



Neonatal Herpes: What Have We Learned

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Neonatal herpes simplex virus (HSV) infection usually is acquired during the birth process, as the neonate comes in contact with the virus during passage through an infected birth canal. After an incubation period which can last as long as 2 to 4 weeks, neonatal HSV disease then manifests in 1 of 3 ways: (1) disseminated disease, with visceral organ involvement (including infection of the brain in two-thirds to three-quarters of patients); (2) central nervous system disease (with no other visceral organ involvement, but with skin lesions in two-thirds of patients); or (3) disease limited to the skin, eyes, and/or mouth (ie, SEM disease). Diagnostic advances in recent years have focused primarily on applying polymerase chain reaction technology to babies suspected of having neonatal HSV disease. Treatment of neonatal HSV disease with intravenous acyclovir has improved the likelihood of survival substantially, although neurologic morbidity remains a common sequelae, especially among survivors of central nervous system disease. Despite these advances, the duration of time from onset of symptoms and initiation of antiviral therapy has remained unchanged for the past 20 years. The surest way to improve outcomes rapidly at this point is to raise awareness of neonatal HSV disease, resulting in the establishment of earlier diagnoses and more rapid institution of antiviral therapy. In the longer term, development of a bedside nucleic acid detection kit for real-time detection of HSV DNA in the maternal genital tract at the time of delivery could identify which babies are at risk of developing neonatal HSV disease.

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Despite significant advances that have been made during the past 2 decades, neonatal herpes simplex virus (HSV) disease still occurs too frequently and results in death or permanent neurologic debility too commonly. Beginning with vidarabine in the 1970s and early 1980s and continuing with acyclovir from the 1980s to the current time, efficacious parenteral antiviral agents have been available to treat babies who acquire HSV during the neonatal period. The beneficial impact of treating such patients has been greater when mortality is considered, with only 6 percent of infants with central nervous system (CNS) disease and 20 percent of babies with disseminated disease succumbing to their illness today. Among survivors, however, two-thirds of infants with CNS

disease and approximately one-fifth of infants with disseminated disease experience neurologic sequelae. During the past 20 years, the time period between initial onset of symptoms and initiation of antiviral therapy has not diminished. Because neonatal HSV disease still is a rare occurrence, with only approximately 1500 cases occurring each year in the United States, treating all sick neonates with acyclovir until HSV disease is ruled out simply is not an option. Rather, physicians need to remain keenly aware of neonatal herpes in the development of their differential diagnoses and to initiate antiviral therapy as quickly as possible in high-risk, sick neonates. A complete understanding of the biology, epidemiology, diagnosis, and treatment of neonatal herpes aids in this endeavor.

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Biology

A critical aspect of the biology of HSV is the establishment of latency. During primary HSV infection, virions are transported by retrograde flow along axons that connect the point of entry into the body to the nuclei of sensory neurons.¹ Viral multiplication occurs in a small number of sensory neurons, and the viral genome then remains in a latent state for the life of the host. With periodic reactivation brought on by events

such as physical or emotional stress, fever, ultraviolet light, and tissue damage, the virus is transported back down the axon to replicate again at or near the original point of entry into the body. Such reactivation can result in clinically apparent disease (lesions) or clinically inapparent (asymptomatic, or subclinical) infection. Transmission to the infant can occur if HSV is present in the maternal genital tract at the time of delivery, regardless of whether it is a primary maternal genital infection or symptomatic or asymptomatic reactivation of latent virus within the genital tract.

Epidemiology

Risk of Maternal Infection and Disease During Pregnancy

When a person with no prior HSV-1 or -2 antibody acquires either virus in the genital tract, a *first-episode primary infection* results. If a person with preexisting HSV-1 antibody acquires HSV-2 genital infection, a *first-episode nonprimary infection* ensues. Viral reactivation from latency and subsequent antegrade translocation of virus back to skin and mucosal surfaces produces a *recurrent infection*. Recurrent genital herpes infections are the most common form of genital HSV during gestation.² However, as discussed below, it is the woman with primary genital HSV disease who is at highest risk of transmitting the virus to her child. Approximately 10 percent of HSV-2-seronegative pregnant women have an HSV-2-seropositive sexual partner and thus are at risk of contracting a primary HSV-2 infection.³ Equally important are women seronegative for both HSV-1 and HSV-2 who are in relationships with partners who are seropositive for HSV-1. Such women can acquire HSV-1 genital infection after engaging in oral-genital sex, with equally devastating consequences for the neonate. Among such discordant couples, women who are seronegative for both HSV-1 and HSV-2 have an estimated chance of seroconversion for either virus of 3.7 percent, whereas those women who are already seropositive for HSV-1 have an estimated chance of HSV-2 seroconversion of 1.7 percent.⁴ Approximately two-thirds of women who acquire genital herpes during pregnancy have no symptoms to suggest a genital HSV infection,⁴ which is consistent with the finding that 60 to 80 percent of women who deliver an HSV-infected infant have no evidence of genital HSV infection at the time of delivery and no past history of genital herpes or a sexual partner reporting a history of genital HSV.⁵⁻⁷

Risk of Neonatal Infection

HSV disease of the newborn is acquired during one of three distinct periods: intrauterine (in utero), peripartum (perinatal), and postpartum (postnatal). Among infected infants, the time of transmission for the overwhelming majority (~85%) of neonates is the peripartum period. An additional 10 percent of infected neonates acquire the virus postnatally, and the final 5 percent are infected with HSV in utero. The five factors known to influence transmission of HSV from mother to neonate are:

1. Type of maternal infection (primary versus recurrent);⁸⁻¹²
2. Maternal antibody status;^{7,12-14}
3. Duration of rupture of membranes;¹¹
4. Integrity of mucocutaneous barriers (eg, use of fetal scalp electrodes);^{12,15,16} and
5. Mode of delivery (cesarean versus vaginal delivery).¹²

Infants born to mothers who have a first episode of genital HSV infection near term are at much greater risk of developing neonatal herpes than are those whose mothers have recurrent genital herpes.⁸⁻¹² This increased risk is caused both by lower concentrations of transplacentally passaged HSV-specific antibodies (which also are less reactive to expressed polypeptides) in women with primary infection and by the higher quantities of HSV that are shed for a longer period of time in the maternal genital tract when compared with women who have recurrent genital HSV infection. The largest assessment of the influence of the type of maternal infection on the likelihood of neonatal transmission involved almost 40,000 women without clinical evidence of genital HSV infection who were cultured within 48 hours of delivery (Fig 1). Of these, 121 women were identified who both were asymptotically shedding HSV and for whom sera were available for serologic analysis. In this large trial, 57 percent of babies delivered to women with first episode primary infection developed neonatal HSV disease compared with 25 percent of babies delivered to women with first-episode, nonprimary infection and 2 percent of babies delivered to women with recurrent HSV disease (Fig 1).¹²

Neonates with higher neutralizing antibody titers are less likely to become infected with HSV after perinatal exposure during passage through an infected birth canal,¹³ illustrating the protective effects of preexisting antibody in preventing the acquisition of neonatal HSV disease. Among HSV-infected neonates, anti-HSV neutralizing antibody titers also correlate with the extent of the disease,¹⁷ with babies with higher neutralizing antibody titers being more likely to have localized disease (and less likely to have disseminated disease) once they are infected. Similarly, high maternal or neonatal anti-HSV ADCC antibody levels or high neonatal antiviral neutralizing levels each are associated independently with an absence of disseminated HSV infection.¹⁸

The duration of rupture of membranes and mode of delivery also appear to impact the risk for acquisition of neonatal infection. A small study published in 1971 suggested that cesarean delivery in a woman with active genital lesions can reduce the infant's risk of acquiring HSV if performed within 4 hours of rupture of membranes.¹¹ Based on this observation, the recommendation for more than 3 decades has been that women with active genital lesions at the time of onset of labor be delivered by cesarean section.¹⁹ Not until 2003, however, was cesarean delivery definitively proven to be effective in the prevention of HSV transmission to the neonate from a mother actively shedding virus from the genital tract.¹² Importantly, neonatal infection has occurred despite cesarean delivery performed before the rupture of membranes.^{5,20}

though the presence of a vesicular rash can greatly facilitate establishing the diagnosis of HSV infection, more than 20 percent of neonates with disseminated HSV disease will not develop cutaneous vesicles during the course of their illness.^{5,26,30,31} Events associated with disseminated neonatal HSV infection that can result in death relate primarily to the severe coagulopathy, liver dysfunction, and pulmonary involvement of the disease.

CNS Disease

Almost one-third of all neonates with HSV infection are categorized as having CNS disease (with or without SEM involvement).⁵ Clinical manifestations of CNS disease include seizures (both focal and generalized), lethargy, irritability, tremors, poor feeding, temperature instability, and bulging fontanelle. Between 60 and 70 percent of babies classified as having CNS disease have associated skin vesicles at any point in the course of the disease.^{26,30} With CNS neonatal HSV disease, death usually is the product of devastating brain destruction, with resulting acute neurologic and autonomic dysfunction.

Disease Limited to the Skin, Eyes, and/or Mouth (SEM Disease)

SEM disease historically has accounted for approximately 20 percent of all cases of neonatal HSV disease. With the introduction of early antiviral therapy, this frequency has increased to approximately 45 percent.⁵

Diagnosis

Serologic Testing

Until recently, the commercially available serologic assays were unable to distinguish between HSV-1 and HSV-2 antibodies, severely limiting their utility. In the past few years, two type-specific antibody assays manufactured by Focus Technologies, Inc., (Herndon, VA)³² have received the approval of the Food and Drug Administration (FDA): the HerpeSelect® HSV-1 and HSV-2 ELISA and the HSV-1 and HSV-2 Immunoblot tests. Another type-specific serologic assay manufactured by Diagnology (Research Triangle Park, NC) and known as POckit® HSV-2³³⁻³⁵ was approved by the FDA for the rapid type-specific detection of HSV-2 IgG but has been taken off the U.S. market. However, this product will be available again in the United States beginning in September 2004, under the new name of "biokitHSV-2," marketed by Biokit USA (Lexington, MA). This assay also will be marketed in the clinical laboratory by Fisher Healthcare (Houston, TX) under the trade name of Sure-View HSV-2. Several additional tests that claim to distinguish between HSV-1 and HSV-2 antibody are commercially available, but high cross-reactivity rates resulting from their use of crude antigen preparations limit their utility to documentation of primary seroconversion, rather than distinguishing among viral types.³⁶

In contrast to its use in other congenital and neonatal infections, serologic diagnosis of neonatal HSV infection is

not of great clinical value. With the availability of reliable type-specific assays, one barrier to interpreting serologic results in babies with suspected HSV disease has been removed. However, the presence of transplacentally acquired maternal IgG still confounds the assessment of the neonatal antibody status during acute infection, especially given the large proportions of the adult American population who are HSV-1- and HSV-2-seropositive. Serial antibody assessment may be useful in the very specific circumstance of a mother who has a primary infection late in gestation and transfers very little or no antibody to the fetus. In general, however, serologic studies play no role in establishing the diagnosis of neonatal HSV disease.

Viral Culture

Isolation of HSV by culture remains the definitive diagnostic method of establishing neonatal HSV disease. If skin lesions are present, a scraping of the vesicles should be transferred in appropriate viral transport media on ice to a diagnostic virology laboratory.³⁷ Such specimens are inoculated into cell culture systems, which then are monitored for cytopathic effects characteristic of HSV replication. Typing of an HSV isolate then may be done by one of several techniques. Other sites from which virus may be isolated include the cerebrospinal fluid (CSF), urine, blood, stool or rectum, oropharynx, and conjunctivae.³⁷ Specimens for viral culture from multiple body sites (with the exception of CSF) 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.

Of the sites routinely cultured for HSV, skin or eye/conjunctival cultures consistently provided the greatest yields regardless of disease classification, with 90 percent or more of cultures being positive. In a recent study, 58 (94%) of 62 patients had a positive skin or eye culture; 33 (48%) of 69 patients had a positive mouth/oropharyngeal culture; and 17 (40%) of 42 patients with CNS involvement (CNS disease or disseminated disease with CNS involvement) had a positive CSF or brain biopsy culture.²⁶

Polymerase Chain Reaction (PCR)

The diagnosis of neonatal HSV infections has been revolutionized by the application of PCR to clinical specimens, including CSF³⁸⁻⁴⁴ and blood.^{42,44-48} Because of the very power of the technology, however, the variability in performance of PCR among laboratories warrants brief consideration. Interlaboratory standards that assure that identical specimens processed in two different laboratories will yield identical results are lacking. Furthermore, the performance of PCR is highly dependent on the manner in which the specimen was collected and maintained before reaching the laboratory for PCR analysis.⁴⁹ Given these caveats, 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

Table 1 PCR Results from Neonatal CSF*

PCR Result	Disease Classification (%)		
	SEM (n = 29)	CNS (n = 34)	Disseminated (n = 14)
Positive	7 (24)	26 (76)	13 (93)
Negative	22 (76)	8 (24)	1 (7)

*Data are from Reference 43.

significance. A negative PCR result does not in and of itself rule out neonatal HSV disease.

CSF

In the largest report of PCR in neonatal herpes, CSF specimens from 77 neonates in the United States with culture-proven HSV disease were evaluated retrospectively by PCR.⁴³ These 77 infants previously had been enrolled during the 1980s in a comparative study of vidarabine and acyclovir for the treatment of neonatal HSV disease. As such, categorization of infants by extent of disease (eg, SEM disease, CNS disease, and disseminated disease) reflected the laboratory technologies available at the time. As shown in Table 1, HSV DNA was detected by PCR in the CSF of 7 (24%) of the 29 infants who had been categorized previously as having SEM disease, 13 (93%) of the 14 infants previously classified as having disseminated disease, and 26 (76%) of the 34 infants previously categorized as having CNS disease.⁴³ This finding is remarkably similar to the Swedish experience of applying PCR to stored specimens from patients with neonatal HSV diagnosed between 1973 and 1996, in which 78 percent of neonates with CNS HSV disease were found to be PCR-positive from CSF.⁴⁴ Thus, the PCR assay in the U.S. investigation had an overall sensitivity of 80 percent (because of the failure to detect HSV DNA from CSF specimens of 8 infants with CNS disease) and an overall specificity of 71 percent (because of the finding of HSV DNA in the CSF of 7 infants with presumed SEM disease).⁴³ In comparison, the sensitivities of PCR assays used in two other retrospective investigations of neonatal HSV disease were 100 percent⁴² and 75 percent,³⁹ and the specificities were 100 percent in both studies.^{39,42}

Given the lack of systematic and large-scale prospective investigation of CSF PCR in the diagnosis and management of neonates with HSV disease, the clinical significance of positive and of negative CSF PCR results at the end of intravenous therapy has yet to be fully delineated. In the U.S. trial cited previously, infants who had HSV DNA detected in the CSF by PCR after completing intravenous antiviral therapy were more likely to either die or suffer moderate-to-severe neurologic impairment than were those infants whose post-therapy CSF specimens were PCR-negative (Table 2).⁴³ Differences in disease classifications between the PCR-positive and PCR-negative groups, as well as possible sampling bias (only those patients with a clinical indication for repeat lumbar puncture such as persistent seizures, fever, or neurologic deterioration were evaluated) of this retrospective analysis, complicate one's ability to draw definitive conclusions from these find-

ings and further emphasize the need for prospective data on which informed clinical decisions can be based. Nonetheless, the available data suggest that having HSV DNA detected in CSF at or after completion of intravenous therapy is associated with poor outcomes.^{43,44} All patients with CNS HSV involvement should have a repeat lumbar puncture performed in a reliable laboratory at the end of intravenous acyclovir therapy to determine that the specimen is PCR-negative and to document the end-of-therapy CSF indices.²⁶ Those persons who remain PCR-positive should continue to receive intravenous antiviral therapy until PCR-negativity is achieved.^{26,43}

Blood

PCR analyses of stored blood components from HSV-infected neonates have been reported in six studies involving a total of 108 infants. One of these studies evaluated stored plasma samples,⁴⁶ two evaluated whole blood samples obtained in dried blood spots on filter papers (Guthrie cards),^{45,47} and three evaluated stored serum samples.^{42,44,48} Overall, 26 (96%) of 27 infants classified as having disseminated neonatal HSV disease were PCR-positive (plasma: 1 [100%] of 1⁴⁶; whole blood: 6 [86%] of 7^{45,47}; serum: 19 [100%] of 19^{42,44,48}); 29 (45%) of 64 babies classified as having CNS neonatal HSV disease were PCR-positive (plasma: 1 [33%] of 3⁴⁶; whole blood: 3 [14%] of 22^{45,47}; serum: 25 [64%] of 39^{42,44,48}); and 8 [47%] of 17 babies classified as having SEM neonatal HSV disease were PCR-positive (plasma: 2 [100%] of 2⁴⁶; whole blood: 2 [100%] of 2^{45,47}; serum: 4 [31%] of 13^{42,48}). Case reports have documented that serum PCR can remain positive at least 10 days into acyclovir therapy.⁴²

Serum viral load correlates with classification of disease.⁴⁸ Viral load is statistically higher in the serum of babies with disseminated disease (mean \pm SE: $10^{5.9} \pm 0.6$ copies/mL) compared with that of infants with CNS disease (mean \pm SE:

Table 2 PCR Results After Completion of Antiviral Therapy*

Infant Characteristic	PCR (%)	
	Negative†	Positive‡
Disease classification		
CNS	4 (36.4)	14 (73.7) <i>P</i> < 0.001
Disseminated	0 (0.0)	5 (26.3)
SEM	7 (63.6)	0 (0.0)
CSF indices		
Normal	6 (54.5)	1 (5.3)
Abnormal	3 (27.3)	17 (89.4)
Morbidity and mortality after 12 months		
Normal	6 (54.5)	1 (5.3) <i>P</i> < 0.001
Mild	0 (0.0)	0 (0.0)
Moderate	1 (9.1)	3 (15.8)
Severe	2 (18.2)	10 (52.6)
Dead	0 (0.0)	5 (26.3)
Unknown	2 (18.2)	0 (0.0)

*Adapted from Reference 43.

†All samples negative after treatment.

‡One or more positive result(s).

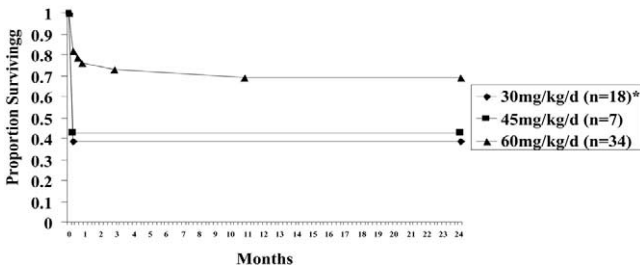


Figure 2 Mortality in patients with disseminated neonatal HSV disease. (From Reference 25.)

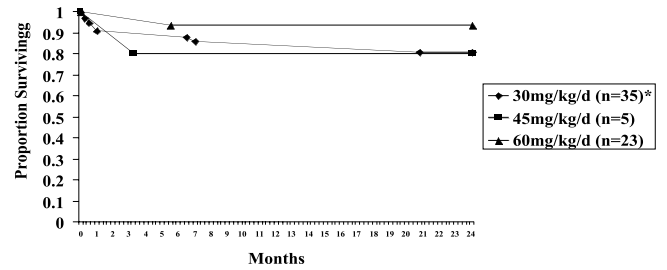


Figure 3 Mortality in patients with CNS neonatal HSV disease. (From Reference 25.)

$10^{1.5} \pm 0.8$ copies/mL; $P < 0.001$) or with SEM disease (mean \pm SE: $10^{0.5} \pm 0.3$ copies/mL; $P < 0.001$).⁴⁸ Serum viral load also is significantly higher ($>10^6$ copies/mL) in patients who die from their neonatal herpes than in those who survive and are neurologically normal ($P = 0.005$) or those who survive with neurologic sequelae ($P = 0.0008$).⁴⁸

Thus, PCR from blood components appears to be a promising diagnostic modality. Each of the studies to date is relatively small, and all are retrospective in nature. Despite these limitations, serum for PCR analysis appears to be most promising for the diagnosis of disseminated neonatal HSV disease but is of much lower utility in the diagnosis of CNS or SEM disease. Further study is needed, however, as illustrated by one recent report questioning the sensitivity of serum PCR analysis from neonates with disseminated HSV disease.⁵⁰ Data are insufficient at the current time to allow the use of serial blood PCR measurements to establish response to antiviral therapy or guide determinations regarding the appropriate time to discontinue therapy. Only the prospective application of PCR to larger numbers of babies with neonatal herpes ultimately will define the optimal manner in which this powerful technology can aid the diagnosis and management of neonatal HSV disease.

Treatment

Antiviral Therapy

Mortality

In the pre-antiviral era, 85 percent of patients with disseminated neonatal HSV disease died by the time they were 1 year of age, as did 50 percent of patients with CNS neonatal HSV disease.²⁹ Evaluations of two different doses of vidarabine and of a lower dose of acyclovir (30 mg/kg/d for 10 days) documented that both of these antiviral drugs reduce the rate of mortality to comparable degrees,^{27,29,51} with mortality rates at 1 year from disseminated disease decreasing to 54 percent and from CNS disease decreasing to 14 percent.²⁷ Despite its lack of therapeutic superiority, the lower dose of acyclovir quickly supplanted vidarabine as the treatment of choice for neonatal HSV disease because of its favorable safety profile and its ease of administration. Unlike acyclovir, vidarabine had to be administered during prolonged infusion times and in large volumes of fluid.

With the use of a higher dose of acyclovir (60 mg/kg/d for 21 days), 12-month mortality is reduced further to 29 per-

cent for disseminated neonatal HSV disease and to 4 percent for CNS HSV disease (Figs 2 and 3, respectively).²⁵ Lethargy and severe hepatitis are associated with mortality among patients with disseminated disease, as are prematurity and seizures in patients with CNS disease.²⁶

Morbidity

Disseminated and CNS Neonatal HSV Disease. 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 percent in the pre-antiviral era²⁹ to 83 percent today.²⁵ In the case of CNS neonatal HSV disease, no change at all has occurred, with 33 percent of patients in the pre-antiviral era and 31 percent of patients today having normal neurologic development (Fig 4).^{25,29} Although these differences illustrate areas in which an improvement unquestionably is needed, it is important to note that as more neonates survive neonatal HSV disease, the total numbers of patients who subsequently develop normally is higher today, even while the percentages of survivors with normal development are not dramatically different. Seizures that occur 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.²⁶

SEM Neonatal HSV Disease. Unlike disseminated or CNS neonatal HSV disease, morbidity after SEM disease has improved dramatically during the antiviral era. Before the development of vidarabine or acyclovir, 38 percent of patients with SEM experienced developmental difficulties at 12 months of age.²⁹ Today, fewer than 2 percent of acyclovir

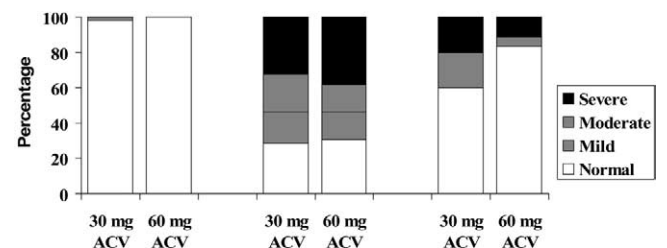


Figure 4 Morbidity among patients with known outcomes after 12 months of life. (From Reference 25.)

recipients have developmental delays after recovering from SEM disease (Fig 4).^{25,27}

Current Antiviral Treatment Recommendations

The improvements in mortality and morbidity achieved with the use of higher doses of acyclovir support the use of acyclovir at 60 mg/kg/d delivered intravenously in three divided daily doses, as is currently recommended.^{25,37} The dosing interval of intravenous acyclovir may need to be increased in premature infants, based on their creatinine clearance.⁵² 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.⁵³ As noted previously, all patients with CNS HSV involvement should have a repeat lumbar puncture in a reliable laboratory at the end of intravenous acyclovir therapy to determine that the specimen is PCR-negative and to document that the end-of-therapy CSF indices have been achieved.²⁶ Those persons who remain PCR-positive should continue to receive intravenous antiviral therapy until PCR negativity is achieved.^{26,43}

The primary apparent toxicity associated with the use of intravenous acyclovir administered at 60 mg/kg/d is neutropenia, with approximately one-fifth of patients developing an absolute neutrophil count of 1000/ μ L or less.²⁵ Although the neutropenia resolves either during continuation of intravenous acyclovir or after its cessation, it is prudent to monitor neutrophil counts at least twice weekly throughout the course of intravenous acyclovir therapy, with consideration being given to decreasing the dose of acyclovir or administering granulocyte colony stimulating factor if the absolute neutrophil count remains less than 500/ μ L for a prolonged period of time.²⁵

Antibody Therapy

The natural immune responses to HSV infection, both humoral and cellular, are directed strongly against the surface glycoproteins gB and gD, and both human and humanized antibodies directed against gB and gD have been shown to be beneficial as prophylactic and therapeutic agents in animal models of HSV infection.⁵⁴⁻⁵⁷ However, human studies have yet to be performed. In addition, an HSV hyperimmune globulin preparation does not exist, and the amount of anti-HSV antibodies present in conventional intravenous gamma-globulin (IVIG) preparations is low and variable, such that unacceptably large volumes would need to be injected to confer potentially protective immunity. For these reasons, use of IVIG in the management of neonates with HSV disease cannot be recommended at this time.

The development of human and humanized monoclonal antibodies obviates the current problems with pooled intravenous immunoglobulin preparations and may allow for the systematic evaluation of the therapeutic benefit of passive immunization in neonatal HSV disease. Human monoclonal antibodies offer further potential advantages over murine and chimeric antibodies such as longer circulating half-life and reduced or possibly undetectable immunogenicity. At least

two human monoclonal antibodies exist that could one day be evaluated in neonatal HSV disease. HSV 863 is an HSV gD group 1b human monoclonal antibody of IgG1 gamma isotype. In vitro studies showed that HSV 863 reacts with all of the 99 strains of HSV-1 and HSV-2 tested. It has potent neutralizing activity in the absence of complement, with an IC₅₀ range of 0.05 to 0.35 μ g/mL, with intravenous immunoglobulin being approximately 128 to 256 times less potent. Production of this product, however, currently is on hold pending discussions with potential manufacturers of a commercial-grade product. HX-8 is a human monoclonal antibody that neutralizes both HSV-1 and HSV-2. It is being developed as a topical human antibody, but to date, has not been tested in humans.

Prevention

Cesarean Delivery

As noted previously, cesarean delivery in a woman with active genital lesions can reduce the infant's risk of acquiring HSV.^{11,12} In 1999, the American College of Obstetricians and Gynecologists updated its management guidelines for genital herpes in pregnancy.¹⁹ To prevent neonatal HSV disease, a cesarean delivery should be performed if genital HSV lesions or prodromal symptoms are present at the time of delivery. As a method to reduce the incidence of neonatal HSV disease, however, cesarean delivery has a number of drawbacks, including the fact that 60 to 80 percent of babies who develop neonatal HSV disease are born to women without a history of genital herpes,⁵⁻⁷ and thus the disease will not be prevented with this approach. Decision analyses estimate that 1580 excess cesarean deliveries are performed for every poor neonatal outcome from neonatal HSV prevented, 0.57 maternal deaths occur for every neonatal death from HSV prevented, and an estimated \$2.5 million is spent for every neonatal case of HSV averted with this approach.^{58,59} These figures contrast with ones regarding cesarean deliveries for women with no history of genital herpes, which result in only nine excess cesarean deliveries per poor neonatal outcome prevented and 0.004 maternal deaths for every neonatal death prevented. The issue of cesarean delivery is complicated even further by the fact that neonatal infection has occurred despite cesarean delivery performed before the rupture of membranes.^{5,20}

Antiviral Prophylaxis During Pregnancy

Because of acyclovir's safety record in pregnancy, along with a desire to decrease neonatal HSV disease and reduce the number of cesarean deliveries performed for the indication of herpes, the use of oral acyclovir near the end of pregnancy to suppress genital HSV recurrences has become increasingly common clinical practice. During a 14-year period from 1984 to 1998, the Acyclovir in Pregnancy Registry recorded outcomes of pregnancies in which in utero exposure to acyclovir or valacyclovir occurred.⁶⁰ No differences were observed with respect to fetal outcomes or birth defects, although the numbers of subjects captured in the registry were too small to draw definitive conclusions. During the course of

this registry, deliberate use of acyclovir near the end of pregnancy to suppress genital HSV recurrences became an increasingly common clinical practice. Several small studies suggest that suppressive acyclovir therapy administered during the last weeks of pregnancy decreases the occurrence of clinically apparent genital HSV disease at the time of delivery,⁶¹⁻⁶³ with an associated decrease in cesarean rates for the indication of genital HSV.^{61,62} However, because viral shedding still occurs (albeit with reduced frequency),^{63,64} the potential for the acquisition of neonatal infection likely is not avoided completely. Additional studies are needed to establish more definitively the safety and effectiveness of late-pregnancy maternal HSV suppressive therapy, including the potential for neutropenia to develop in neonates that are born to women receiving antiviral suppressive therapy.⁶⁵⁻⁶⁷ Data currently do not support the routine use of suppressive oral acyclovir or valacyclovir in gravid women with a history of recurrent genital herpes.²¹

Vaccine Development

Numerous efforts have been made to create a vaccine for genital herpes. Until recently, all had been failures. However, a candidate HSV-2 glycoprotein D subunit vaccine adjuvanted with alum combined with 3-deacylated monophosphoryl lipid A (MPL) recently demonstrated promising results. In two large Phase III studies, the vaccine was demonstrated to be safe and, in a subset of volunteers, effective in preventing HSV-1 or -2 genital herpes disease (vaccine efficacy ~ 75%) and HSV-2 infection (vaccine efficacy ~ 40%).⁶⁸ In both studies, efficacy was limited to women who were HSV-1 and -2 seronegative before receiving vaccination. No evidence was noted of vaccine efficacy in men or in women who were HSV 1+/2- before vaccination. Because these earlier trials were neither designed nor powered to assess efficacy in HSV 1-/2- women, another Phase III trial is being undertaken by GlaxoSmithKline and the National Institute of Allergy and Infectious Disease.

The Future

So where should we go from here? A clear way to improve our understanding of the epidemiology of neonatal HSV infection is to make it a reportable disease, as has been considered recently by the International Herpes Management Forum and suggested by U.S. investigators (Handsfield HH, Waldo AB, Brown ZA, Corey L, Drucker JL, Ebel CE, Leone PA, Stanberry LR, Whitley RJ, submitted for publication). Epidemiologic studies of mother-to-child transmission of HSV are required in both developed and developing countries. Efforts such as these then will allow for development of country- or region-specific obstetrical practice guidelines that fit the medical needs of the locale. In the United States, guidelines for pre- and perinatal management of group B streptococcal infections have had a marked impact on the development of early-onset group B strep disease.⁶⁹ No reason exists to think that similar results could not be attained for HSV, using markedly different paradigms, of course, that would be based

on the results of these national or regional epidemiologic investigations. Development of a bedside nucleic acid detection kit for real-time detection of HSV DNA in the maternal genital tract at the time of delivery would have the potential to revolutionize the management⁷⁰ and should be encouraged. Finally, ultimate elimination of neonatal HSV likely will require development of an effective HSV vaccine that protects against genital HSV-2 and HSV-1 infection and/or disease. The most promising candidate vaccine currently is in Phase III clinical trials in women who are HSV-1 and -2 seronegative before immunization (but not in men).⁶⁸ If the current Phase III trial confirms efficacy, investigating this vaccine in a prepubescent female population will be imperative because it will be the only group in which one can realistically hope to be able to administer the vaccine before their acquisition of HSV-1 orolabial infection. Vaccine strategies then could be envisioned along the lines of Great Britain's rubella vaccination strategies focusing on young girls.

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