Association of Herpes Simplex Virus Testing with Hospital Length of Stay for Infants ≤60 Days of Age Undergoing Evaluation for Meningitis

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Although neonatal herpes simplex virus (HSV) causes significant morbidity, utilization of the cerebrospinal fluid (CSF) HSV polymerase chain reaction (PCR) test remains variable. Our objective was to examine the association of CSF HSV PCR testing with length of stay (LOS) in a 20-center retrospective cohort of hospitalized infants aged ≤60 days undergoing evaluation for meningitis after adjustment for patient-level factors and clustering by center. Of 20,496 eligible infants, 7,399 (36.1%) had a CSF HSV PCR test performed, and 46 (0.6% of those tested) had a positive test. Infants who had a CSF HSV PCR test performed had a 23% longer hospital LOS (incident rate ratio 1.23; 95% CI: 1.14-1.33). Targeted CSF HSV PCR testing may mitigate the impact on LOS for low-risk infants. *Journal of Hospital Medicine* 2019;14:492-495. Published online first May 10, 2019. © 2019 Society of Hospital Medicine

Neonatal herpes simplex virus (HSV) is associated with significant morbidity and mortality,[1] particularly when the diagnosis or treatment is delayed.[2] Therefore, many infants aged ≤60 days being evaluated for meningitis undergo cerebrospinal fluid (CSF) HSV polymerase chain reaction (PCR) testing even though the risk of HSV infection is low [estimated at 0.4% of those undergoing evaluation for central nervous system (CNS) infection].[3] A single-center study demonstrated that CSF HSV PCR testing increases the hospital length of stay (LOS) for infants aged ≤56 days,[4] although these single-center findings may not be generalizable. To this end, we measured the association between CSF HSV PCR testing and LOS in a multicenter cohort of hospitalized young infants.

METHODS

Study Design

We conducted a planned secondary analysis of a retrospective cohort of infants aged ≤60 days who presented to the emergency department (ED) between January 1, 2005 and December 31, 2013, enrolled in the Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) HSV study.[3] Our study was limited to the 20 hospitals that contributed hospital LOS data. The study protocol was approved by each site's institutional review board with permission for data sharing.

Study Population

Eligible infants were identified at each site using a site-specific electronic search strategy. Infants were eligible for inclusion if a CSF culture was obtained in the ED or within 24 hours of ED arrival. We excluded infants who were discharged from the ED and those with missing hospital LOS data.

Data Collection

Site investigators extracted the following data elements either electronically or from medical records: patient demographics; ED arrival date and time; hospital discharge date and time; urinalysis results; peripheral and CSF cell counts; blood, urine, and CSF bacterial culture results; as well as the results of HSV PCR and viral cultures. Infants with growth of a pathogen in blood or CSF, or a catheterized urine culture with ≥50,000 colony-forming units (CFUs)/mL of a single pathogenic bacteria, or 10,000-50,000 CFUs/mL of a single pathogenic bacteria with

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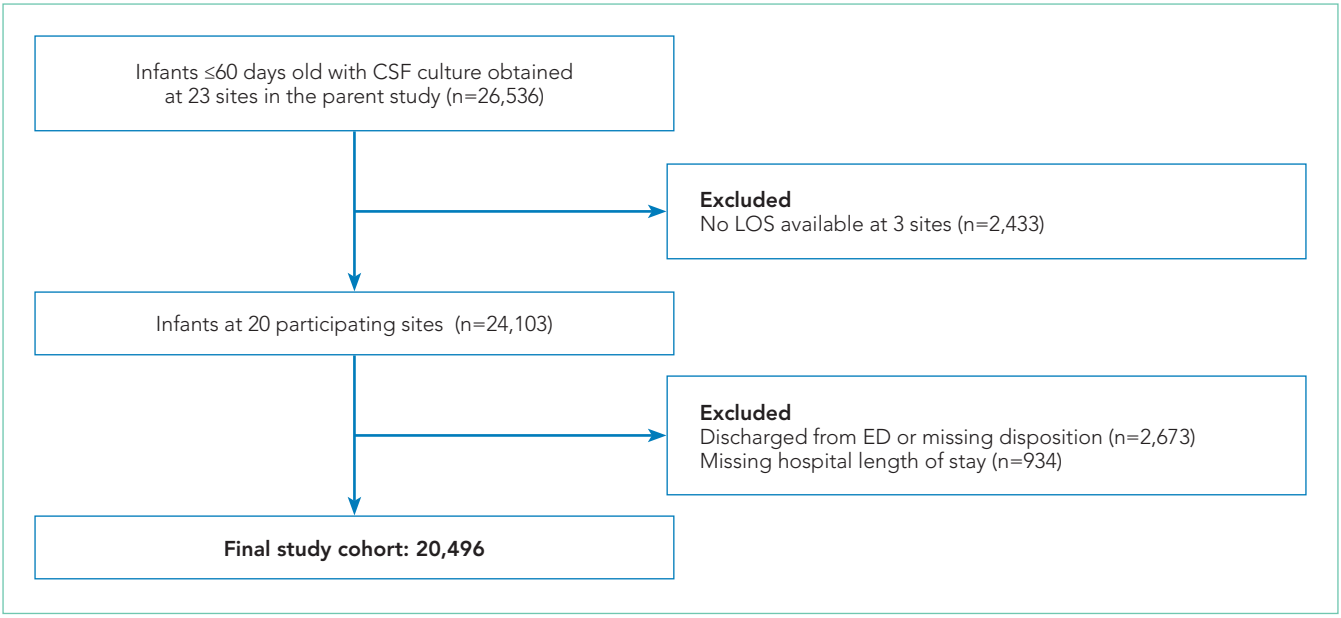

FIG. Study Cohort.

Abbreviations: CSF, cerebrospinal fluid; ED, emergency department; LOS, length of stay.

an abnormal urinalysis (ie, positive nitrite or leukocyte esterase on urine dipstick or >5 white blood cells [WBCs] per high power field on urine microscopy) were classified as having a serious bacterial infection (SBI).[5,6] Infants with a positive HSV PCR or viral culture from any site were classified as having HSV infection.[3] Hospitalized infants who did not have an HSV PCR test performed were assumed not to have HSV disease if not diagnosed during the hospital stay or repeat ED encounter.[3]

Outcome Measures

The primary outcome was hospital LOS, defined at all hospitals as the time from ED arrival to provider signature of the hospital discharge order, calculated in minutes and then converted into days.

Statistical Analysis

We described LOS using medians with interquartile ranges (IQR) and compared between infants with and without a CSF HSV PCR test performed using the Mann–Whitney U test. To evaluate the association between performance of CSF HSV PCR testing and hospital LOS, we used negative binomial regression given the count variable outcome (LOS) with an overdispersed distribution. For this analysis, we clustered by hospital after adjusting for the following factors determined *a priori*: age, gender, study year, and presence of serious bacterial or HSV infection. Using the relative marginal modeled estimates of LOS (tested vs not tested), we determined the percentage increase in LOS. We then repeated the analyses after stratifying by the location of testing (ie, in-house vs send-out), age (≤28 days vs 29-60 days), and presence or absence of CSF pleocytosis (defined as a CSF WBC of ≥16 cells/mm^3 for infants aged ≤28 days and ≥10 cells/mm^3 for infants aged 29-60 days),[7] because infants aged 29-60 days and those without CSF pleocytosis are reported to be at very low risk for CNS HSV infection.[3,8] We utilized Stata Data Analysis and Statistical Software, version 15.0 (StataCorp, Inc.; College Station, Texas) for statistical analyses.

RESULTS

Of 24,103 infants with CSF cultures obtained at the 20 participating sites, we excluded 2,673 (11.1%) discharged from the ED or with missing disposition and 934 (3.9%) with missing LOS, leaving a study cohort of 20,496 infants (Figure). Overall, 1,780 infants (8.7%) had an SBI and 99 (0.5%) had an HSV infection, of which 46 (46.5%) had a CNS HSV infection.

Among the 20,496 study infants, 7,399 (36.1%) had a CSF HSV PCR test performed; 5,935 infants (80.2% of those tested) had in-house and 1,464 (19.8%) had send-out testing. Among infants with available CSF cell counts, a CSF HSV PCR test was more commonly performed in infants with CSF pleocytosis than in those without (1,865/4,439 [42.0%] with CSF pleocytosis vs 3,705/12,002 [30.9%] without CSF pleocytosis; odds ratio [OR] 1.6, 95% CI 1.5-1.7). Of the 7,399 infants who had a CSF HSV PCR test performed, 46 (0.6%) had a positive test. Of the tested infants, 5,570 (75.3%) had an available CSF WBC count; a positive CSF HSV PCR test was more common in infants with CSF pleocytosis than in those without (25 positive tests/1,865 infants with CSF pleocytosis [1.3%] vs 9/3,705 [0.2%] without CSF pleocytosis; OR 5.6, 95% CI 2.6-12.0). Among the 5,308 infants aged 29-60 days without CSF pleocytosis, 1,110 (20.9%) had a CSF HSV PCR test performed and only one infant (0.09% of those tested) had a positive test.

Without adjustment, infants with a CSF HSV PCR test had a longer median LOS than infants who were not tested (2.5 vs 2.3 days; $P < .001$). After adjustment, infants with a CSF HSV PCR test performed had a 23% longer duration of hospitalization. The association between testing and LOS was similar for older

TABLE. **Length of Stay for Hospitalized Infants with a CSF HSV PCR Test Performed versus Infants without a CSF HSV PCR Test Performed**

	N	CSF HSV PCR LOS in Days Median (IQR)[a]	No CSF HSV PCR LOS in Days Median (IQR)[a]	IRR (95% CI)[b]	% Increase in LOS[c]
Overall	20,496	2.5 (2.0-3.8)	2.3 (1.9-3.0)	1.23 (1.14-1.33)	23%
Age					
≤28 days	11,269	2.6 (2.1-3.9)	2.4 (2.0-3.4)	1.19 (1.13-1.27)	19%
29-60 days	9,227	2.4 (2.0-3.5)	2.2 (1.8-2.9)	1.28 (1.12-1.47)	28%
CSF Pleocytosis					
CSF Pleocytosis	4,439	2.6 (2.1-3.9)	2.3 (1.8-2.9)	1.23 (1.15-1.31)	23%
No CSF pleocytosis	12,002	2.6 (2.1-4.0)	2.3 (1.9-3.0)	1.24 (1.15-1.35)	24%
Testing Location					
In house	14,928	2.5 (2.0-3.7)	2.3 (1.9-3.0)	1.22 (1.12-1.33)	22%
Send out	5,568	2.7 (2.1-4.3)	2.3 (1.9-3.1)	1.28 (1.05-1.57)	28%

[a]Unadjusted LOS

[b]Adjusted for age, gender, presence of serious bacterial or HSV infection, and study year, clustered by hospital using robust standard errors

[c]Using relative marginal modeled estimates of LOS (Tested vs Not Tested) from adjusted model

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; IRR, internal rate of return, HSV, herpes simplex virus; LOS, length of stay; PCR, polymerase chain reaction.

vs younger infants, infants with and without CSF pleocytosis, and in-house vs send-out testing (Table).

DISCUSSION

In a large, multicenter cohort of more than 20,000 hospitalized infants aged ≤60 days undergoing evaluation for meningitis, we examined the association of CSF HSV PCR testing with hospital LOS. Approximately one-third of study infants had a CSF HSV PCR test obtained. After adjustment for patient- and hospital-level factors, the treating clinician's decision to obtain a CSF HSV PCR test was associated with a 23% longer hospital LOS (nearly one-half day).

Our findings are consistent with those of previous studies. First, our observed association of the decision to obtain a CSF HSV PCR test and LOS was similar in magnitude to that of a previous single-center investigation.[4] Second, we also found that older infants and those without CSF pleocytosis were at very low risk of HSV infection.[3,8] For the otherwise low-risk infants, the longer LOS may be due to delays in obtaining CSF HSV PCR test results, which should be explored in future research. Our study has greater generalizability than previous single-center studies by substantially increasing the population size as well as the variety of clinical settings. Ensuring clinicians' access to rapid HSV PCR testing platforms will further mitigate the impact of HSV testing on LOS.

When deciding to perform a CSF HSV PCR test for infants aged ≤60 days, clinicians must balance the low incidence of neonatal HSV[3] with the risk of delayed diagnosis and treatment of HSV infection, which include neurologic sequelae or even death.[1,2] As infants with CNS HSV infection commonly present nonspecifically and only a minority of infected infants have skin vesicles,[1] controversy exists as to which infants should be evaluated for HSV infection, resulting in considerable variability in HSV testing.[3] Some clinicians advocate for more conservative testing strategies that include the performance of CSF HSV PCR testing in all febrile infants aged ≤21 days.[9] Others suggest limiting testing to infants who meet high-risk criteria (eg, seizures, ill-appearance, or CSF pleocytosis).[10,11] Further investigation will need to elucidate the clinical and laboratory predictors of HSV infection to identify those infants who would benefit most from HSV testing as well as the outcomes of infants not tested.

Our study has several limitations. First, we could not determine the reason why clinicians elected to obtain a CSF HSV PCR test, and we do not know the test turnaround time or the time when results became available to the clinical team. Second, we did not abstract clinical data such as ill-appearance or seizures. Although we adjusted for the presence of serious bacterial or HSV infection as proxy measures for illness severity, it is possible that other clinical factors were associated with HSV testing and LOS. Third, although we adjusted for patient- and hospital-level factors in our regression model, the potential for residual confounding persists. Fourth, we did not explore acyclovir administration as a factor associated with LOS as some sites did not provide data on acyclovir. Fifth, we did not evaluate the impact of HSV testing of other sample types (eg, blood or skin) on LOS. Sixth, our study was conducted primarily at children's hospitals, and our findings may not be generalizable to general hospitals with hospitalized neonates.

CONCLUSIONS

For infants aged ≤60 days undergoing evaluation for meningitis, CSF HSV PCR testing was associated with a slightly longer hospi-

tal LOS. Improved methods to identify and target testing to higher risk infants may mitigate the impact on LOS for low-risk infants.

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