Herpes Simplex Virus Infections of the Newborn

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Herpes simplex virus (HSV) infections are fortunately quite rare in the neonatal population. Nevertheless, due to their life-threatening nature and the tremendous damage that surviving infants can incur, neonatal HSV is actually considered in a differential diagnosis relatively commonly. The availability of safe and effective antiviral therapy for the management of neonatal HSV also can accelerate a clinician’s decision to consider HSV as the cause of a neonate’s disease presentation, and then to obtain appropriate diagnostic studies and empirically institute antiviral treatment. Decisions on whether to continue antiviral therapy for a full course are predicated on the appropriate interpretation of these diagnostic studies as they subsequently are reported to the treating physician. For HSV-infected neonates, the duration of parenteral acyclovir therapy ranges from 14 to 21 days, depending on the extent of disease. Use of subsequent oral suppressive antiviral therapy is under investigation in randomized controlled trials, and at this time cannot be routinely recommended. This article will summarize the current state of neonatal HSV disease presentation, diagnosis, and management.

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Neonatal infections with herpes simplex virus (HSV) were first reported in the mid-1930s, when Hass described the histopathologic findings of a fatal case and when Batignani reported a newborn with herpes simplex keratitis. In the 1960s and 1970s, the natural history of neonatal HSV infections was described in a series of elegant reports. Shortly thereafter, the early antiviral drugs which fortuitously were active against human herpesviruses were developed and systematically evaluated in the treatment of neonatal HSV. The road to safe and effective antiviral therapies for neonatal HSV was not a completely smooth one, however. The earliest antiviral agents with in vitro activity against HSV, including 5-iodo-2’-deoxyuridine (IDU) and 1-β-D-arabinofuranosylcytosine (ara-C), proved too toxic in humans to be useful. Vidarabine (1-β-D-arabinofuranosyladenine, ara-A) was the first systemically administered antiviral medication with activity against HSV for which therapeutic efficacy outweighed toxicity for the management of life-threatening HSV disease. Intravenous vidarabine was licensed in 1977, but due to toxicity when administered systemically was restricted by the Food and Drug Administration to life-threatening HSV and VZV infections. Multicenter collaborative clinical trials conducted by The National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CAGS) established its efficacy in the treatment of neonatal HSV infections, providing the foundation for subsequent comparative trials with intravenous acyclovir in the 1980s. A relatively low dose of intravenous acyclovir (30 mg/kg/d administered intravenously in three divided doses for 10 days) was proven to be as effective in the treatment of neonatal HSV as vidarabine, to have fewer toxicities, and to be better tolerated. Subsequently, a higher dose of acyclovir (60 mg/kg/d administered intravenously in three divided doses for 21 days) has been shown to produce even better outcomes for neonatal HSV infections.

Additional improvements in the outcomes of neonates with HSV disease have been achieved through advances in the diagnostics available to clinicians, the most powerful of which is the application of the polymerase chain reaction (PCR) to patients with neonatal HSV disease. Polymerase chain reaction analysis of cerebrospinal fluid has eliminated the need for brain biopsy to diagnose HSV infections in the central nervous system (CNS). For the diagnosis of HSV outside of the CNS, though, viral culture remains the gold standard.

The scope of this review includes consideration of the natural history of neonatal HSV infections and their extent of involvement in neonates. The effect of parenteral antiviral
treatment on outcomes will be discussed, and unanswered questions regarding long-term antiviral suppression following completion of treatment of acute disease will be explored. Finally, mention will be made of the increasingly common obstetrical practice of placing women with a history of genital HSV on suppressive therapy, with an emphasis on the impact that this may have on the subsequent development of neonatal HSV.

**Epidemiology**

**Timing of Acquisition of Neonatal Infection**

Neonatal HSV disease is acquired in one of three distinct times: intrauterine (in utero), peripartum (perinatal), and postpartum (postnatal). The vast majority (85%) of infected infants acquire their infection during birth, in the peripartum period. An additional 10% of infected neonates acquire the virus postnatally (eg, from someone shedding HSV from the mouth who then kisses the baby, from exposure to HSV from a breast lesion, or from a herpetic whitlow exposure in the nursery). The final 5% are infected with HSV in utero.

**Incidence of Neonatal HSV**

Currently, neonatal HSV disease in the United States occurs in approximately 1 in 3200 deliveries,\(^1\) resulting in an estimated 1500 cases of neonatal HSV infection annually. As the baseline prevalence of HSV-2 genital infection increases in the overall population\(^15,16\) and the incidence of HSV-1 genital disease rises,\(^17,18\) it will become increasingly likely that a gravid woman may acquire HSV-2 for the first time during her pregnancy through sexual contact with a partner with a genital HSV-2 or an oral HSV-1 infection. As such, it is possible that the incidence of neonatal HSV disease may increase in the years to come. Fortunately, neonatal HSV disease occurs much less frequently in other countries of the world, although the reasons for these geographic disparities are not fully understood.\(^19\)

**Clinical Presentations**

Herpes simplex virus infections acquired either peripartum or postpartum can be classified as: (1) disseminated disease involving multiple visceral organs, including lung, liver, adrenal glands, skin, eye, and/or the brain (disseminated disease); (2) central nervous system disease, with or without skin lesions (CNS disease); and (3) disease limited to the skin, eyes, and/or mouth (SEM disease). This classification system is predictive of both morbidity and mortality.\(^8,10,11,20,21\) Patients with disseminated or SEM disease generally present to medical attention at 10 to 12 days of life, whereas patients with CNS disease on average present somewhat later at 16 to 19 days of life.\(^20\)

**Disseminated Disease**

Historically, disseminated HSV infections have accounted for approximately one-half to two-thirds of all children with neonatal HSV disease. However, this figure has been reduced to about 25% since the development and utilization of antiviral therapy, likely the consequence of recognizing and treating SEM infection before its progression to more severe disseminated disease.\(^22\) Central nervous system involvement is a common component of this category of infection, occurring in about 60% to 75% of infants with disseminated disease.\(^23\) Although the presence of a vesicular rash can greatly facilitate the diagnosis of HSV infection, over 20% of neonates with disseminated HSV disease will not develop cutaneous vesicles during the course of their illness.\(^20,22,24,25\) Patients commonly present with viral sepsis, including respiratory collapse, liver failure, and disseminated intravascular coagulopathy (DIC). Hepatitis and pneumonitis are common in disseminated neonatal HSV disease. Disease presentation is usually around day 10 to 12 of life. Death from disseminated neonatal HSV infection is usually the result of the severe coagulopathy, liver dysfunction, and pulmonary involvement.

**CNS Disease**

Almost one-third of all neonates with HSV infection are categorized as having CNS disease (with or without SEM involvement).\(^22\) Clinical manifestations of CNS disease include seizures (both focal and generalized), lethargy, irritability, tremors, poor feeding, temperature instability, and bulging fontanelle. Disease presentation is usually around day 16 to 19 of life. Between 60% and 70% of babies classified as having CNS disease have associated skin vesicles at any point in the disease course.\(^20,24\) In the absence of skin lesions and frank CNS signs, the initial presentation can be indistinguishable from other viral and bacterial infections that lead clinicians to suspect possible sepsis in neonates. With CNS neonatal HSV disease, mortality is usually the product of devastating brain destruction, with resulting acute neurologic and autonomic dysfunction. Neonatal HSV can involve any and often multiple parts of the brain, in contrast with the typical temporal lobe predilection seen with herpes simplex encephalitis with onset beyond the neonatal period.

**Differential Diagnosis**

A number of other conditions, both infectious and noninfectious, can mimic neonatal HSV infection. These include hyaline membrane disease, intraventricular hemorrhage, necrotizing enterocolitis, and various ocular or cutaneous disorders. Bacterial pathogens of newborns with systemic and/or cutaneous manifestations which can be confused with
neonatal HSV disease include group B Streptococcus, Staphylococcus aureus, Listeria monocytogenes, and Gram-negative bacteria. Exanthemous viral agents which can be confused for neonatal HSV infection include varicella-zoster virus infection, enteroviral disease, and disseminated cytomegalovirus infection. Other infectious pathogens which are on the differential diagnosis list include toxoplasmosis, rubella, and syphilis. Noninfectious cutaneous disorders should also be considered, including erythema toxicum, neonatal melanosis, acrodermatitis, and incontinentia pigmenti.

**Evaluation of the Neonate with Suspected HSV Infection**

**Serologic Testing**

Serologic diagnosis of neonatal HSV infection is not of great clinical value due to the presence of transplacentally acquired maternal IgG which can confound the assessment of the neonatal antibody status during acute infection. This is especially true given the large proportions of the adult American population who are seropositive for HSV-1 and HSV-2.

**Viral Culture**

Isolation of HSV by culture remains the definitive diagnostic method of documenting an HSV infection, including establishing neonatal HSV disease. Skin or mucous membrane lesions or surfaces are scraped and transferred in appropriate viral transport media on ice to a diagnostic virology laboratory. Such specimens are inoculated into cell culture systems, which are then monitored for cytopathic effects characteristic of HSV replication. Typing of an HSV isolate may then be done by one of several techniques. Other sites from which virus may be isolated in neonatal HSV disease include the CSF, urine, blood, stool or rectum, oropharynx, and conjunctivae. Specimens for viral culture from multiple body sites (with the exception of CSF) of babies suspected of having neonatal herpetic may be combined before plating in cell culture to decrease costs since, with the exception of CNS involvement, the important information gathered from such cultures is the presence or absence of replicating virus, rather than its precise location.

**Polymerase Chain Reaction**

The diagnosis of neonatal HSV infections has been revolutionized by the application of PCR to clinical specimens, including CSF, urine, blood, stool or rectum, oropharynx, and conjunctivae. Specimens for viral culture from multiple body sites (with the exception of CSF) of babies suspected of having neonatal herpetic may be combined before plating in cell culture to decrease costs since, with the exception of CNS involvement, the important information gathered from such cultures is the presence or absence of replicating virus, rather than its precise location.

Because the very power of the technology, however, performance of PCR is highly dependent on the manner in which the specimen was collected and maintained before reaching the laboratory for PCR analysis. Interpretation of PCR results, either positive or negative, must be correlated with the patient’s clinical presentation and disease course in determining their ultimate clinical or diagnostic significance. A negative PCR result does not in and of itself rule out neonatal HSV disease.

In two relatively large reports of PCR in neonatal herpetic, 76% to 78% of neonates with CNS HSV disease had HSV detected in their CSF by PCR. Overall sensitivities of CSF PCR in neonatal HSV disease have ranged from 75% to 100%, with overall specificities ranging from 71% to 100%. In comparison, PCR of blood components has been evaluated to a much lesser extent, with only six relatively small studies reported to date in the literature. Further study of blood PCR in neonatal HSV infection is needed, as illustrated by one recent report questioning the sensitivity of serum PCR analysis from neonates with disseminated HSV disease.

**Specimens to Obtain Before Starting Intravenous Acyclovir**

Certain clinical circumstances warrant the empiric initiation of intravenous acyclovir pending additional diagnostic and clinical data. Before beginning antiviral therapy, however, sufficient diagnostic tests should be gathered to allow for informed decisions within several days as to whether acyclovir treatment should be continued for a full treatment course or discontinued when HSV is ruled out. The ability to gather these studies before initiating antiviral therapy is dependent on the clinical stability of the patient at the time. Ideally, the following studies should be collected before starting parenteral antiviral therapy: (1) CSF for indices, bacterial culture, and HSV PCR; (2) viral culture of any suspicious skin or mucous membrane lesions; and (3) surface cultures from the mouth, nasopharynx, conjunctivae, and rectum. Additionally, urine, stool, blood, and CSF can also be sent for viral culture. By gathering these specimens, the physician will have enough data over the ensuing 4 to 5 days to determine whether or not to continue acyclovir therapy.

**Treatment of Neonatal HSV**

Neonates with HSV disease should be treated with intravenous acyclovir at 60 mg/kg/d divided every 8 hours (20 mg/kg/dose). The dosing interval of intravenous acyclovir may need to be increased in premature infants, based on their creatinine clearance. Duration of therapy is 21 days for patients with disseminated or CNS neonatal HSV disease, and 14 days for patients with HSV infection limited to the SEM. All patients with CNS HSV involvement should have a repeat lumbar puncture at the end of intravenous acyclovir therapy to determine that the specimen is PCR-negative in a reliable laboratory, and to document the end-of-therapy CSF indices. Those persons who remain PCR-positive should continue to receive intravenous antiviral therapy until PCR-negativity is achieved. Absolute neutrophil counts should be followed about twice a week during the course of therapy.

**Prognosis/Outcomes of Neonatal HSV**

**Mortality**

In the preantiviral era, 85% of patients with disseminated neonatal HSV disease died by 1 year of age, as did 50% of patients with CNS neonatal HSV disease. With current an-
tiviral therapy, 12-month mortality has been reduced to 29% for disseminated neonatal HSV disease and to 4% for CNS HSV disease (Figs. 1 and 2, respectively). Lethargy and severe hepatitis are associated with mortality among patients with disseminated disease, and prematurity and seizures are associated with mortality in patients with CNS disease.

Morbidity

Improvements in morbidity rates with antiviral therapies have not been as dramatic as with mortality. The proportion of survivors of disseminated neonatal HSV disease who have normal neurologic development has increased from 50% in the preantiviral era to 83% today. In the case of CNS neonatal HSV disease, there has been no change at all, with 33% of patients in the preantiviral era and 31% of patients today having normal neurologic development (Fig. 3). Seizures at or before the time of initiation of antiviral therapy are associated with increased risk of morbidity both in patients with CNS disease and in patients with disseminated infection.

In contrast to disseminated or CNS neonatal HSV disease, morbidity following SEM disease has dramatically improved,

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**Figure 1** Mortality in patients with disseminated neonatal HSV disease by daily dosage of acyclovir. Dosage was divided every 8 hours. Recipients of the 45 mg/kg/d and 60 mg/kg/d dosing were treated for 21 days, whereas recipients of the 30 mg/kg/d dosing (*) were from a historical cohort treated for 10 days.11

**Figure 2** Mortality in patients with CNS neonatal HSV disease by daily dosage of acyclovir. Dosage was divided every 8 hours. Recipients of the 45 mg/kg/d and 60 mg/kg/d dosing were treated for 21 days, whereas recipients of the 30 mg/kg/d dosing (*) were from a historical cohort treated for 10 days.11

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during the antiviral era. Before the development of vidarabine or acyclovir, 38% of SEM patients experienced developmental difficulties at 12 months of age. Today, fewer than 2% of acyclovir recipients have developmental delays following recovery from SEM disease (Fig. 3).

Follow-Up of Neonatal HSV

The most significant sequelae of neonatal HSV disease is neurologic impairment. Survivors of neonatal HSV infections should be followed closely for the achievement of developmental milestones, and should undergo developmental assessments as needed. Early intervention programs, including physical therapy, occupational therapy, and speech therapy, should be employed at the first sign of the potential for or risk of impairment. Cutaneous recurrences, although not of the same significance as neurologic sequelae, nevertheless are common and oftentimes are quite disruptive to the lives of the patients and their families, including impacting child care arrangements.

The role of suppressive oral acyclovir currently is being evaluated in randomized controlled trials being conducted by the NIAID CASG. However, an earlier small Phase I/II study suggested that almost half of babies on suppressive oral acyclovir for 6 months can experience significant neutropenia, raising questions about the safety of such therapy. Pending the results of the placebo-controlled Phase III studies to define risk versus benefit, there are insufficient data to recommend routine utilization of suppression therapy following the acute management of neonatal HSV disease. Additionally, the development of CNS disease in a former premature infant on suppressive therapy raises questions about the efficacy of such an approach and, indeed, whether acyclovir suppression could have even contributed to the extent of the disease recurrence by masking early symptoms.

Special Considerations

A number of approaches are employed by obstetricians to try to prevent neonatal HSV disease. Cesarean delivery in a woman with active genital lesions can reduce the infant’s risk of acquiring HSV and is recommended when genital HSV lesions or prodromal symptoms are present at the time of delivery. Physicians caring for neonates delivered by cesarean section should be aware that neonatal HSV infections have occurred despite cesarean delivery performed before the rupture of membranes.

An increasingly common practice among obstetricians is the use of oral antiviral suppressive therapy near the end of pregnancy to prevent genital HSV recurrences at delivery. Several small studies suggest that suppressive acyclovir or valacyclovir therapy during the last weeks of pregnancy decreases the occurrence of clinically apparent genital HSV disease at the time of delivery, with an associated decrease in cesarean section rates for the indication of genital HSV. However, because viral shedding still occurs (albeit with reduced frequency), the potential for neonatal infection is not completely avoided. Cases of neonatal HSV disease have occurred among babies born to women who were on suppressive antiviral therapy at the end of pregnancy. Of the small studies evaluating suppressive antiviral therapy near the end of pregnancy, only 2 have investigated the babies for evidence of toxicity. Although these studies did not identify any neonatal side effects from maternal suppression, only 123 babies whose mothers received valacyclovir were evaluated. Given how widespread the use of antiviral suppression has become in pregnant women and the suggestion of toxicity in infants receiving suppressive therapy following neonatal HSV, additional studies are urgently needed to define the safety and efficacy of this approach. Pending these data, pediatricians should not assume that the risk of neonatal HSV is completely eliminated by a woman receiving suppressive oral antiviral therapy at the time of delivery.
Conclusions

Neonatal HSV disease remains a significant cause of morbidity and mortality among affected babies. Following the acquisition of appropriate diagnostic tests, intravenous acyclovir should be started at 60 mg/kg/d. For babies with proven or highly suspected disease, the duration of therapy should be 14 to 21 days, depending on extent of disease involvement. All babies with CNS involvement should have a repeat lumbar puncture near the end of therapy to document virologic clearance from the CSF. The role of subsequent oral suppressive therapy with acyclovir remains under investigation at this time.

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