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CONGENITAL ANOMALIES AND RESOURCE UTILIZATION IN NEONATES INFECTED WITH HERPES SIMPLEX VIRUS

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Abstract

Background—Neonatal herpes simplex virus (HSV) infection, while uncommon, is associated with substantial morbidity and mortality. However, there is little nationally representative data describing resource utilization.

Methods—This retrospective cohort study was conducted using the Pediatric Health Information System (PHIS), an administrative database that contains discharge diagnosis and resource utilization data from 35 free-standing children's hospitals. Patients <60 days of age with a primary discharge diagnosis of HSV were study eligible if they received intravenous acyclovir and were discharged between January 1, 2003 and December 31, 2005.

Results—There were 406 patients with HSV. The median age was 16 days (interquartile range: 8–31 days); 52% of patients were female. Congenital heart disease, the most common congenital anomaly, occurred in 10% of patients. The median length of stay was 15 days; 21 (5%) patients died. HSV was associated with substantial resource utilization. The median hospital charge was $37,431 (interquartile range: $14,667-$74,559) per infant. The presence of congenital heart disease independently increased the hospital length of stay by 93% (adjusted LOS ratio, 1.8; 95% CI: 1.5–2.5).

Conclusion—HSV infection in neonates and young infants was associated with substantial resource utilization. The presence of an underlying congenital cardiac anomaly was associated with a significantly longer length of stay and higher hospital charges.

Keywords

Herpes simplex virus; congenital anomaly; resource utilization

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Introduction

Neonatal herpes simplex virus (HSV) infection, although rare, is associated with substantial morbidity and mortality.[1, 2] Preventative efforts targeted at the mother during pregnancy are limited in their effectiveness. The cost-effectiveness of routine screening for maternal HSV antibodies to reduce the incidence of neonatal HSV is controversial.[3–5] Furthermore, while cesarean sections reduce HSV transmission from mother to child, they may increase maternal morbidity and mortality compared with vaginal deliveries and, therefore, are only recommended in the presence of documented primary HSV infection or visible genital lesions at the time of delivery.[6]

An alternate approach would be to minimize HSV-related morbidity by facilitating earlier diagnosis and treatment of affected infants. Caviness et al. used a decision model to determine the cost-effectiveness of various HSV testing and treatment strategies for febrile infants evaluated by lumbar puncture.[7] They determined that testing and empirically treating all febrile infants with cerebrospinal fluid pleocytosis would be the most cost-effective approach. However, this model assumed that the costs and outcomes are equivalent among infants with a similar spectrum of findings. For other infections, children with specific comorbid conditions are at higher risk of severe illness and prolonged hospitalization.[8–10] The characteristics of infection and associated complications of neonatal HSV have been described in depth,[1, 2] however, patient characteristics associated with poor clinical outcomes and increased resource utilization have not been described.

The economic burden of neonatal HSV may be substantial though few studies have attempted to determine the costs of care for infants infected with HSV during their acute hospitalization.[11] Additionally, data quantifying the burden of neonatal HSV is incomplete particularly with regard to factors associated with increased resource utilization. The objective of this study was to quantify the economic burden of neonatal HSV during initial hospitalization while focusing on factors, such as congenital anomalies and HSV-associated complications, that increase hospital charges and length of hospital stay among neonates with HSV.

Methods

Data Source

Data for this cohort study were obtained from the Pediatric Health Information System (PHIS), an administrative database that contains inpatient discharge records from 42 not-for profit, freestanding, tertiary care pediatric hospitals in the United States. The participating hospitals are affiliated with the Child Health Corporation of America, a business alliance of children's hospitals (Shawnee Mission, KS). The PHIS hospitals represent 70% of all freestanding pediatric hospitals in the U.S. Seventeen of the twenty major metropolitan areas in the US are covered. The data warehouse function for the PHIS database is managed by Thomson Healthcare (Durham, NC). Data quality and reliability are assured through a joint effort between the Child Health Corporation of America and participating hospitals. Systematic monitoring occurs on an ongoing basis to ensure data quality. Specific processes include bimonthly coding consensus meetings, coding consistency reviews, and quarterly data quality reports.

Participating hospitals provide discharge records for the purposes of external benchmarking. Data provided for each discharge include demographic characteristics, admission and discharge diagnoses, and medical, surgical, and laboratory procedures. Thirty-five hospitals also submit additional resource utilization data. Patients from the 35 hospitals submitting resource utilization data were eligible for inclusion in this study. Total hospital charges, which include all hospital-level charges (e.g., laboratory services, radiologic imaging,

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pharmaceutical) but not physician charges, for each patient stay are adjusted for hospital location using the Centers for Medicare and Medicaid price/wage index; the index is calculated separately for each year of the study. Data are de-identified prior to inclusion in the database, however encrypted medical record numbers allow for tracking individual patients across hospital admissions. The protocol for the conduct of this study was reviewed and approved by The Children's Hospital of Philadelphia Committees for the Protection of Human Subjects and the Drexel University College of Medicine Institutional Review Board.

Participants

Patients ≤60 days of age at the time of hospital admission were eligible for this study if they were diagnosed with HSV infection between January 1, 2003 and December 31, 2005. We chose to include infants up to 60 days of age since perinatally-acquired HSV may manifest beyond the first month of life.[2] If a patient was hospitalized more than once, the first reported hospitalization was used.

Patients were considered to have HSV if they received intravenous acyclovir during their hospitalization and if they were assigned a primary discharge diagnosis of HSV as indicated by the presence of one of the following *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) discharge diagnoses codes: 054.xx (herpes simplex virus with the last two digits representing any combination of one or two-digit codes) or 771.2 (other congenital infections including herpes simplex virus infection). Four hundred and six infants met inclusion criteria; 84 (21%) of these infants had ICD-9 code 771.2.

Measured Patient Characteristics

The independent variables included patient age (in days), sex, race (White, Black, Hispanic, and other, including Asian, Native American and other), principal payer of medical and hospital costs (government, non-government, and other, including self-pay, workers compensation, and other), HSV-associated complications and comorbid conditions. Patients were classified into five age groups: 0–7, 8–14, 15–21, 22–28, and 29–60 days of age. Complications were classified according to organ system involvement: respiratory, cardiovascular, renal, hepatic, hematologic, and neurologic. Since the study population consisted of young infants, comorbid conditions were limited to congenital anomalies in the following categories: neurological, cardiac, pulmonary, gastrointestinal, gastrourinary, and genetic. Due to small case numbers, pulmonary, gastrointestinal, gastrourinary and genetic anomalies were grouped into a single "other anomalies" category. The specific ICD-9 discharge diagnosis codes used to define the congenital anomaly and complication categories are detailed in the Appendix.

Outcomes

The resource utilization outcome indicators were total days of hospital stay and total hospital billing charges. Secondary outcomes included pharmaceutical charges and imaging charges; these charges represent a subset of the total hospital billing charges.

Statistical Analysis

Continuous variables were described by using mean, median, range, and interquartile range values. Dichotomous variables were described by using counts and percentages. Bivariable and multivariable analyses were performed. Negative binomial regression was used to model length of stay because of evidence of over dispersion in the outcome data.[12] For all statistical analysis, length of stay was treated as a count of the number of days from admission to discharge or death. Because billing charges (total, pharmaceutical and imaging) violated the criteria of a Gaussian distribution, a normal distribution was approximated using a logarithmic transformation. Linear regression was used to model the log-transformed billing charges.

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Building of the multivariable model began with the inclusion of congenital anomalies based on our *a priori* hypothesis. Variables with a p-value <0.20 on bivariable analysis were also considered for inclusion in the multivariable model. These variables remained in a final model if they remained statistically significant in the adjusted model or if their inclusion in the model resulted in a ≥ 10% change in the measure of association observed in another independent variable (i.e., if they were confounders).[13] A 2-tailed p-value of <0.05 was determined *a priori* as the criterion for statistical significance. All statistical analysis was preformed by using the statistical software SAS (version 9.1, SAS Institute, Inc, Cary, NC).

The use of administrative data to identify infants with HSV may lead to the inadvertent inclusion of infants without HSV. For example, an infant who received intravenous acyclovir empirically based on presenting clinical symptoms may also have been assigned a discharge diagnosis of HSV because this disease figured prominently in the initial differential diagnosis even if another cause was subsequently determined. It is possible that surviving infants treated with relatively short courses of acyclovir therapy did not have HSV. To address such potential misclassification, we repeated the analyses while restricting the cohort to the infants who received acyclovir at least 7 days.

Results

Patient Characteristics

Patient characteristics of the 406 infants under 60 days of age with a primary discharge diagnosis of HSV are summarized in Table 1. The median age was 16 days (interquartile range [IQR]: 8–31 days). A congenital anomaly was present in 49 (12%) infants; cardiac anomalies were the most commonly found anomalies. Two infants had multiple congenital anomalies, both had a combination of neurological and cardiac anomalies, one had an additional genetic anomaly.

Ninety-seven (24%) infants experienced a complication; 39 (40%) experienced more than one. Nineteen percent (n=79) of the infants experienced respiratory complications. Twenty-one infants (5%) died during hospitalization. There was no significant difference in mortality among those infants with (2 of 40 died, 5%) and without (19 of 366 died, 5.2%; P=0.959, chi-square) underlying cardiac abnormalities. All 21 (100%) infants who died experienced at least one complication while 76 (20%) of the 385 survivors experienced at least one complication. The most common complications among infants who died were respiratory (n=20, 95%), hematologic (n=14, 67%), and renal (n=9, 43%).

Resource Utilization

HSV was associated with substantial resource utilization. The total hospital charge for all 406 infants was $25,192,665. The median hospital charge for an infant with HSV was $37,431 (IQR: $14,667–$74,559). Median pharmaceutical and imaging charges were $4,231 (IQR: $1,584–$11,226) and $2,010 ($279–$4,412) respectively. Pharmaceutical charges accounted for 15% of total hospital charges while imaging charges made up 5% of total hospital charges.

In the bivariable analysis, all congenital anomalies and complications were associated with statistically significant increases in total hospital charges. In the multivariable analysis, age groups, cardiac anomalies, neurologic complications and respiratory complications were associated with higher hospital charges (Table 2). These same factors were also associated with higher charges in the pharmacy and imaging subcategories.

Compared to infants ages 29–60 days, hospital charges were higher for all other age groups. Infants between 22–28 days had the highest total hospital charge of $30,031 compared with the other age groups. The youngest age group had the lowest total hospital charges of $27,173.

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The presence of a cardiac anomaly was associated with significantly higher pharmaceutical charges (adjusted beta-coefficient, 0.18; 95% CI: 0.43–1.31; P<0.001) and significantly higher radiologic imaging charges (adjusted beta-coefficient, 0.19; 95% CI: 0.39–1.23; P<0.001) compared to those without such an anomaly. Children with cardiac anomalies had pharmaceutical charges of $4,629 and radiologic imaging charges of $2,416. Among HSV-associated complications, neurologic and respiratory complications were associated with higher pharmaceutical and radiologic imaging charges. For patients with neurologic complications, the charges for pharmaceuticals and radiologic imaging were $3,790 and $2,720, respectively. For patients with respiratory complications, the charges for pharmaceuticals and radiologic imaging were $5,432 and $2,893, respectively.

Length of Hospital Stay

The median length of stay was 13 days (IQR: 4–21). In the bivariable analysis, age, the presence of cardiac or other congenital anomalies, and the occurrence of respiratory and neurological complications were associated with a statistically significant increase in the length of stay. In the multivariable analysis, statistically significant associations with length of stay were observed for age, cardiac congenital anomalies and respiratory complications (Table 3). Cardiac anomalies were associated with a statistically significant length of stay increase of 93% compared with infants with no congenital anomalies. Those with a respiratory complications had a 64% increase in length of stay compared to infants with no complications.

The analyses were repeated while limiting the cohort to infants documented as having received more than 7 days of acyclovir therapy. This subgroup accounted for approximately 60% of the total cohort and had similar demographic characteristics as the total cohort. The results of these additional analyses were comparable to the primary analysis, indicating an absence of misclassification in coding for neonatal HSV. For length of stay the adjusted IRR for cardiac anomaly was 1.93 for the total cohort and 1.89 for the restricted cohort. Differences in the length of stay for infants with neurological and respiratory complications were also statistically significant, with a 28% increase in hospital length of stay for infants with either neurological or respiratory complications. The magnitude of the association of cardiac anomalies or neurologic or respiratory complications and total hospital charges were virtually identical between the total cohort and the subgroup receiving prolonged acyclovir, with <5% difference in the adjusted standardized beta-coefficients between the two groups.

Discussion

We found that the presence of congenital cardiac anomalies and the development of respiratory and neurologic complications were associated with a longer length of stay and higher hospital charges among infants with HSV. Infants 28 days of age and younger had higher hospital charges than infants 29–60 days of age. To date, measures to decrease the burden of HSV have mainly focused on the transmission of HSV from the mother to child. These strategies include performing cesarean sections on women with genital HSV lesions present at the time of labor.[14] However, many women with primary HSV infection are either unaware of their HSV status or are asymptomatic at the time of delivery. Consequently, there has been little reduction in the incidence or severity of perinatally-acquired HSV using this strategy.[15] Furthermore, there is substantial controversy regarding the cost-effectiveness of screening pregnant women for HSV.[3–5, 16] For these reasons, it is also important to consider tertiary prevention mechanisms, such as identifying those infants at highest risk at hospital admission for morbidity or mortality and proactively implementing specific treatment in this subpopulation.

Perinatally-acquired HSV is associated with substantial resource utilization. Tao et al. estimated the total cost to care for an infant with HSV; the costs ranged from $13,638 for mucocutaneous HSV to $50,858 for meningocephalitis.[11] In order to determine the direct

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medical costs for neonatal HSV, Tao et al.[11] used ICD-9 codes to identify cases from the National Hospital Discharge Survey database (NHDS). They found the estimated direct medical costs for infants infected with HSV who were being treated with acyclovir to exceed $15 million.[11] We extend the findings of Tao et al. by illustrating how the presence of underlying congenital anomalies and HSV-associated complications affect hospital charges. Our estimates of total charges spent on infants infected with HSV are somewhat higher than those of Tao et al. There are several possible reasons for this difference. Our study was limited to children treated at free-standing children's hospitals. This population may have been more critically ill and, therefore, required greater resource utilization than patients in the study by Tao et al. which included infants treated at non-children's hospitals and tertiary care children's hospitals based in larger medical centers. Another reason for the difference could be our use of hospital charges rather than payment received for service. The charges and payment differ depending on the negotiated price between the insurance companies and hospitals. Additionally, Tao et al. was also able to group HSV infection as mucocutaneous, CNS or disseminated infection. Since the ICD-9 codes do not distinguish between the different manifestations of HSV infections, we were unable to analyze the charges in those specific categories. However, we determined that the presence of neurologic and respiratory complications were associated with substantially higher hospital charges.

Our data suggest that infants with underlying congenital heart disease (CHD) may have a more severe course of illness attributable to HSV than infants without underlying congenital heart disease. This finding has been observed with other viruses in infants with CHD. For example, infants with CHD who acquire respiratory syncytial virus (RSV) have longer hospital stays and use more healthcare resources than infants without CHD.[9] Overall the mortality in infants with RSV has significantly decreased in the past thirty years mainly through the use of preventative measures but also with the initiation of ribavirin therapy in some cases. For perinatally-acquired HSV, acyclovir remains the only effective therapy. Caviness et al.[7] used a decision model to determine the cost-effectiveness of various diagnosis and treatment strategies for febrile infants evaluated by lumbar puncture. The most cost-effective strategy in their analysis was routine performance of cerebrospinal fluid HSV PCR with empiric acyclovir administration for all infants with cerebrospinal fluid pleocytosis. The approach by Caviness et al.[7] assumed that the probability for poor outcomes was consistent across all infants. In our analysis, however, infants with congenital cardiac anomalies were at substantially higher risk for prolonged hospitalization even after adjusting for age and HSV-associated complications, suggesting that specific subpopulations may warrant alternate and perhaps more aggressive testing and treatment strategies. Congenital cardiac anomalies are relatively uncommon, occurring in approximately 1% of the population.[17] In our study 10% of our neonates had cardiac anomalies. There is no data to suggest that infants with congenital heart disease are at disproportionate risk of acquiring HSV. A more likely explanation for this finding is referral bias. Infants with congenital cardiac anomalies, particularly those who are critically ill (i.e., those with HSV), are more likely than non-critically ill infants to be transferred to tertiary care children's hospitals.

In our study pharmaceutical charges accounted for 16% of total hospital charges and imaging charges accounted for 5%. The pharmaceutical and imaging charges showed that infants with cardiac anomalies, neurologic complications and respiratory complications were more likely to require a larger amount or more expensive medications and radiologic exams. It is also possible that infants who had higher pharmaceutical and imaging charges were far more ill when first admitted and therefore required greater care from the beginning. This in turn may reflect the intensity of care which the infants received during their hospitalization.

This study had several limitations. First, the use of ICD-9 discharge diagnosis codes to identify patients with HSV may lead to the inadvertent inclusion of patients without HSV. To minimize

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such misclassification, eligible patients had to receive intravenous acyclovir in addition to having a primary discharge diagnosis of HSV. We further tested the robustness of this assumption by repeating the analysis while only including infants receiving acyclovir for 7or more days. The results of this secondary analysis did not differ from our primary analysis, suggesting that misclassification of patients without HSV had little impact on the study conclusions. Reasons for a shorter duration of acyclovir therapy include transfer to another institution or identification of another cause of illness warranting cessation of acyclovir therapy. Second, only free-standing children's hospitals were included in this study. Most infants with HSV are likely to be seen in a tertiary care children's hospital located within general hospitals or non-tertiary care centers, causing us to overestimate the severity of illness in patients with underlying congenital heart disease. Furthermore, limitations of administrative data preclude us from identifying specific cardiac lesions associated with excess morbidity in the context of HSV. Third, as with any observational study, some potential confounders such as prematurity could not be measured. Finally, the cost of caring for HSV acquired during the neonatal period includes costs of short- (i.e., medical follow-up and evaluation) and long-term (i.e., lifetime costs of caring for a disabled child or adult) sequelae. While consideration of these costs was beyond the scope of the current study, they remain an important consequence of neonatal HSV infection and an important contributor to resource utilization attributable to such infection. Despite these limitations, our study has several strengths. For a rare condition such as HSV, the use of administrative data allows for efficient analysis of large numbers of patients from multiple hospitals. An additional strength of this multi-center study lies in the inclusion of an ethnically and geographically heterogeneous population.

In summary, this study highlights the costs of caring for infants with perinatally-acquired HSV. We have identified subgroups of patients with HSV whose underlying medical conditions lead to substantially increased resource utilization. Future studies should explore interventions to reduce the occurrence of complications in this subset of infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Characteristics of 406 patients with herpes simplex virus infection.

Description of Study Population	HSV		LOS*	Total Hospital Charges*
Race/Ethnicity	Count	Percentage		
Non-Hispanic White	221	54.4	10 (2–20)	$29,133 ($12,973–$62,952)
Non-Hispanic Black	69	17.0	14 (6–22)	$49,487 ($21,098–$85,811)
Hispanic	55	13.6	15 (2–22)	$42,645 ($14,817–$93,032)
Other	43	10.6	13 (4–22)	$44,183 ($11,216–$80,544)
Missing	18	4.4	14.5 (9–22)	$47,402 ($20,558–$81,032)
Sex				
Male	194	47.8	13 (5–21)	$39,815 ($15,771–$72,053)
Female	212	52.2	11.5 (4–21)	$33,850 ($13,632–$77,169)
Principal Payer				
Government	257	63.3	13 (5–21)	$39,610 ($15,124–$81,409)
Non-Government	97	23.9	9 (4–21)	$28,880 ($11,930–$68,142)
Other	52	12.8	14 (7–20.5)	$37,796 ($14,819–$63,309)
Age				
0–7 days	91	22.4	14 (5–23)	$55,129 ($15,913–$124 ,038)
8–14 days	95	23.4	14 (6–21)	$39,126 ($17,959–$71,911)
15–21 days	75	18.5	14 (6–22)	$49,928 ($20,992–108,470)
22–28 days	32	7.9	13.5 (6–21)	$48,531 ($26,309–$77,934)
29–60 days	113	27.8	6 (3–14)	$18,124 ($9,436–$36,074)
Congenital Anomaly				
Neurologic	5	1.2	25 (24–28)	$109,721 ($86,787–$117,066)
Cardiac	40	9.9	21 (10.5–28)	$110,194 ($43,671–$190,158)
Pulmonary	2	0.5	77.5 (23–132)	$391,489 ($105,318–$677,659)
Gastrointestinal	3	0.7	38 (4–88)	$104,263 ($14,174–$267,851)
Gastrourinary	1	0.3	2	$40,019
Genetic	1	0.3	21	$65,475
HSV-Associated Complication				
Respiratory	79	19.5	22 (11–28)	$124,038 ($68,651–181,452)
Renal	12	3.0	8.5 (5–20)	$77,444 ($69,908–$215,160)
Hepatic	9	2.2	11 (8–26)	$124,163 ($75,008–$141,395)
Hematologic	27	6.7	17 (6–25)	$124,163 ($71,911–$196,654)
Neurologic	23	5.7	25 (21–39)	$125,956 ($74,559–$190,250)
Cardiovascular	9	2.2	22 (9–24)	$109,721 ($67,904–$151,186)

* Values presented as median (interquartile range).

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TABLE 2

Multivariable linear regression model for factors associated with total hospital charges

Independent Variable	Unadjusted Standardized Beta Coefficient	Adjusted Standardized Beta Coefficient*	95% Adj. CI*	P-Value*	Predicted Hospital Charges Ŧ
Age Group					
29–60days	Reference	Reference	Reference	Reference	$19,341
22–28 days	0.20	0.14	0.24, 0.92	<0.001	$30,031
15–21 days	0.31	0.18	0.25, 0.77	<0.001	$28,001
8–14 days	0.25	0.20	0.28, 0.76	<0.001	$28,283
0–7 days	0.38	0.18	0.23, 0.72	<0.001	$27.173
Anomalies					
Neurological	0.11	0.04	−0.041, 1.21	0.33	$25,084
Cardiac	0.30	0.16	−0.29, 0.88	<0.001	$30,031
Other	0.12	0.60	−0.15, 1.16	0.13	$27,723
HSV-Associated Complications					
Cardiac	0.14	0.019	−0.50, 0.78	0.67	$19,341
Hematologic	0.29	0.04	−0.23, 0.62	0.37	$20,333
Hepatic	0.15	0.003	−0.65, 0.69	0.96	$17,154
Neurologic	0.29	0.14	0.26, 1.02	0.001	$31,888
Renal	0.18	0.014	−0.49, 0.68	0.76	$18,398
Respiratory	0.55	0.41	0.88, 1.39	<0.001	$52,052

*Variables: gender, race, and principal payer were excluded because the P-value was >0.2 on unadjusted analysis

ŦHospital charges for each individual predictor were calculated using the unstandardized coefficients in the regression equation. Charges experienced by the reference group are also shown.

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TABLE 3

Multivariable negative binomial regression model for factors associated with length of stay

Predictors	Unadjusted IRR [T]	Adjusted IRR [T,*]	Adjusted 95% CI [*]	Adjusted P-Value [*]
Age Group				
0–7 days	2.09	1.34	1.07, 1.70	0.01
8–14 days	1.66	1.62	1.30, 2.02	<0.001
15–21 days	2.08	1.61	1.27, 2.03	<0.001
22–28 days	1.42	1.32	0.97, 1.80	0.08
29–60 days	Reference	Reference	Reference	Reference
Anomalies				
Neurological Anomaly	1.73	1.13	0.55, 2.30	0.74
Cardiac Anomaly	2.22	1.93	1.47, 2.53	<0.001
Other Anomaly	3.02	2.16	1.21, 3.83	0.01
HSV-Associated Complications				
Cardiac	1.76	1.35	0.78, 2.32	0.29
Hematologic	1.36	0.96	0.64, 1.44	0.86
Hepatic	1.24	1.01	0.57, 1.80	0.97
Neurological	2.52	1.72	1.24, 2.38	0.0012
Renal	1.15	0.68	0.40, 1.18	0.17
Respiratory	2.05	1.64	1.32, 2.04	<0.001

[T] Incidence Rate Ratio;

[*] Models adjusted for variables listed. Variables: gender, race, and principal payer were excluded because the P-value was >0.2 on unadjusted analysis.