The Prevalence of Neonatal Herpes Simplex Virus Infection Compared with Serious Bacterial Illness in Hospitalized Neonates

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Objective To determine the prevalence of herpes simplex virus (HSV) relative to other viral infections and serious bacterial illnesses (SBIs) in hospitalized neonates admitted from a pediatric emergency department over a 5-year period.

Study design Retrospective prevalence study of laboratory-confirmed viral infections and culture-proven SBIs, with electronic databases and medical record review.

Results A total 5817 neonates were included: 8.4% with viral infection, 4.6% with SBIs. Of 960 neonates with documented fever, 17.2% had viral infections (0.3% HSV infection) and 14.2% had SBIs (1.3% bacterial meningitis). Of 204 neonates with fever and cerebrospinal fluid (CSF) pleocytosis, 1.0% had HSV infection and 5.4% had bacterial meningitis. Of 124 neonates with fever and mononuclear CSF pleocytosis, 1.6% had HSV and 0.8% had bacterial meningitis. Of 187 neonates with hypothermia, 1.1% had HSV infection presenting as a sepsis-like syndrome.

Conclusions In febrile neonates admitted to the hospital from the emergency department, the prevalence of HSV infection was similar to that of bacterial meningitis, suggesting that HSV infection be considered in the differential diagnosis of neonatal fever, especially in the presence of mononuclear CSF pleocytosis. HSV infection should also be considered in neonates with hypothermia and a sepsis-like syndrome. *(J Pediatr 2008;153:164-9)*

Herpes simplex virus (HSV) infection can cause significant morbidity and death in neonates. Because fever can be a manifestation of HSV infection[1] and fever is a common symptom in neonates evaluated in the emergency department (ED),[2-4] the American Academy of Pediatrics Committee on Infectious Diseases suggests that HSV infection be considered in "neonates with fever, irritability, and abnormal cerebrospinal fluid (CSF) findings, especially in the presence of seizures."[5] However, it remains unclear whether the approach to the febrile neonate should routinely include the evaluation and treatment of serious viral infections, including HSV infection.

Information on the prevalence and relative importance of HSV in neonates who are admitted with fever would be valuable to the medical decision-making process regarding optimal management of these neonates. However, there has been only 1 small retrospective study with information related to prevalence of HSV. In that study, there was 1 case of HSV in 113 febrile neonates, but the study did not include all febrile neonates and therefore was unable to provide an estimate of HSV prevalence.[6]

It is standard practice in most centers to admit febrile neonates to the hospital for evaluation and treatment of serious bacterial illnesses (SBIs), including meningitis, bloodstream infection, and urinary tract infection (UTI).[2-4,7,8] However, even though HSV is a treatable serious viral infection, it is not standard practice in most institutions to evaluate for HSV and initiate acyclovir in all febrile neonates. We sought to determine the prevalence of HSV infection relative to other viral infections and SBIs in neonates admitted to a children's hospital from a pediatric ED over a 5-year period.

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METHODS

Study Population

The study population included every infant aged 28 days or younger evaluated in the ED with any chief complaint and admitted to Texas Children's Hospital (TCH) for any reason between January 1, 2001, and December 31, 2005. TCH is a tertiary care center with approximately 2000 neonatal admissions per year.

CI	Confidence interval	PMN	Polymorphonuclear leukocyte
CSF	Cerebrospinal fluid	RBC	Red blood cell
DVL	Diagnostic Virology Laboratory	SBI	Serious bacterial illness
ED	Emergency department	TCH	Texas Children's Hospital
HSV	Herpes simplex virus	UTI	Urinary tract infection
PCR	Polymerase chain reaction	WBC	White blood cell

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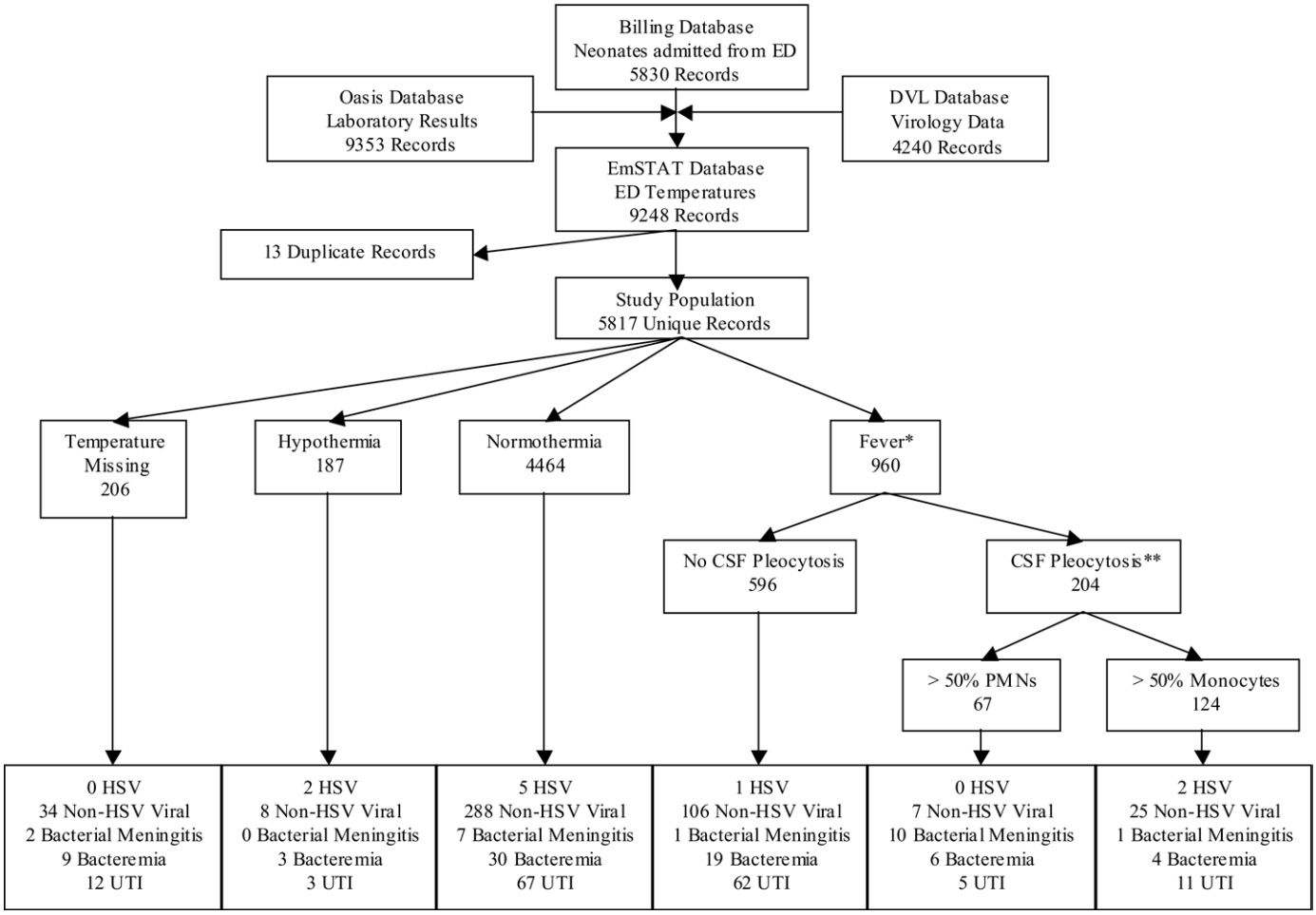

Figure. Flowchart of data sources reviewed, temperature status, and diagnoses for neonates hospitalized from a pediatric emergency department over a 5-year period. *Missing CSF WBCs for 160: 0 HSV, 19 non-HSV viral, 0 bacteremia, and 14 UTI. **Missing CSF WBC differential for 13: 0 HSV, 2 non-HSV viral, 0 bacteremia, and 3 UTI.

An electronic database of TCH billing records was used to identify the study population and combined with 3 additional electronic databases to acquire clinical, laboratory, bacterial, and virologic information for these neonates (Figure). All datasets were merged by medical record number and date of visit. The TCH database of electronic billing records was used to identify neonates hospitalized from the ED. The chief complaint and temperature were obtained from the database used in the TCH ED (EmSTAT; Allscripts, Chicago, Ill). One hundred ED charts were randomly selected and reviewed to verify that the electronically recorded chief complaint and temperature were accurate. The laboratory findings and bacterial culture results were obtained from an electronic database used throughout TCH (Oacis; Dinmar, Santa Clara, Calif). Electronic records from TCH Diagnostic Virology Laboratory (DVL) were used to identify neonates with viral infections, including HSV.[9] Not all neonates had all or the same laboratory tests, bacterial cultures, and viral tests performed. The study was approved by the Baylor College of Medicine Institutional Review Board and The University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects.

Case Identification

Neonates were classified as having HSV infection if they had both a positive HSV test result performed in the TCH DVL that was recorded in the DVL HSV dataset and neonatal HSV infection confirmed in the review of their medical record. HSV tests included in the DVL HSV dataset include the following: HSV DNA detection by polymerase chain reaction (PCR), HSV antigen detection by direct fluorescence assay, and viral culture, on any tissue or body fluid obtained before or after death.

The principal investigator and a neonatologist independently reviewed the medical records of all 10 neonates with HSV infection.[9] Neonatal HSV classification was assigned on the basis of the system adapted from that used by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group for their therapeutic trials.[10] Cases were independently confirmed by an infectious disease expert and virologist (G.J.D.).

Neonates with non-HSV viral infections were included if they had positive viral test results for a virus other than HSV from any source. Viral tests included viral cultures, viral

nucleic acid (DNA or RNA) identification by PCR, and rapid viral antigen detection by immunochromatographic or immunofluorescence assays. Records were not reviewed to confirm non-HSV viral diagnoses.

Neonates with positive bacterial culture results from CSF, blood, or urine were identified from the electronic database, and their medical records were reviewed. Subjects were classified as having meningitis if CSF bacterial culture was positive, bloodstream infection (bacteremia or septicemia) if blood culture was positive, and UTI if their urine culture had isolation of 10,000 CFU/mL or greater of a urinary pathogen, and they were diagnosed with meningitis, bacteremia, or UTI, respectively, by review of medical records. Positive bacterial cultures were considered contaminants if they were documented as such in the medical record or if the neonate was not discharged with a diagnosis of bacterial meningitis, bloodstream infection, or UTI. Neonates with positive bacterial cultures regarded as contaminants were excluded from the numerator of the prevalence estimates. A random sample of 100 medical records for neonates not identified through the previously described case identification process was reviewed to confirm that infants did not have a clinical diagnosis of HSV or serious bacterial infection.

Analysis

Analysis was performed with Intercooled Stata 9.0. (Statacorp, College Station, Texas). Demographic information for the study population was described by use of frequencies and measures of central tendency and dispersion. Neonates with HSV infection also were described individually in detail.

Prevalence proportions and 95% confidence intervals (CIs) of neonatal HSV infection, non-HSV viral infection, and SBIs were estimated for the 5-year study period. The numerators were determined from the case identification process to be the number of neonates with HSV, positive non-HSV viral test results, or SBIs for that time period. The denominator was the total number in the study population as identified from the TCH billing dataset and further described with information from the EmSTAT and Oasis datasets. Ninety-five percent CIs were calculated with exact binomial methods. In addition, the prevalence proportion for each infection type was calculated for the following categories: age group (0-7 days, 8-14 days, 15-21 days, and 22-28 days), temperature in the ED (hypothermic [a rectal temperature less than or equal to 36.4° C], normothermic, and febrile [a rectal temperature greater than or equal to 38.0° C]), CSF white blood cell (WBC) category (0-19 WBCs/mm^3, ≥20 WBCs/mm^3), CSF red blood cell (RBC) category (0-49 RBCs/mm^3, ≥50 RBCs/mm^3). CSF pleocytosis was defined as ≥20 WBCs/mm^3 and more than 1 WBC per 500 RBCs/mm^3.

RESULTS

Of 5817 neonates admitted from the ED, 56% were male, 41% were Hispanic, 33% were white, 18% were African American, 3% were Asian, 3% were another ethnicity, and 2% were unknown. The median age was 15 days (interquartile range 8-22), and the median length of stay was 3 days (interquartile range 1-4). Of the study population, 4464 were normothermic, 960 were febrile, 187 were hypothermic, and 206 did not have temperature recorded in the ED.

For all 5817 subjects included in the study, viral tests were performed on 28%, CSF bacterial cultures on 45%, blood cultures on 53%, and urine cultures on 49%. Of the 5817 neonates, 8.6% (95% CI 7.9%-9.3%) had viral infections (8.4% non-HSV and 0.2% HSV), and 4.6% (95% CI 4.1%-5.2%) had SBIs (Table I). Non-HSV viral infections were the most common type of infections in all neonates and within all age, temperature, CSF RBCs, and CSF pleocytosis subgroups. However, infants in the second week of life had the highest HSV prevalence (0.6%) of all the age groups, and the prevalence of HSV infection was higher in hypothermic (1.1%) than febrile neonates (0.3%), although this difference was not statistically significant. Although the general prevalence of HSV (0.2%) was two times lower than bacterial meningitis (0.4%), confidence intervals of point estimates overlap. Febrile neonates with CSF pleocytosis and polymorphonuclear cell predominance had a statistically higher prevalence of bacterial meningitis (14.9%) than HSV infection (0.0%) and febrile neonates with CSF pleocytosis and mononuclear cell predominance had a significantly higher prevalence of HSV infection (1.6%) than bacterial meningitis (0.8%).

Of the 960 neonates with fever documented in the ED, viral cultures were performed on 42%, CSF bacterial cultures on 91%, blood cultures on 93%, and urine cultures on 94%. Of all febrile neonates, 17.2% (95% CI 14.9%-19.7%) had viral infections, and 14.2% (95% CI 12.0%-16.5%) had SBIs (Table I). There were 160 without CSF analyses performed: none had HSV infection, 19 had non-HSV viral infections, none had bloodstream infection, and 14 had UTI.

There were 204 neonates with fever and CSF pleocytosis. Of these, 1.0% (95% CI 0.1%-3.5%) had HSV and 5.4% (95% CI 2.7%-9.4%) had bacterial meningitis. Of the 2 with HSV, both were classified as having CNS disease, 1 CSF had 3% polymorphonuclear leukocytes (PMNs) and 97% mononuclear cells while the other had 100% mononuclear cells, 1 had a positive CSF HSV PCR, and the other had a negative CSF HSV PCR. The negative PCR was added to the routine CSF studies 12 hours after the lumbar puncture at the time when acyclovir was initiated, and it is possible that the specimen was then suboptimal for HSV PCR testing or that the test was done early in illness when the HSV PCR sensitivity is low relative to late in illness.[11] Of the 11 neonates with bacterial meningitis, all CSF WBC reports included PMNs and 10 had more than 50% PMNs. There were 13 neonates in whom differential analysis of CSF WFBs was not performed: none had HSV infection, 2 had non-HSV viral infections, none had bacteremia, and 3 had UTI.

There were 499 viral pathogens identified in the study population of which 10 (2.0%) were HSV. Of the viral pathogens, 46.7% were respiratory syncytial virus, 16.0% were rhinoviruses, and 13.4% were enteroviruses. There were 269

Table I. Prevalence proportions by age, year, temperature, chief complaint, and CSF findings*

Characteristic	N	Viral infection		Serious bacterial infection		
		HSV % (95% CI)	Non-HSV % (95% CI)	Meningitis % (95% CI)	Bacteremia % (95% CI)	UTI % (95% CI)
All neonates	5817	0.2 (0.1, 0.3)	8.4 (7.7, 9.1)	0.4 (0.2, 0.6)	1.2 (1.0, 1.5)	3.0 (2.6, 3.5)
Age						
0-7 days	1376	0.0 (0.0, 0.2)	1.9 (1.2, 2.8)	0.4 (0.1, 0.8)	1.1 (0.6, 1.8)	1.1 (0.6, 1.8)
8-14 days	1400	0.6 (0.3, 1.2)	9.7 (8.2, 11.4)	0.2 (0.0, 0.6)	1.3 (0.8, 2.0)	3.4 (2.5, 4.4)
15-21 days	1449	0.1 (0.0, 0.4)	10.4 (8.8, 12.0)	0.6 (0.2, 1.1)	1.4 (0.8, 2.1)	4.1 (3.1, 5.2)
22-28 days	1592	0.0 (0.0, 0.2)	11.7 (10.2, 13.4)	0.3 (0.1, 0.7)	1.1 (0.7, 1.8)	3.5 (2.7, 4.5)
Temperature						
<36.4° C	187	1.1 (0.1, 3.8)	5.3 (2.6, 9.6)	0.0 (0.0, 2.0)	1.6 (0.3, 4.6)	1.6 (0.3, 4.6)
36.5°-37.9° C	4464	0.1 (0.0, 0.3)	6.6 (5.9, 7.3)	0.2 (0.1, 0.3)	0.6 (0.4, 0.9)	1.5 (1.2, 1.9)
>38.0° C	960	0.3 (0.1, 0.9)	16.9 (14.6, 19.4)	1.3 (0.6, 2.2)	3.1 (2.1, 4.4)	9.9 (8.1, 12.0)
Missing	206	0.0 (0.0, 1.8)	16.5 (11.7, 22.3)	1.0 (0.1, 3.5)	4.4 (2.0, 8.1)	5.8 (3.0, 10.0)
CSF RBCs/mm^3						
0-49	1263	0.2 (0.1, 0.7)	14.3 (12.4, 16.4)	0.2 (0.1, 0.7)	2.7 (1.9, 3.7)	6.5 (5.2, 8.0)
>50	1113	0.4 (0.1, 1.0)	11.5 (9.7, 13.5)	1.6 (1.0, 2.5)	2.6 (1.8, 3.7)	6.5 (5.1, 8.1)
CSF Pleocytosis						
No	1904	0.3 (0.1, 0.6)	12.9 (11.4, 14.5)	0.3 (0.1, 0.7)	2.3 (1.6, 3.0)	6.3 (5.3, 7.5)
Yes	472	0.6 (0.1, 1.9)	13.6 (10.6, 17.0)	3.2 (1.8, 5.2)	4.2 (2.6, 6.5)	7.2 (5.0, 9.9)
>50% PMNs	102	0.0 (0.0, 3.6)	11.8 (6.2, 19.6)	13.7 (7.7, 22.0)	10.8 (5.5, 18.5)	6.9 (2.8, 13.6)
>50% Monos	330	0.9 (0.2, 2.6)	13.9 (10.4, 18.2)	0.3 (0.0, 1.7)	2.4 (1.1, 4.7)	6.7 (4.2, 9.9)
Fever and CSF pleocytosis						
Yes	204	1.0 (0.1, 3.5)	17.6 (12.7, 23.6)	5.4 (2.7, 9.4)	4.9 (2.4, 8.8)	9.3 (5.7, 14.2)
>50% PMNs	67	0.0 (0.0, 5.4)	10.4 (4.3, 20.3)	14.9 (7.4, 25.7)	9.0 (3.4, 18.5)	7.5 (2.5, 16.6)
>50% Monos	124	1.6 (0.2, 5.7)	21.8 (14.9, 30.1)	0.8 (0.0, 4.4)	3.2 (0.9, 8.1)	8.9 (4.5, 15.3)

*CSF studies were not performed on all neonates.
Monos, mononuclear cells; *CSF pleocytosis,* >20 WBCs/mm^3 and >1 WBC per 500 RBCs/mm^3; *PMNs,* polymorphonuclear leukocytes.

neonates with SBIs (21 bacterial meningitis, 71 bloodstream infections, and 177 UTI). Of the bacterial meningitis pathogens, 57.1% were *Streptococcus agalactiae* and 14.3% were *Escherichia coli*. Of the bloodstream pathogens, 29.6% were *S. agalactiae* and, 26.8% were *E. coli*. Of the UTI pathogens, 73.4% were *E. coli*. No neonate had concomitant bloodstream infection, UTI, and meningitis whereas 20 had both bacteremia and UTI with the same organism and 11 had bloodstream infection and meningitis with the same organism. One neonate had a UTI caused by one organism (*E. coli*) and meningitis caused by a different organism (*Enterococcus faecalis*). Of the positive bacterial cultures, 1.3% of CSF culture results, 6.6% of blood culture results, and 11.4% of urine culture results were deemed to be contaminants by review of the medical records.

The number of neonates with HSV CNS disease was similar during the enteroviral and non-enteroviral seasons. Of the 146 febrile neonates admitted with CSF pleocytosis in the enteroviral seasons (March through September), 20 had enterovirus, and 1 had HSV infection. Of the 58 febrile neonates admitted with CSF pleocytosis in the non-enteroviral seasons (October through February), 6 had enterovirus, and 1 had HSV infection.

Of the 10 neonates with HSV infection, 3 had disseminated disease, 3 had CNS disease, and 4 had skin, eye, and mouth HSV disease (Table II). Of the 3 neonates with fever documented in ED and confirmed HSV infections, one was noted to be well appearing, one was noted to be lethargic, and one was noted to have a vesicular rash on the eyelid. Of the 6 neonates with HSV who presented with a chief complaint of rash, 5 (1 with CNS disease and 4 with skin, eye, and mouth HSV disease) were noted to have vesicular lesions on the scalp (n = 3), eyelid (n = 1), and generalized (n = 1) in the ED, and 1 (with fever and CNS disease) was noted to have vesicular lesions in the genitourinary area after admission to the hospital.

DISCUSSION

This study indicated that the prevalence of HSV infection (0.2%) was not statistically different from that of bacterial meningitis (0.4%) but lower than that of all SBIs (4.6%) in all hospitalized neonates. The results are consistent with estimates from the 2003 Healthcare Cost and Utilization Project Kids' Inpatient Database in which neonatal HSV infection accounted for 0.2% of pediatric hospitalizations in the United States that year.[12] For febrile neonates, our estimate of HSV infection (0.3%) was lower than that reported previously (0.9%) by Filipine and Katz[6] in the only other study to make this estimate. In that study, of only 113 neonates identified by International Classification of Disease, 9th Revision (ICD-9) code for an illness likely to cause fever (bacteremia, UTI, and meningitis, but not pneumonia), 0.9% (95% CI 0.0%-4.8%) had disseminated HSV and 1.8% (95% CI 0.0%-6.2%) had bacterial meningitis. The study by Filipine and Katz[6] likely overestimated the prevalence of HSV infection and bacterial meningitis,

Table II. Description of 10 neonates with HSV infection

Age (days)	Chief complaint	Rectal temperature (°C)	CSF WBC/ mm^3	CSF RBC/ mm^3	AST (U/L)	Death in hospital	HSV classification	HSV type	Positive HSV test result
8	Fever	39.2	18	5	15930	Yes	Disseminated	2	Blood PCR
8	Respiratory distress	33.3	NA	NA	13870	Yes	Disseminated	1	Nasal wash culture
11	Respiratory distress	33.7	4	3430	1548 1	Yes	Disseminated	2	Liver culture At autopsy
8	Eyelid vesicles	37.8	250	2	36	No	CNS	2	Skin culture CSF PCR
17	Lethargy	38.1	836	62	41	No	CNS	2	Skin culture
13	Rash	38.0	1008	10	69	No	CNS	2	Skin culture CSF culture CSF PCR
12	Rash	37.9	16	118	34	No	SEM	1	Skin culture
10	Rash	37.4	11	55	None	No	SEM	1	Skin culture
9	Rash	37.3	9	310	49	No	SEM	2	Skin culture
8	Rash	36.8	9	206	45	No	SEM	1	Skin culture

AST, Asparate aminotransferase; *CNS,* central nervous system; *SEM,* skin, eye, mouth.

because it relied on diagnostic codes rather than presenting signs and therefore did not include all febrile neonates over the study period. The estimates from our study are more likely to be accurate because they are based on all neonates admitted with fever over a specified time period and our large sample size provides more precise prevalence estimates. However, the estimates from our study and the previous study[6] both may have underestimated the prevalence of HSV infection because viral testing was not performed prospectively on all neonates but rather was performed according to physician discretion.

In our study, 50% of neonates with HSV infection were fever free, 30% were febrile, and 20% were hypothermic at presentation. Furthermore, the prevalence of HSV infection was not statistically different in neonates who were hypothermic (1.1%), normothermic (0.1%), and febrile (0.3%). These findings are consistent with previous findings that although fever occurs in neonates with HSV infection, fever is not a unique identifying feature of neonatal HSV disease.[1,9] In fact, in our study, only 1 neonate with HSV infection presented with fever as an isolated complaint. Moreover, the 2 HSV-infected neonates with hypothermia presented with a sepsis-like syndrome, including respiratory distress requiring mechanical ventilation, emphasizing that clinicians must be vigilant to the presence of HSV in hypothermic neonates presenting with sepsis-like syndromes.

In febrile neonates with CSF pleocytosis, bacterial meningitis (5.4%) was more likely than HSV infection (1.0%), but the difference was not statistically significant. In febrile neonates with CSF pleocytosis and polymorphonuclear cell predominance, bacterial meningitis was statistically more likely than HSV infection (14.9% versus 0.0%). Although there were no cases of HSV infection in this group, the confidence interval of the estimate includes prevalence up to 5.4%, emphasizing that HSV may not be excluded in neonates with CSF polymorphonuclear pleocytosis. Although, in febrile neonates with mononuclear CSF pleocytosis, the prevalence of HSV infection was higher than bacterial meningitis, the difference also was not statistically significant. In addition, although there were more neonates with CSF pleocytosis during enteroviral season, the number of neonates with HSV infection was constant throughout the year, indicating although the relative importance of HSV infection may be lower in the enteroviral than non-enteroviral season, HSV infection remains an important cause of CSF pleocytosis in neonates throughout the year.

The primary limitation of our study is its retrospective design. Because not all neonates were tested for viral and bacterial pathogens, it is possible that the prevalence of both viral and bacterial infections were underestimated in our study. In a small prospective study of "sick" febrile infants younger than 3 months of age, a viral pathogen was identified in 41% and a bacterial pathogen in 15%.[13] In a more recent prospective study, a viral pathogen was identified in 35% and a bacterial pathogen in 9.5% of infants aged 0 to 90 days.[14] It is possible that the prevalence estimates from our study underestimated the true prevalence of neonatal HSV infection. Moreover, the selection bias introduced by selective testing would likely have biased the prevalence estimates to be higher for neonates with symptoms of HSV infection (particularly vesicular rash) than for those neonates without symptoms. It is partly for this reason we included only hospitalized neonates; given that HSV infection results in symptomatic disease in neonates and is associated with a relatively severe clinical course, it is likely that most HSV infections were diagnosed. Follow-up of hospitalized neonates, some of whom may have received acyclovir, was not performed. Limitations taken together, this study is likely to underestimate the true prevalence of HSV infection in hospitalized neonates.

It is also possible that the frequencies of SBIs were underestimated because we chose to define these diagnoses by

the presence of a positive CSF, bacterial, or urine culture performed at TCH. It is likely, however, that subjects transferred to TCH with positive cultures at other institutions were not included in our estimates of bacterial illnesses. In addition, to increase accuracy of our positive bacterial diagnoses, we did not include pneumonia, a radiographically based diagnosis, in our definition of SBIs.

Our findings suggest HSV infection should be considered in the differential diagnosis of neonates who are febrile and evaluated for SBI, especially if a mononuclear CSF pleocytosis is present. Infection with HSV also should be considered in neonates with vesicular rash and in ill neonates with a sepsis-like syndrome (hypothermia, respiratory distress, and very elevated hepatic enzymes), especially if they become ill during the second week of life.

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REFERENCES

1. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Frenkel LM, Gruber WC, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 2001;108:223-9.

2. King C. Evaluation and management of febrile infants in the emergency department. Emerg Med Clin North Am 2003;21:89-99., vi-vii.

3. Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH Jr., Powell KR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Agency for Health Care Policy and Research. Ann Emerg Med 1993;22:1198-210.

4. Baraff LJ. Management of fever without source in infants and children. Ann Emerg Med 2000;36:602-14.

5. American Academy of Pediatrics. Committee on Infectious Diseases. Red Book: 2006 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2006.

6. Filippine MM, Katz BZ. Neonatal herpes simplex virus infection presenting with fever alone. J Hum Virol 2001;4:223-5.

7. Avner JR, Baker MD. Management of fever in infants and children. Emerg Med Clin North Am 2002;20:49-67.

8. Clinical policy for children younger than three years presenting to the emergency department with fever. Ann Emerg Med 2003;42:530-45.

9. Caviness A. Herpes simplex virus infection in hospitalized neonates: clinical epidemiology and cost-effectiveness analysis of testing and treatment strategies [Unpublished Dissertation]. Houston: UT School of Public Health; 2007.

10. Whitley R, Arvin A, Prober C, Burchett S, Corey L, Powell D, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. Infectious Diseases Collaborative Antiviral Study Group. N Engl J Med 1991;324: 444-9.

11. Troendle-Atkins J, Demmler GJ, Buffone GJ. Rapid diagnosis of herpes simplex virus encephalitis by using the polymerase chain reaction. J Pediatr 1993; 123:376-80.

12. Healthcare Cost and Utilization Project Kids' Inpatient Database (KID) 2003. Rockville, MD: Agency for Healthcare Research and Quality; 2003. Available at: www.hcup-us.ahrq.gov/kidoverview.jsp.

13. Krober MS, Bass JW, Powell JM, Smith FR, Seto DS. Bacterial and viral pathogens causing fever in infants less than 3 months old. Am J Dis Child 1985; 139:889-92.

14. Byington CL, Enriquez FR, Hoff C, Tuohy R, Taggart EW, Hillyard DR, et al. Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. Pediatrics 2004;113:1662-6.