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Natural History of Neonatal Herpes Simplex Virus Infections in the Acyclovir Era

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ABSTRACT. *Objective.* **During the 2 decades in which effective antiviral therapies have been available for neonatal herpes simplex virus (HSV) disease, changes have been documented not only in the outcomes of infected infants, but also in the natural history of the disease itself. Numerous studies previously have reported that early institution of antiviral therapy is beneficial to the outcome of the disease. The objective of this study was to provide an update of neonatal HSV disease to identify means by which future improvements in the management of HSV-infected neonates can be made.**

Design/Methods. **Neonates enrolled in 2 studies of parenteral acyclovir for the treatment of neonatal HSV disease provided the data source. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group conducted the studies between 1981 and 1997. A total of 186 patients are summarized, all of whom were treated with acyclovir. Demographic and clinical characteristics of these patients are reported.**

Results. **Comparisons between patients treated in the periods between 1981–1988 and 1989–1997 according to extent of disease revealed that the mean time between the onset of disease symptoms and initiation of therapy has not changed significantly from the early 1980s to the late 1990s. Of all patients evaluated, 40% had fetal scalp monitors during the delivery process. A significant minority of patients did not have skin vesicles at the time of their presentation and did not develop them during the acute HSV disease (39% of patients with disseminated disease; 32% of patients with central nervous system [CNS] disease; and 17% of patients with skin, eye, and/or mouth disease). Among patients with CNS disease, mortality was associated with prematurity. Among patients with disseminated HSV disease treated with acyclovir at 30 mg/kg/d, mortality was associated with aspartate transaminase elevations of ≥10 times the upper limit of normal at the time of initiation of acyclovir therapy. Mortality was also associated with lethargy at initiation of antiviral therapy for patients with disseminated disease. Patients' morbidity status was associated with the extent of disease (skin, eye, and/or mouth disease vs CNS vs disseminated). For those patients with CNS disease, morbidity was also associated with seizures at initiation of antiviral therapy.**

Conclusion. **Data presented in the current comparison of neonatal HSV disease over the 2 periods (1981–1988 vs 1989–1997) demonstrate that no progress has been made in decreasing the interval between onset of HSV symptoms and initiation of antiviral therapy. Additional strides in the improvement of disease outcome may occur only if the interval between onset of symptoms and initiation of therapy is shortened. The means by which this will be accomplished lie in increased consideration of neonatal HSV infections in acutely ill infants. Specific**

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data and recommendations to facilitate this goal are contained within. ***Pediatrics*** **2001;108:223–229;** ***newborn, herpes simplex virus, acyclovir.***

ABBREVIATIONS. HSV, herpes simplex virus; CNS, central nervous system; SEM, skin, eyes, or mouth; NIAID, National Institute of Allergy and Infectious Diseases; CASG, Collaborative Antiviral Study Group; CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulopathy; SD, standard dose; ID, intermediate dose; HD, high dose; AST, aspartate transaminase; EEG, electroencephalogram; PCR, polymerase chain reaction.

The introduction of effective antiviral agents for the treatment of neonatal herpes simplex virus (HSV) disease, beginning in the late 1970s, has had a profound impact on the management and outcome of this potentially devastating infection. Medical advances first involved the use of vidarabine[1,2] and then acyclovir[3] in the treatment of affected neonates. Very recently, utilization of higher doses of acyclovir for longer periods of time has been demonstrated to further improve the outcome of neonatal HSV disease.[4] Despite these achievements, however, morbidity and mortality from neonatal HSV infections remain unacceptably high.

To achieve maximal benefit from antiviral therapy, acyclovir must be initiated before widespread viral dissemination throughout the body or to significant replication within the central nervous system (CNS).[5] The initiation of acyclovir therapy frequently is dependent on a high index of suspicion on the part of the clinician, especially when overt signs of neonatal HSV disease, such as cutaneous vesicles, are not present. An appreciation of the natural history of neonatal HSV disease provides the basis for such an index of suspicion, which can be problematic given that neonatal HSV disease presentation has been documented to change over time.[6,7] The data presented herein documents changes in the natural history of neonatal HSV disease in the 12 years since the last major report[7] appeared in the literature. Descriptions of disease presentation are provided, factors associated with adverse outcomes are enumerated, and areas where improvement is required are identified.

METHODS

Study Population

Neonates with HSV infections manifest in 3 distinct clinical groups: 1) those with disease localized to the skin, eye, and/or mouth (SEM disease); 2) those with encephalitis with or without skin involvement (CNS disease); and 3) those with disseminated infection that involves multiple organs, including the CNS, lung, liver, adrenals, skin, eye, and/or mouth.[8] These classifications have been used in all studies of neonatal HSV conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG).

Demographic and clinical characteristics of patients who received acyclovir in 2 studies conducted by the NIAID CASG are reported herein. The first study was conducted from 1981 to 1988,[3] and the second from 1989 to 1997.[4] All patients had virologically confirmed HSV disease. Study methods were identical between these 2 trials, with the exception of the dose of acyclovir used and the duration of therapy. Additionally, the second study[4] selectively enrolled patients with either CNS or disseminated neonatal HSV infections. A small number of patients with SEM HSV disease also were enrolled in the second study[4] on a compassionate basis at the discretion of the participating investigator. Such compassionate enrollment reflected a desire to gather additional information on the use of high-dose acyclovir and was not related to a greater severity of the patients' illness. Thus, by design the proportion of patients in the second study[4] with CNS or disseminated HSV disease exceeds that reported in the first study,[3] where all patients (including those with SEM involvement only) were actively recruited for study participation. Where appropriate, comparisons are made between these 2 groups of patients to evaluate differences in the 2 time periods.

Clinical Observations

Neonates in both studies were evaluated prospectively, and data were recorded on standardized case record forms that were identical for the 2 periods. Baseline demographic information, symptoms, and signs of illness immediately preceding presentation to medical care, acute disease course, and long-term follow-up were obtained as previously described.[3,4] Assessment of function was made at each of the long-term follow-up visits. Function was assessed as: 1) normal; 2) impaired but able to live at home; 3) institutionalized; and 4) deceased. Impairment was further quantitated as mild (ocular sequelae [recurrent keratoconjunctivitis], speech delay, mild motor delay [in the absence of hemiparesis]); moderate (hemiparesis, persistent seizure disorder, $<$3 month developmental delay); and severe (microcephaly, spastic quadriplegia, blindness/chorioretinitis; $>$3 month developmental delay).[3,4]

Laboratory and Radiographic Observations

Virus Isolation and Typing

Specimens for HSV isolation were obtained from the oropharynx, cerebrospinal fluid (CSF), conjunctivae, and skin vesicles (if present).[2,6] These samples were inoculated onto cell cultures suitable for virus isolation at each participating institution. Isolates of HSV were typed with monoclonal antibodies as previously described.[9]

Neuroimaging Studies

Enrolled patients received a baseline imaging study of the brain. Computed tomography scans were the modality of choice, although magnetic resonance imaging and ultrasonography were also used.

Statistical Analysis

Fisher's exact test and the 2-sample t-test were used to investigate the changes in characteristics between neonates treated from 1981 to 1988 and from 1989 to 1997 according to extent of disease. The Cox proportional hazards model was used to investigate the association of the mortality rates with ethnicity, prematurity, disease severity indicators (pneumonia, disseminated intravascular coagulopathy [DIC], seizures, hepatitis, fever, skin vesicles, lethargy, and conjunctivitis), and HSV type, with adjustment for the acyclovir treatment dose for the CNS and disseminated patients, respectively. The Fisher's exact test was applied to explore the effect of viral types on combined morbidity and morbidity status for each of the 3 disease categories, respectively. Additional investigation with the logistic regression analysis using conditional exact inference[10] was used to assess the impact on morbidity at 12 months after enrollment of viral type, ethnicity, prematurity, and disease severity indicators, with adjustment for the acyclovir treatment dose for CNS and disseminated patients, respectively. The logistic regression analysis using conditional maximum likelihood inference,[10] with stratification for the disease categorization and adjustment for the acyclovir treatment dose, was used to assess the impact of these factors on morbidity at 12 months after enrollment on the whole. All hypothesis tests are performed by exact conditional score tests.

RESULTS

Population Characteristics

A total of 186 patients were included in these analyses. Of these, 107 received standard-dose (SD) acyclovir (30 mg/kg/d) between 1981 and 1988 in a previous CASG controlled clinical trial,[3] and 79 patients received intermediate-dose (ID) acyclovir (45

TABLE 1. Characteristics at Enrollment of Mothers and Their Neonates, 1981–1997

Characteristic	Number (%) (n = 186)
Infants	
Sex	
Male	96 (52)
Female	90 (48)
Race	
White	128 (69)
Black	40 (21)
Hispanic	11 (6)
Other	7 (4)
Gestational age (wk ± SE)	37.8 ± 0.23
Premature (≤37 wk gestation)	63 (35)
Birth weight (kg ± SE)	2.95 ± 0.06
Scalp monitor used	
Yes	74 (40)
No	70 (38)
Unknown	42 (22)
Time of disease onset	
<24 h after birth	16 (9)
1–5 d after birth	56 (30)
>5 d after birth	112 (60)
Unknown	2 (1)
Extent of disease*	
SEM	64 (34)
CNS	63 (34)
Disseminated	59 (32)
Mothers	
Age (y ± SE)	22.3 ± 0.38
Marital status	
Married	101 (54)
Divorced	3 (2)
Widowed	1 (0.5)
Single	80 (43)
Unknown	1 (0.5)
Number of other children	
0–1	121 (65)
2–3	57 (31)
≥4	5 (3)
Unknown	3 (1)

SE indicates standard error.
* Patients with CNS and disseminated HSV disease were disproportionately enrolled in the high-dose acyclovir study spanning 1989 to 1997. This fact accounts for the relatively lower percentage of patients with SEM disease in this report.

mg/kg/d) or high-dose (HD) acyclovir (60 mg/kg/d) between 1989 and 1997 in a recently completed CASG trial.[4] The combined population characteristics of all 186 patients are presented in Table 1. The mean gestational age (± standard error) was 37.8 ± 0.23 weeks, and 35% of the infants were delivered prematurely (≤37 weeks' gestation). The use of fetal scalp electrodes was documented in 40% of neonates.

Sixteen (9%) of the 186 patients exhibited onset of disease symptoms and signs within the first 24 hours of life, suggesting in utero acquisition of the HSV infection. Ten of these patients received SD acyclovir and 6 received HD acyclovir. Six of the 16 patients were premature. The median gestational age was 39 weeks (range: 27–41 weeks), and the median birth weight was 2863 g (range: 790-4409 g). The mothers of these 16 patients had a median duration of rupture of membranes of 270 minutes (range: 0–1440 minutes). Five patients had scalp electrodes and 9 did not, with the fetal scalp monitor status of 2 patients being not recorded. Two of the mothers had peripartum fever believed to be not related to HSV, 2 women had peripartum fever of unknown cause, 7 women had no fever, and the fever status of 5 women was unknown. Two neonates had HSV-1 disease, 7 neonates had HSV-2 disease, and the viral type was unknown in 7 infants.

Comparisons between patients treated from 1981 to 1988 and from 1989 to 1997 are presented in Table 2, according to extent of disease. The percentage of patients delivered prematurely has not changed significantly between 1981–1988 and 1989–1997. Furthermore, the mean time between the onset of disease symptoms and initiation of therapy also has not changed significantly between 1981–1988 and 1989–1997. Although the mean age (days ± standard error) of the patients with CNS disease at initiation of therapy was older in the cohort treated between 1989 and 1997 as compared with the cohort treated between 1981 and 1988 (19.7 ± 1.6 vs 15.2 ± 1.3; $P = .031$), the

TABLE 2. Changes in Characteristics of Neonates According to Extent of Disease

	SEM			CNS			Disseminated		
Characteristic	1981–1988 n = 54	1989–1997* n = 10	P†	1981–1988 n = 35	1989–1997 n = 28	P†	1981–1988 n = 18	1989–1997 n = 41	P†
Number premature	20 (41%)	2 (20%)	.294	9 (27%)	10 (36%)	.582	5 (28%)	17 (41%)	.389
Mean age at study enrollment (d ± SE)	11.2 ± 0.9	12.0 ± 2.2	.719	15.2 ± 1.3	19.7 ± 1.6	.031	10.3 ± 1.1	11.4 ± 0.8	.442
Mean time (d ± SE) between earliest HSV symptom and enrollment	5.9 ± 0.7	5.7 ± 1.3	.901	6.6 ± 0.8	7.4 ± 1.3	.607	5.3 ± 0.7	5.6 ± 0.7	.764
Time between earliest HSV symptom and age at enrollment									
0–1 d	9 (17%)	2 (20%)	.524	3 (9%)	2 (7%)	.895	1 (6%)	8 (20%)	.314
2–4 d	16 (31%)	2 (20%)		12 (35%)	9 (33%)		8 (44%)	10 (25%)	
5–8 d	17 (33%)	2 (20%)		8 (24%)	9 (33%)		7 (39%)	14 (35%)	
>8 d	10 (19%)	4 (40%)		11 (32%)	7 (26%)		2 (11%)	8 (20%)	
Unknown	2 (–)	0 (–)		1 (–)	1 (–)		0 (–)	1 (–)	

SE indicates standard error.
* Patients with CNS and disseminated HSV disease were disproportionately enrolled in the high-dose acyclovir study spanning 1989 to 1997. This fact accounts for the relatively lower percentage of patients with SEM disease in this report.
† Based on Fisher's exact tests or t-tests.

TABLE 3. Signs and Symptoms Before Study Enrollment

	Disease Classification			
	SEM (n = 64)	CNS (n = 63)	Disseminated (n = 59)	Total (n = 186)
Skin Vesicles				
Number of patients	53 (83%)	40 (63%)	34 (58%)	127 (68%)
Duration of symptoms (d ± SE)	3.8 ± 0.5	6.1 ± 1.0	3.7 ± 0.6	4.5 ± 0.4
Lethargy				
Number of patients	12 (19%)	31 (49%)	28 (47%)	71 (38%)
Duration of symptoms (d ± SE)	3.3 ± 0.7	4.6 ± 0.7	3.4 ± 0.7	3.9 ± 0.4
Fever				
Number of patients	11 (17%)	28 (44%)	33 (56%)	72 (39%)
Duration of symptoms (d ± SE)	4.6 ± 1.5	3.1 ± 0.4	4.6 ± 0.6	4.0 ± 0.4
Conjunctivitis				
Number of patients	16 (25%)	10 (16%)	10 (17%)	36 (19%)
Duration of symptoms (d ± SE)	6.5 ± 1.5	4.1 ± 1.3	5.9 ± 1.9	5.7 ± 0.9
Seizure				
Number of patients	1 (2%)	36 (57%)	13 (22%)	50 (27%)
Duration of symptoms (d ± SE)	7.0	2.9 ± 0.5	2.5 ± 0.7	2.9 ± 0.4
DIC				
Number of patients	0 (0%)	0 (0%)	20 (34%)	20 (11%)
Duration of symptoms (d ± SE)	–	–	1.5 ± 0.3	1.5 ± 0.3
Pneumonia				
Number of patients	0 (0%)	2 (3%)	22 (37%)	24 (13%)
Duration of symptoms (d ± SE)	–	9.0 ± 6.0	4.0 ± 0.8	4.5 ± 0.9

SE indicates standard error.

overall importance of this finding remains to be determined.

Disease Presentation and Course

The frequency and duration of patients' presenting symptoms and signs are represented in Table 3, according to extent of disease. The presence of skin vesicles among patients in any of the disease categories and of seizures in patients with CNS HSV disease seem to be among the most suggestive findings of HSV infection. The absence of fever is common at the time of presentation of neonatal HSV disease. As Table 3 illustrates, no single constellation of presenting symptoms and signs identifies all infants with neonatal HSV disease.

As the most outwardly apparent clinical sign of neonatal HSV disease, the development of cutaneous lesions warrants additional summation. As demonstrated in Table 4, 53 (83%) of 64 SEM patients had skin vesicles at some point during their disease course. In comparison, 43 (68%) of the 63 patients classified as having CNS disease had skin vesicles during their disease course, and 36 (61%) of 59 neonates with disseminated HSV disease had the characteristic skin lesions of neonatal HSV infection. The vast majority of patients in each disease category with skin lesions had clinically apparent vesicles before initiation of therapy, and continued to have new lesions develop early into the course of antiviral treatment. It should be emphasized, however, that 17% to 39% of all patients never had skin vesicles throughout the course of their acute HSV disease.

Disease Outcome

Mortality

Because no patients with SEM disease died, mortality analyses were performed only on the patients with CNS and disseminated diseases. The Cox regression analyses, which controlled for the treatment dose (SD versus ID versus HD acyclovir), were used to explore the impact on mortality of: 1) ethnicity (white vs others); 2) prematurity; and 3) indicators of disease severity at the initiation of therapy, including pneumonia, DIC, seizures, hepatitis, fever, skin vesicles, lethargy, and conjunctivitis. These factors had been identified on the basis of their clinical relevance to disease outcome and of previous univariate analysis.

For patients with CNS disease, mortality was borderline significantly associated with: 1) prematurity (P = .0493); and 2) seizures at initiation of therapy (P = .0637).

For patients with disseminated disease, the interaction effect of aspartate transaminase (AST) and treatment dose was statistically significant. Among patients treated with SD acyclovir, AST elevations of ≥10 times the upper limit of normal at the initiation

TABLE 4. Progression of Skin Vesicles Before and During Therapy

	Skin Lesions Before or at Enrollment	Skin Lesions Before or at Enrollment + New Lesions During Therapy	No Skin Lesions Before or at Enrollment but Developed New Lesions During Therapy	Total
SEM (n = 64)	5	48	0	53 (83%)
CNS (n = 63)	14	26	3	43 (68%)
Disseminated (n = 59)	6	28	2	36 (61%)

of therapy were associated with significantly increased mortality ($P = .0006$). However, such elevations of AST at the initiation of acyclovir therapy were not associated with significantly increased mortality among patients treated with ID or HD acyclovir. Mortality was also significantly associated among patients with disseminated disease with the presence of lethargy at initiation of antiviral therapy ($P = .0194$).

Morbidity

Among surviving patients with known morbidity after 12 months of age, 47 (98%) of 48 of patients with SEM disease, 13 (30%) of 43 patients with CNS disease, and 18 (75%) of 24 patients with disseminated disease had normal development at 12 months of life. The logistic regression analysis using conditional exact inference was used to assess the impact on morbidity (normal versus abnormal) at 12 months of age of ethnicity (white versus others), prematurity, and indicators of disease severity at the initiation of therapy (including pneumonia, DIC, seizures, hepatitis, fever, skin vesicles, lethargy, and conjunctivitis), with adjustment for treatment dose (HD versus SD or ID).

Among patients with CNS disease, seizures at the initiation of therapy significantly increased the chance of abnormal development at 12 months, compared with patients who did not have seizures ($P = .0001$). Among patients with disseminated disease, seizures at the initiation of therapy were also borderline significantly associated with abnormal development at 12 months, compared with patients who did not have seizures ($P = .076$).

Additional logistic regression analysis with adjustments both for acyclovir treatment dose (HD versus SD or ID) and for seizures at the initiation of therapy revealed that patients with CNS and disseminated disease were less likely to develop normally at 12 months compared with patients with SEM disease ($P = .000008$ and .0309, respectively).

Viral Type

The percentage of patients whose neonatal HSV disease was caused by HSV-2 increased between 1981–1988 and 1989–1997 from 64% to 73%. Reciprocally, the percentage of neonatal disease caused by HSV-1 decreased from 36% to 27% during the same time periods. These changes were not statistically significant ($P = .251$).

The effects of viral type on disease outcome for the 186 patients who received acyclovir in CASG studies between 1981 to 1997 are presented in Fig 1 and Table 5. Differences in combined morbidity and mortality status in HSV-1 disease compared with HSV-2 disease were not statistically significant for patients with SEM disease ($P = .455$), with CNS disease ($P = .278$), or with disseminated disease ($P = .595$).

The Cox regression analysis was used to assess the impact of viral type on mortality rate, with stratification for disease category (CNS vs disseminated) and with adjustment for acyclovir treatment dose (SD versus ID versus HD), AST, interaction of AST and treatment dose, prematurity, lethargy (at baseline), and seizures (at baseline). On the whole, the survival rate of the patients infected with HSV-2 was higher compared with those infected with HSV-1; however, the difference was not statistically significant ($P = .546$).

The logistic regression was used to compare the difference in morbidity at 12 months (normal vs abnormal) between surviving patients infected with HSV-1 and HSV-2 on the whole, with stratification for the extent of disease (CNS vs SEM vs disseminated), and adjustment for acyclovir treatment dose (HD versus SD or ID) and seizures at initiation of therapy. The impact of viral type was borderline significantly associated with abnormal development at 12 months ($P = .10$), with patients infected with HSV-2 being more likely to develop abnormally at 12 months as compared with HSV-1-infected patients.

Diagnostic Evaluations

Abnormalities of electroencephalograms (EEGs) and neuroimaging studies as a function of the extent of HSV disease are presented in Table 6. Among patients with CNS involvement of their neonatal HSV infection (those patients classified with either CNS disease or with disseminated disease with CNS involvement), 36 (82%) of 44 patients had an abnormal EEG during treatment for their acute HSV disease (within 10–21 days). These same patients with CNS involvement were somewhat less likely to have abnormal neuroimaging studies during this same time frame, with 31 (65%) of 48 patients having radiographic evidence of HSV disease of the brain.

Of the sites routinely cultured for HSV, skin or conjunctival cultures consistently provided the greatest yields regardless of disease classification, with ≥ 90% of cultures being positive. Overall, 58

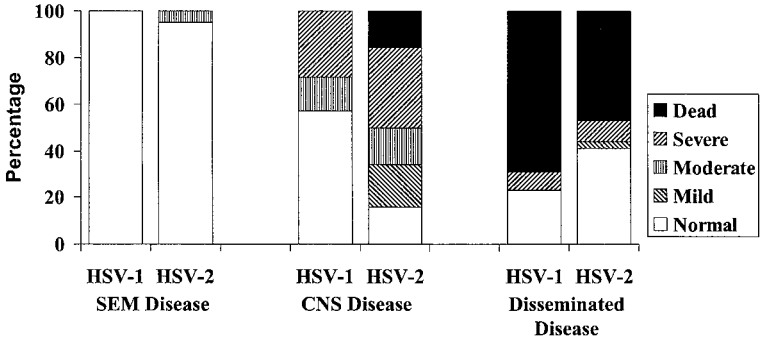

Fig 1. Morbidity and mortality among patients after 12 months of age by viral type, 1981–1997.

TABLE 5. Morbidity and Mortality Among Patients After 12 Months by Viral Type, 1981–1997

	Disease Classification					
	SEM		CNS		Disseminated	
Outcome	HSV-1	HSV-2	HSV-1	HSV-2	HSV-1	HSV-2
Normal	24 (100%)	19 (95%)	4 (57%)	7 (17.5%)	3 (23%)	14 (41%)
Mild impairment	0 (0%)	0 (0%)	0 (0%)	7 (17.5%)	0 (0%)	1 (3%)
Moderate impairment	0 (0%)	1 (5%)	1 (14%)	7 (17.5%)	0 (0%)	0 (0%)
Severe impairment	0 (0%)	0 (0%)	2 (29%)	13 (32.5%)	1 (8%)	3 (9%)
Death	0 (0%)	0 (0%)	0 (0%)	6 (15%)	9 (69%)	16 (47%)
Unknown	Total of 20		Total of 16		Total of 12	

TABLE 6. Diagnostic Abnormalities During Treatment of Acute HSV Disease, 1989–1997

	Diagnostic Abnormality Due to HSV	
Extent of Disease	Abnormal EEG	Abnormal Neuroimaging Study
CNS disease	22/26 (85%)	20/27 (74%)
Disseminated + CNS	14/18 (78%)	11/21 (52%)
Disseminated without CNS	0/12 (0%)	0/13 (0%)
SEM disease	0/9 (0%)	0/10 (0%)

(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.

DISCUSSION

Early initiation of antiviral therapy has been proven to favorably impact the outcome of neonatal HSV disease.[7] With the availability of safe and effective antiviral therapy, awareness of neonatal HSV disease has increased over the past two decades. However, we have yet to fully capitalize on the opportunity to initiate antiviral therapy very early in the disease course. The data presented in the current comparison of neonatal HSV disease over 2 time periods (1981–1988 vs 1989–1997) suggests that no progress has been made in decreasing the time interval between onset of HSV symptoms and initiation of antiviral therapy. It is unlikely that additional strides can be made in improvement of disease outcome unless the interval between onset of symptoms and initiation of therapy is shortened, and the means by which this will be accomplished lie in increased consideration of neonatal HSV infections.

Although it is the opinion of the authors that acyclovir should *not* be added routinely to standard antibiotics as management for neonates admitted to rule out sepsis, HSV should be considered in the differential diagnosis of acutely ill infants under 1 month of age. If the presentation is compatible with neonatal HSV disease, appropriate laboratory specimens should be obtained and then acyclovir initiated. This is especially true if the patient's bacterial cultures are negative at 48 to 72 hours and the neonate has not improved clinically. The diagnostic evaluations obtained before initiation of acyclovir therapy should include HSV cultures of skin vesicles (if present), oropharynx, conjunctivae, urine, blood, stool or rectum, and CSF.[11] CSF should also be sent to a reliable laboratory for HSV DNA polymerase chain reaction (PCR).[12] Evaluation of blood by PCR for HSV DNA may also be beneficial, although application of this powerful diagnostic tool to the evaluation of HSV viremia currently is less advanced than is the case with PCR evaluation of CSF.[13–15] Liver transaminases should also be obtained, as their elevation could suggest disseminated HSV infection. The recently completed CASG evaluation of high-dose acyclovir supports the use of intravenous acyclovir at a dose of 60 mg/kg/d administered in 3 divided daily doses for a duration of 21 days in patients with CNS or disseminated neonatal HSV disease,[4] and for 14 days in patients with SEM disease.[11] 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.

In considering whether a neonate may have HSV disease, it is essential to remember that 17% to 39% of all patients in the current report did not have skin vesicles at the time of their presentation, nor did they develop them during their disease course. Additionally, patients with proven HSV disease with possible involvement of the CNS should have an EEG, and strong consideration should be given to performing a computed tomography scan or magnetic resonance imaging during the acute period.

The patient population reported herein includes the largest number of patients with disseminated neonatal HSV disease reported to date in the medical literature. Despite this, the sample sizes for the 3 disease classifications were still insufficient to definitively prove or disprove an association between viral type and disease outcome. In the current study, differences in mortality rates for patients infected with HSV-1 versus HSV-2 were not statistically significantly different. On the other hand, morbidity seemed greater with HSV-2 infections, with the results achieving borderline significance ($P = .10$). These results are similar to those suggested in previous studies.[5,16]

In summary, much work remains to be performed in raising awareness of neonatal HSV infection. Cooperative efforts during the 1980s proved that acyclovir is a safe and effective treatment for neonates with HSV disease. Diagnostic and laboratory advances during the 1990s have included the routine

application of PCR technology in the evaluation of clinical CSF specimens to either diagnose patients with HSV disease or to monitor their response to therapy.[12] Enhanced appreciation of neonatal HSV infection, in conjunction with judicious utilization of these diagnostic modalities, represent the most immediate manner in which additional improvements in the outcome of neonatal HSV disease can be accomplished.

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