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Herpes simplex virus testing and hospital length of stay in neonates and young infants

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Abstract

Objectives—To determine whether ordering cerebrospinal fluid (CSF), herpes simplex virus (HSV), and polymerase chain reaction (PCR) testing in neonates and young infants is associated with hospital length of stay (LOS) or increased hospital charges.

Study design—This retrospective cohort study enrolled infants ≤ 56 days of age who had a lumbar puncture in the emergency department in 2005–2006. The primary “exposure” was CSF HSV PCR and the primary outcomes were LOS and hospital charges.

Results—CSF HSV PCR was performed in 282 (31.7%) of 889 eligible infants. Median HSV PCR turnaround time was 22 hours. Median LOS was 2 days and median charges were \$10,166. In multivariable analysis, HSV PCR testing was associated with increases in LOS of 28% and 39% for infants ≤ 28 and 29–56 days of age, respectively. LOS increased by 22% for every 12 hour increase in PCR turnaround time. HSV testing was associated with a 41% increase in hospital charges.

Conclusions—Among infants evaluated by lumbar puncture in the emergency department, HSV PCR testing was associated with a significantly longer LOS and higher hospital charges.

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Keywords

cerebrospinal fluid; herpes simplex virus; polymerase chain reaction; infant, newborn; lumbar puncture

Neonatal herpes simplex virus (HSV) infection, although uncommon,(1) results in significant morbidity and mortality.(2) Early diagnosis of HSV in this population can be difficult as some infants initially present with only non-specific findings such as fever and lethargy.(3) The HSV polymerase chain reaction (PCR) test accurately detects HSV DNA in the cerebrospinal fluid (CSF).(4) This test, available at most commercial reference laboratories and tertiary care hospitals, has revolutionized the diagnosis of neonatal HSV central nervous system infection. However, no consensus exists on which febrile infants merit testing.(5) As a consequence, many low-risk infants undergo testing.(5) Although early diagnosis of HSV is important, over-testing may also lead to harm or inefficient care.

Potential consequences of HSV testing include increased resource utilization and increased likelihood of exposure to unnecessary medications and other risks of hospitalization (e.g., medication errors, hospital-acquired infections). In addition to the costs of performing HSV PCR, other costs associated with testing may include costs of intravenous acyclovir (which is usually initiated at the time of testing) and requisite supplies and nursing care, and costs of prolonged hospitalization while physicians wait for the test result. The risks of testing young febrile infants for HSV have not previously been examined. The objective of this study was to determine whether HSV PCR testing of infants evaluated by lumbar puncture is associated with prolonged hospital stay and increases hospital charges. Quantifying how testing influences these outcomes will allow clinicians to more completely understand the collateral effects of testing neonates and young infants for HSV infection.

METHODS

This retrospective cohort study was conducted at The Children's Hospital of Philadelphia (Philadelphia, Pennsylvania), an academic tertiary care children's hospital. The Committees for the Protection of Human Subjects of The Children's Hospital of Philadelphia approved this study with a waiver of informed consent.

Infants 56 days of age and younger who had a lumbar puncture performed in the emergency department between January 1, 2005 and December 31, 2006 were eligible. Even though perinatally-acquired HSV infection usually manifests within the first month of life, infants between 29–56 days of age were included because HSV PCR testing is commonly performed in this older age group.(5) At our institution, infants ≤ 56 days of age with fever routinely undergo lumbar puncture as part of the initial emergency department evaluation.(6–8) Potential study patients were identified using two data sources, Emergency Department billing records and Clinical Virology Laboratory records for HSV PCR testing.

Study Definitions

All data were obtained by review of medical records from the initial evaluation. Fever was defined as a temperature $\geq 38.0^{\circ}\text{C}$. Hypoxia was defined as a percutaneous oxygen saturation less than 90% or receipt of supplemental oxygen. Tachypnea was defined as a respiratory rate greater than 70 breaths per minute.(9) Hypotension was defined as a systolic blood pressure less than 63 mmHg.(10) Prematurity was defined as a gestational age less than 37 weeks.

Laboratory values for hepatic transaminases were considered abnormal if the value was 50% greater than the upper limit of normal defined by our laboratory. Thrombocytopenia was

defined as a platelet count less than 150,000/mm³. Hyponatremia was defined as a serum sodium less than 131 mmol/L. CSF glucose values <40 mg/dL were considered low and CSF protein values >170 mg/dL (for infants ≤28 days) or >85 mg/dL (for infants 29–56 days) were considered elevated.(11) CSF pleocytosis was defined as >22 white blood cells (WBC)/mm³ for infants ≤28 days of age and >15 WBC/mm³ for infants 28–56 days of age.(11) Traumatic lumbar puncture was defined as a lumbar puncture with >500 red blood cells/mm³.(12) CSF HSV PCR turnaround time was defined as the difference in time (in hours) from ordering of the test to availability of the result.

Serious bacterial infection was defined by the diagnosis of urinary tract infection, bacteremia, or bacterial meningitis. Urinary tract infection was defined as growth of a single known pathogen meeting one of three criteria: (1) ≥1000 colony-forming units (cfu)/mL for urine cultures obtained by suprapubic aspiration, (2) ≥50,000 cfu/mL from a catheterized specimen, or (3) ≥10,000 cfu/mL from a catheterized specimen in association with a positive urinalysis. (13–15) Bacteremia was defined as isolation of a known bacterial pathogen (excluding commensal skin flora) from blood culture. Bacterial meningitis was defined as either the isolation of a known bacterial pathogen from the CSF or, in patients who received antibiotics prior to evaluation, the combination of CSF pleocytosis and bacteria detectable on CSF Gram stain.

HSV PCR technique

Qualitative real-time TaqMan PCR was performed in 50 µL volumes using primers and probe from a portion of the HSV genome that encodes for the polymerase gene.(16) Positive and negative controls consisted of purified HSV-1 (MacIntyre strain) and HSV-2 (Strain G) DNA (Advanced Biotechnologies, Inc., Columbia, MD) and uninfected A549 human lung carcinoma cells. A human albumin gene was amplified as an internal positive control for human nucleic acid to ensure that negative results were not due to poor nucleic acid extraction or inhibition of the PCR assay.

Outcome Measures

The main outcome measures were LOS and total hospital charges.

Data Analysis

Data were analyzed using STATA version 10 (Stata Corp., College Station, TX). Continuous variables were described using median and interquartile range (IQR) or range values and compared using the Wilcoxon rank-sum test. Categorical variables were described using counts and frequencies and compared using the chi-square test. Multivariable analysis was performed to assess the independent impact of CSF HSV PCR testing on hospital LOS. We used negative binomial regression rather than log-linear models to account for overdispersion in LOS which would otherwise lead to biased standard errors.(17) The negative binomial model produced a ratio of lengths of stay or incidence rate ratio (IRR), where a ratio greater than one indicates that the risk factor was associated with a longer length of stay.

Building of the multivariable model began with inclusion of the variable for the performance of CSF HSV PCR testing based on our *a priori* hypothesis. Variables associated with LOS on univariate analysis ($P < 0.20$) were then considered for inclusion as potential confounding factors of the association between performance of CSF HSV PCR testing and LOS.(18) These variables were included in the final multivariable model if they remained significant after adjusting for other factors or if their inclusion in the model resulted in a 15% or greater change in the effect size of the primary association of interest (i.e., performance of CSF HSV PCR and LOS).(19) Statistical significance was determined *a priori* as a two-tailed P -value <0.05. An interaction term between performance of CSF HSV PCR and age category was included

(likelihood ratio test, $P=0.161$) because of known age-related differences in the risk of HSV infection and signs of serious illness. The possibility of other important subgroup effects (for example, differences in outcomes between those with and without CSF pleocytosis) was also explored using interaction terms; their significance in multivariable analysis was evaluated with the likelihood ratio test. There was no interaction between performance of CSF HSV PCR and CSF pleocytosis in the final multivariable model (likelihood ratio test, $P=0.744$).

Residual confounding by indication for testing may be present despite our attempts to adjust for severity of illness. To verify that the longer LOS in the subgroup of infants who had CSF HSV PCR testing performed was not due to residual confounding by indication, we examined the association between the CSF HSV PCR turnaround time and LOS in the subset of infants in whom CSF HSV PCR testing had been performed using negative binomial regression. As association between test turnaround time and LOS would suggest that HSV PCR testing itself, rather than other confounders, influenced LOS.

Multivariable linear regression was used to assess the impact of CSF HSV PCR testing on total hospital charges. Because the charge outcome data had a skewed distribution, our analyses were performed using logarithmically transformed charge values as the dependent variable. The resulting beta-coefficients were transformed to reflect the percent difference in total hospital charges between infants in whom CSF HSV PCR testing was performed and not performed. Similar to the comparison of LOS between the two groups of infants, an interaction term was included in the final model to explore subgroup effects comparing infants ≤ 28 days and 29–56 days.

RESULTS

During the study period, 889 infants ≤ 56 days of age underwent lumbar puncture in the emergency department. CSF HSV PCR was sent in 282 (31.7%) eligible infants; 3 of these infants tested positive for HSV. HSV testing was performed in 218 (51.6%) of 422 infants ≤ 28 days and in 64 (22.7%) of 467 infants 28–56 days of age. None of the patients who did not undergo HSV PCR testing during initial evaluation was subsequently diagnosed with HSV. Three infants died; HSV testing was performed in two of these infants. Characteristics of the eligible patients are presented in Table I. The median age was 30 days (IQR: 14 to 43 days). Endotracheal intubation within 48 hours of hospital arrival was required in 33 (3.7%) infants. Eight infants with hypotension required infusion of vasoactive medications.

The peripheral white blood cell count exceeded $15,000/\text{mm}^3$ in 138 (15.5%) infants, and 27 (3.0%) infants had thrombocytopenia. CSF pleocytosis was present in 224 (25.2%) infants and traumatic lumbar puncture occurred in 270 (30.4%) infants. CSF protein was elevated and CSF glucose was low in 131 (16.5%) and 55 (6.9%), respectively, of 796 infants for whom these values were available. Hyponatremia occurred in 10 (2.2%) of 461 infants with available sodium values.

Hospital Length of Stay

The median LOS was 2 days (IQR: 1–3 days) with a range of 0 to 133 days. In unadjusted analysis, performance of CSF HSV PCR was associated with a greater than 2-fold increase in the LOS (Table II). Among infants < 28 days of age, the median LOS was longer for infants who had HSV testing performed (median, 4 days; IQR: 2–8 days) compared with those who did not have HSV testing performed (median, 2 days; IQR: 2–3 days; $P<0.001$, Wilcoxon rank-sum test). Among infants 29–56 days of age, the median LOS was also longer for infants who had HSV testing performed (median, 2 days; IQR: 1–3.5 days) compared with those who did not have HSV testing performed (median, 2 days; IQR: 1–2; $P<0.001$, Wilcoxon rank-sum test). Other factors associated with a longer LOS on unadjusted analysis included younger age,

transported from another hospital, premature birth, birth by cesarean section, and the presence of apnea, tachypnea, hypoxia, and seizures. Serious bacterial infection and abnormalities in laboratory test results including hyponatremia, leukocytosis, CSF pleocytosis, and traumatic lumbar puncture were also associated with a longer LOS. In multivariable analysis, HSV PCR testing was associated with increases in LOS of 28% among those ≤ 28 days of age and 39% among those 29–56 days of age (Table III). The CSF red blood cell count was not included in the final multivariable model because of collinearity with performance of CSF HSV PCR.

CSF HSV PCR Turnaround Time and Hospital Length of Stay

The median turnaround time (i.e., the difference in time from test ordering to result availability) for CSF HSV PCR testing was 22 hours (IQR: 16–27 hours; range: 3–71 hours). The results of CSF HSV PCR testing were available prior to discharge for 265 (94%) of 282 infants in whom testing was performed. The median turnaround time for CSF HSV PCR testing was 22 hours (IQR: 16–27 hours) for infants discharged after the results were available and 28 hours (IQR: 21–56 hours) for infants discharged before the results were available (Wilcoxon rank-sum, $P=0.016$). The difference in median HSV PCR turnaround time between infants ≤ 28 days (22 hours) and 29–56 days (20 hours) was not significant (Wilcoxon rank-sum, $P=0.346$). In the subset of 265 infants whose HSV PCR results were available prior to discharge, the LOS increased by 22% for each 12 hour increase in HSV PCR turnaround time (IRR, 1.22; 95% confidence interval [CI]: 1.05–1.42; $P=0.009$). When stratifying by age, the LOS increased by 25% for infants ≤ 28 days (IRR, 1.25; 95% CI: 1.06–1.48; $P=0.009$) and 6% for infants 29–56 days (IRR, 1.06; 95% CI: 0.76–1.49; $P=0.725$) for each 12 hour increase in HSV PCR turnaround time.

Hospital Charges

The mean hospital charges were \$26,453 (median, \$10,166; IQR: \$6,844–\$17,218). Total hospital charges exceeded \$30,000 for 15% of infants and \$100,000 for 5% of infants. In unadjusted analysis, median hospital charges were higher in those undergoing CSF HSV PCR testing (median, \$17,777; IQR: \$10,160–\$50,312) compared with those not tested (median, \$8,765; IQR: \$6,041–\$12,281; $P<0.001$, Wilcoxon rank-sum test). Unadjusted hospital charges were also greater among infants in whom CSF HSV PCR testing was performed in the subgroups ≤ 28 days (median values, \$21,656 vs. \$9,923; $P<0.001$, Wilcoxon rank-sum test) and 29–56 days (median values, \$9,816 vs. \$8,074; $P=0.002$, Wilcoxon rank-sum test). In multivariable analysis, CSF HSV PCR testing was associated with significantly higher hospital charges for infants ≤ 28 days and 29–56 days (Table IV).

DISCUSSION

In a large cohort of infants undergoing lumbar puncture, CSF HSV PCR testing was associated with a significantly longer LOS and higher hospital charges. Additionally, in the subset of infants in whom HSV testing was performed, every 12 hour increase in HSV PCR turnaround time was associated with a 22% increase in LOS. These data suggest that simply performing HSV PCR testing, even with rapid turnaround times, may have unintended consequences with regards to resource utilization. Better methods are needed to identify low-risk infants in whom HSV testing is not warranted.

Factors associated with a physician's decision to test for HSV do not best reflect the likelihood of HSV infection; CSF HSV PCR tests are positive in fewer than 2% of infants undergoing testing.^(20,21) “Over-testing” likely occurs for two reasons. First, there is no national consensus on which febrile neonates and young infants merit testing for HSV. Variation in practice patterns have been documented for numerous diseases in the absence of national guidelines.^(22,23) Second, there is concern that delayed diagnosis, and consequently delayed

initiation of acyclovir therapy, could contribute to worse clinical outcomes. However, all interventions carry an associated risk. Knowledge of both the risks and benefits of specific interventions should inform diagnostic and therapeutic decisions.

Infants who underwent HSV testing had a significantly longer LOS than infants who did not undergo HSV testing. This difference persisted after adjusting for measured confounding factors. These findings have important implications for patient safety as hospitalized patients frequently suffer medical errors.(24) Additionally, we expect that infants tested for HSV would receive intravenous acyclovir empirically while clinicians awaited test results. Complications of acyclovir such as neutropenia and renal toxicity likely occur infrequently following short courses of therapy; however, such exposure constitutes a potential risk.

Which infants merit testing for HSV in a way that appropriately balances risk and benefit? Caviness et al.(25) using a decision analysis model, concluded that routine testing of febrile neonates with CSF pleocytosis was cost-effective if test results were available by the third day of hospitalization. Such an approach in our cohort would have reduced testing from approximately one-half to one-quarter of infants ≤ 28 days of age and eliminated testing of most infants 29–56 days of age. However, the model by Caviness et al (25) assumed that patients would be discharged once HSV PCR tests were reported as negative. Our study raises the possibility that HSV testing may change physician perception of tested infants, leading to a longer LOS in these infants. Therefore, rapid test turnaround times may not be cost-effective unless physicians respond to negative HSV PCR tests by discharging patients without specific indications for continued hospitalization.

The cost of diagnostic testing includes not only the cost of performing the test but also the cost of secondary care provided because of the decision to test. In the case of HSV PCR testing, minimum additional costs include the cost of acyclovir and its administration and additional days of hospitalization. We found that HSV testing was associated with significantly higher total hospital charges; the magnitude of the increase was similar for infants ≤ 28 days of age and infants 29–56 days of age. This increase in cost associated with testing argues for clinical prediction rules to identify low risk infants which could lead to better utilization of finite healthcare resources.

This study had several limitations. First, confounding by indication is a limitation of this observational study. We attempted to minimize confounding by performing multivariable analysis to adjust for measured confounding factors. An alternate explanation for our findings is the inability to account for unmeasured confounders; perhaps other factors, such as the physicians initial assessment of the infant, led to both the decision to test and prolonged LOS. Evidence against this possibility includes the association between HSV PCR turnaround time and LOS in the subset of patients ≤ 28 days who had CSF HSV PCR testing performed. At least in this subgroup, the association of PCR turnaround time and LOS suggests that waiting for test results led to delayed LOS. Second, the availability of an HSV PCR result in a clinically relevant time frame depends on the specimen's timely arrival to the laboratory as well as the ability of the laboratory to process the specimen and perform the test quickly. Therefore, we defined turnaround time as the difference in time from when the test was ordered to when the results were available. Although there may be differences among patients in the timing of test ordering, lumbar puncture performance, and specimen receipt by the laboratory, we expect that such differences would be non-differential and bias our results towards finding no difference. Third, generalizability is an important consideration in any single center study. HSV PCR testing is readily available at our institution with a relatively short turnaround time. Since in many hospitals HSV PCR testing is performed only on certain days of the week and in many others, specimens are sent out to commercial reference laboratories for testing, the magnitude of increases in LOS and hospital charges found in this study may underestimat LOS in settings

with longer HSV PCR turnaround times. Fourth, we were limited to information contained in the medical record. Data regarding complications of intravenous catheters and medical errors were infrequently noted in the medical record. Furthermore, as many patients did not have repeated laboratory testing, we could not identify infants with acyclovir-related side effects. Thus, we cannot comment on direct harm attributable with CSF HSV PCR testing. Finally, our data do not permit identification of infants who merit testing but rather clarify the collateral effects of testing. These consequences of HSV testing should be considered in clinical decision-making and in national consensus guidelines. Prediction rules that accurately identify low risk infants in whom HSV testing is not necessary could have meaningful impact on care of the febrile young infant.

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Abbreviations Used in the Manuscript

CFU	Colony-forming units
CSF	Cerebrospinal fluid
HSV	Herpes simplex virus
IQR	Interquartile range
IRR	Incidence rate ratio
LOS	Length of stay
PCR	Polymerase chain reaction
WBC	White blood cell count

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Table 1

Characteristics of Study Population *

Characteristic	Overall
Age Category	
Age 29–56 days	467 (52.5%)
Age ≤28 days	422 (47.5%)
Male sex	324 (54.6%)
Race/Ethnicity **	
Non-Hispanic white	334 (37.6%)
Non-Hispanic black	420 (47.2%)
Hispanic	30 (3.4%)
Other	82 (9.2%)
Presenting during enteroviral season	480 (54.0%)
Transported from other institution	143 (16.1%)
Birth History	
Premature birth	121 (13.6%)
Cesarean section delivery	243 (27.3%)
History of Present Illness	
Apnea	62 (7.0%)
Upper Respiratory symptoms (one or more)	406 (45.7%)
Gastro-intestinal symptoms	302 (34.0%)
Seizures	80 (9.0%)
Physical Examination	
Tachypnea	38 (4.3%)
Hypoxia	27 (3.0%)
Hypotension	35 (3.9%)
Lethargy or irritability	164 (18.5%)

* Values listed as number (percent)

** Race data not available for 23 (2.6%) subjects.

Table 2

Univariate analysis of factors associated with increased length of stay among infants 56 days of age or younger who underwent lumbar puncture.

Variable	Unadjusted Incidence Rate Ratio	95% Confidence Interval	P-value
Age Category			
29–56 days	Reference	-	-
≤28 days	2.43	2.11–2.81	<0.001
Male sex	0.94	0.81–1.09	0.397
Race			
Non-Hispanic White	Reference	-	-
Non-Hispanic Black	0.72	0.62–0.85	<0.001
Hispanic	1.65	1.11–2.45	0.014
Other	0.60	0.45–79	<0.001
Presenting during enterovirus season	0.97	0.84–1.13	0.695
Transported from other institution	3.18	2.69–3.76	<0.001
Birth History			
Premature birth	2.49	2.04–3.03	<0.001
Cesarean section delivery	1.33	1.13–1.57	0.001
History of Present Illness			
Apnea	1.91	1.45–2.52	<0.001
Upper Respiratory Symptoms	1.05	0.99–1.12	0.091
Gastro-intestinal symptoms	0.55	0.47–0.65	<0.001
Physical Examination			
Tachypnea	2.04	1.44–2.89	<0.001
Hypoxia	2.32	1.55–3.49	<0.001
Hypotension	3.64	2.58–5.12	<0.001
Lethargy or irritability	1.02	0.84–1.23	0.868
Seizure	1.84	1.44–2.36	<0.001
Interventions/Studies Obtained			
Required vasopressors	7.02	3.49–14.13	<0.001
Required intubation	7.61	5.68–10.22	<0.001
CSF HSV PCR sent	2.89	2.51–3.33	<0.001
Laboratory Results			
Serious bacterial infection	1.65	1.26–2.17	<0.001
Hyponatremia	3.01	1.61–5.67	0.001
Peripheral WBC count $\geq 15,000 \text{ mm}^3$	2.31	1.91–2.79	<0.001
Thrombocytopenia	3.11	2.09–4.64	<0.001
Low CSF glucose	2.15	1.64–2.81	<0.001
Elevated CSF protein	1.41	1.16–1.71	<0.001
CSF pleocytosis	2.16	1.84–2.53	<0.001
Traumatic lumbar puncture	1.14	0.98–1.32	0.082

Abbreviations: CSF, cerebrospinal fluid; HSV, herpes simplex virus; PCR, polymerase chain reaction; WBC, white blood cell count

Table 3

Multivariable analysis comparing length of stay for infants with and without cerebrospinal fluid testing for herpes simplex virus by polymerase chain reaction, stratified by age.*

Variable	Age ≤28 Days**	Age 29–56 Days**
Adjusted incidence rate ratio (95% CI)	1.28 (1.08–1.51)	1.39 (1.08–1.79)
P-value	0.004	0.010

Abbreviations: CI, confidence interval

* Model adjusted for age category, mode of delivery (i.e., vaginal or cesarean section delivery) preterm birth, transported from another institution, seizures, hypoxia, endotracheal intubation within 48 hours of arrival, the presence of lethargy or irritability, and peripheral white blood cell count, serious bacterial infection, and herpes simplex virus infection.

** Values reflect comparison of infants in whom cerebrospinal fluid herpes simplex virus polymerase chain reaction test was performed vs. not performed (i.e., reference group)

Table 4

Multivariable analysis comparing hospital charges in infants with and without cerebrospinal fluid testing for herpes simplex virus by polymerase chain reaction, stratified by the presence or absence of cerebrospinal fluid pleocytosis.*

Variable	Age ≤28 Days**	Age 29–56 Days**
Beta-coefficient (95% CI)	0.35 (0.18–0.51)	0.34 (0.12–0.57)
Percent increase in hospital charges (95% CI)	41% (19%–67%)	41% (12%–76%)
P-value	<0.001	0.003

Abbreviations: CI, confidence interval

* Model adjusted for age category, mode of delivery (i.e., vaginal or cesarean section delivery) preterm birth, transported from another institution, seizures, hypoxia, endotracheal intubation within 48 hours of arrival, the presence of lethargy or irritability, and peripheral white blood cell count, serious bacterial infection, and herpes simplex virus infection.

** Values reflect comparison of infants in whom cerebrospinal fluid herpes simplex virus polymerase chain reaction test was performed vs. not performed (i.e., reference group)