or Disseminated Disease with CNS involvement, repeat CSF analysis and CSF HSV PCR prior to stopping treatment. If CSF has detectable DNA by PCR at the end of therapy, continue treatment until negative CSF PCR result. Obtain neuroimaging prior to completion of treatment for all disease classifications of infants. Consider neurodevelopmental assessment at 1 year for prognosis.

[¶] Dosage of Acyclovir should be weight adjusted monthly for the entire duration of treatment. Absolute neutrophil counts should be obtained every 2 weeks for the first month and monthly thereafter after initiation of acyclovir suppressive therapy. Most instances of neutropenia are transient. Consider dose reduction to 50% of recommended, granulocyte colony stimulating factor administration, or discontinuation of suppressive therapy if ANC is <500 for a prolonged period.

result and for CSF indices. HSV DNA detected in CSF at or after completion of acyclovir therapy has been associated with poorer outcomes.³¹ In those rare neonates with positive CSF PCR at the end of therapy, antiviral therapy should be continued until PCR negativity is achieved.^{28 29 31} 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.²⁹

Prognosis:

Mortality and morbidity

In the preantiviral 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.²⁴ 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-2.²⁶ Currently, with the use of the higher dose of acyclovir (60 mg/kg/day divided into three doses for 21 days), 1-year mortality has been reduced to 29% for disseminated disease and 4% for CNS disease,²⁷ while 83% of neonates with disseminated disease and 31% with CNS disease develop normally at 12 months of age.^{24 27} Seizures prior to or at the time of initiation of antiviral therapy have been associated with

increased risk of morbidity in neonates with disseminated and CNS disease.²⁷ None of the infants with SEM disease in the high-dose acyclovir study developed developmental disabilities at 12 months of age.²⁷

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 neurologic sequelae compared with 70% of neonates with CNS disease.²⁷ 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 stratified to the treatment arm were found to have better neurodevelopmental outcomes and to have fewer cutaneous recurrences compared with the placebo group, and infants with SEM disease were found to have less frequent recurrence of skin lesions while receiving suppressive therapy.³⁵ The current recommendation is to treat with oral acyclovir at 300 mg/m²/dose, three times a day for 6 months. Absolute neutrophil counts should be monitored at 2 and 4 weeks and monthly thereafter after initiation of suppressive therapy.²⁹ Infection with acyclovir-resistant strains or development of resistance after prolonged exposure to acyclovir has been reported^{36–38} but seems to be an

uncommon event. Events that might cause clinicians to be concerned about infection with resistant strains or development of resistance during the course of treatment include persistence of symptoms despite strict adherence to therapy or clinical worsening while on appropriate therapy.

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

The most recent policy statement endorsed by the American Academy of Pediatrics (AAP) provides evidence-based guidance on the management of neonates born to women with active genital herpetic lesions.³⁹ 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 characterisation of the virus as HSV-1 or HSV-2 is required for correlation with serology to determine the 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 is high and the risk of transmission to infant is low (<3%). At approximately 24 h after delivery, surface cultures (conjunctiva, mouth, nasopharynx, rectum and scalp electrode site when present) and blood DNA PCR should be obtained. It is not required to start acyclovir therapy in these asymptomatic neonates due to lesser risk for acquisition of neonatal HSV. Waiting for 24 h after delivery before collection of samples is recommended to differentiate contamination of neonatal skin by maternal secretions during the birth process versus true HSV infection of the baby. It is acceptable to discharge these infants who continue to be clinically well at 48 h with instructions to caregivers for very close monitoring and immediate medical attention with development of any findings concerning 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 alanine aminotransferase (ALT) level) is recommended to determine the presence and extent of HSV disease. Under these circumstances, therapy with intravenous acyclovir should be initiated in these infants as soon as possible.

If the results of the evaluation are negative (normal CSF indices and negative CSF HSV PCR, normal ALT measurement), suggestive of neonatal HSV infection that has not yet progressed to HSV disease, pre-emptive treatment for 10 days with parenteral acyclovir should be administered to prevent the progression of HSV infection to HSV disease. On the other hand, if the 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, as discussed earlier, 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 labour 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). The information obtained from maternal viral culture/PCR of these lesions and maternal serological status obtained at delivery should guide the clinician in determining the type of maternal infection and thus the risk for transmission to the neonate, and guide approach to management of neonate.

At approximately 24 h after birth, surface cultures (eye, mouth, nasopharynx and rectum) and blood for HSV DNA PCR should be obtained from the neonate. Due to the higher risk of transmission of HSV to neonates in these circumstances, CSF for the determination of indices and HSV PCR and serum for ALT concentration should be obtained simultaneously, followed by initiation of treatment with intravenous acyclovir.

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 (pre-emptive 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 algorithm 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 (pre-emptive therapy), 14 days of parenteral acyclovir for neonatal SEM disease and 21 days of parenteral acyclovir therapy for CNS or disseminated disease. Infants with evidence of CNS involvement should have an end-of-therapy lumbar puncture with documentation of negative CSF HSV PCR prior to stopping parenteral acyclovir therapy. Infants with neonatal HSV disease (SEM, CNS or disseminated) should receive 6 months of oral acyclovir suppressive therapy; however, infants who receive pre-emptive acyclovir therapy do not warrant subsequent oral acyclovir suppression since they never had HSV disease in the first place.

CONCLUSION

Neonatal HSV disease is associated with significant morbidity and mortality. Physicians involved in the care of neonates should consider this infection in the differential for all sick neonates, and when appropriate instigate 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.

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Review

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