Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

ORIGINAL RESEARCH

Impact of Congenital Anomalies and Treatment Location on the Outcomes of Infants Hospitalized With Herpes Simplex Virus (HSV)

Scott A. Lorch, MD, MSCE[1,2,4]
Andrea M. Millman, BA[2]
Samir S. Shah, MD, MSCE[3,4]

[1] Department of Pediatrics, Division of Neonatology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.
[2] Center for Outcomes Research, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.
[3] Department of Pediatrics, Division of Infectious Disease and General Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.
[4] Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Disclosure: Nothing to report.

BACKGROUND: Herpes simplex virus (HSV) is a rare but costly reason for hospitalization in infants under 60 days of age. The impact of coexisting comorbid conditions and treatment location on hospital outcome is poorly understood.
OBJECTIVE: Determine patient and hospital factors associated with poor outcomes or death in infants hospitalized with HSV.
DESIGN: Retrospective cohort study using the 2003 Kids' Inpatient Database (KID).
SETTING: U.S. hospitals.
PATIENTS: Infants under 60 days of age with a diagnosis of HSV.
INTERVENTION: Treatment at different types of hospitals, younger age at admission, and presence of congenital anomalies.
MEASUREMENTS: Serious complications, in-hospital death.
RESULTS: A total of 10% of the 1587 identified HSV hospitalizations had a concurrent congenital anomaly. A total of 267 infants had a serious complication and 50 died. After controlling for clinical and hospital characteristics, concurrent congenital anomalies were associated with higher odds of a serious complication (adjusted odds ratio [OR], 3.34; 95% confidence interval [CI], 2.00–5.56) and higher odds of death (adjusted OR, 4.17; 95% CI, 1.74–10.0). Similar results were found for infants admitted under 7 days of age. Although different hospital types had statistically similar clinical outcomes after controlling for case-mix differences, treatment at a children's hospital was associated with an 18% reduction in length of stay (LOS).
CONCLUSIONS: Infants with concurrent congenital anomalies infected with HSV were at increased risk for serious complications or death. Health resource use may be improved through identification and adoption of care practiced at children's hospitals. ***Journal of Hospital Medicine*** **2010;5:154–159.** © *2010 Society of Hospital Medicine.*

KEYWORDS: children's hospital, congenital anomaly, herpes simplex virus, length of stay, newborn, pediatric hospitalizations.

Additional Supporting Information may be found in the online version of this article.

Herpes simplex virus (HSV) is a significant cause of pediatric hospitalization, morbidity and mortality, particularly in infants under 60 days of age, where HSV can present as meningoencephalitis, skin disease, or sepsis.[1–4] Most prior studies use data from registries taken from single centers or a restricted group of hospitals. Thus, there is a paucity of recent, nationally-representative information about the outcome of infants infected with HSV, especially those treated at nonteaching hospitals or with rarer comorbid conditions. The goal of this project was to determine the patient and hospital characteristics associated with worse clinical outcomes in infants under the age of 60 days admitted with HSV disease. We hypothesized that younger infants, infants with a concurrent congenital anomaly, and infants treated at non-children's hospitals would have worse clinical outcomes. To answer these questions, we used 2003 panel data from the Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID), a nationally representative sample of inpatient hospitalizations in the United States.

Methods

Study Population and Data Collection

We conducted a retrospective population cohort study of all infants admitted at ≤60 days of age who were discharged with a diagnosis of HSV disease between January 1, 2003 and December 31, 2003, using the 2003 KID. The KID is a collaborative project between the Agency for Healthcare Research and Quality AHRQ and 36 states, which includes approximately 2.9 million pediatric discharge records from 3438 hospitals.[5] The KID is the only national, all-payer database of pediatric hospitalizations in the United States.

2010 Society of Hospital Medicine DOI 10.1002/jhm.627
Published online in wiley InterScience (www.interscience.wiley.com).

Patient Eligibility

As in prior studies,[6–11] children were eligible for this project if they were discharged with an *International Classification of Disease*, ninth edition, *Clinical Modification* (ICD-9CM) discharge code of 054.xx (herpes simplex virus), where xx represented any combination of one or two-digit codes, or 771.2 (neonatal viral infection including HSV). However, the 771.2 code may also contain other perinatal infections of relatively rare frequency, such as toxoplasmosis. Thus, we also performed the same set of analyses on the cohort of children who had an 054.xx code alone. No results presented in this study changed in statistical significance when this smaller cohort of infants was examined.

Data Variables and Outcomes

Outcome Variables

We examined 2 primary clinical outcomes in this study: in-hospital death and the occurrence of a serious complication. Complications were identified using ICD-9CM codes from both prior work[12] and examination of all diagnosis and procedure codes for eligible infants by the 2 principal investigators (Appendix). These 2 reviewers had to independently agree on the inclusion of an ICD-9CM code as a complication. In-hospital deaths were captured through a disposition code of 20 in the KID dataset. Length of stay (LOS) and in-hospital costs were examined as secondary outcome measures for specific risk factors of interest.

Demographic and Comorbidity Variables

Demographic and comorbidity variables were included in the analyses to control for the increased cost, LOS, or risk of a complication that result from these factors.[13–15] Demographic information available in the KID included gender, age at admission, race, low birth weight infants, and insurance status. Age at admission was grouped into 4 categories: 0–7 days, 8–14 days, 15–28 days, and 29–60 days. Infants were classified as low birth weight if they had an ICD-9CM code for a birth weight <2000 g (ICD-9CM codes 765.01-07, 765.11-17, or 765.21-27). We used the ICD-9CM codes shown in the Appendix to classify various comorbid conditions. Because of the young age of the cohort, all comorbid conditions consisted of congenital anomalies that were grouped according to the involved organ system. To help classify patients by their illness severity, we used the All-Patient Refined Diagnosis-Related Group (APR-DRG) severity of illness classification for each hospital admission (3M Corporation, St. Paul, MN). The APR-DRG classification system used discharge diagnoses, procedures, and demographic information to assign patients to 4 severity of illness categories.

Hospital Characteristics

We identified the following hospital characteristics from the KID: total bed size, divided as small, medium, and large; hospital status (children's hospital vs. non-children's hospital, teaching hospital vs. nonteaching hospital); source of admission (emergency department, clinic, other hospitals); and location (rural vs. urban). Children's hospitals were identified by the AHRQ using information from the National Association of Children's Hospitals and Related Institutions, while teaching hospital status was determined by the presence of an approved residency program and a ratio of full-time residents to beds of 0.25 or greater.[5]

Statistical Analysis

All analyses accounted for the complex sampling design with the survey commands included in STATA 9.2 (Statacorp, College Station, TX) and report national estimates from the data available in the 36 surveyed states. Because of the complex sampling design, the Wald test was used to determine significant differences for each outcome in univariable analysis. Variance estimates were reported as standard errors of the mean. We constructed multivariable logistic regression models to assess the adjusted impact of patient and hospital-level characteristics on each primary outcome measure; ie, in-hospital death and development of a serious complication. Negative binomial models were used for our secondary outcomes, LOS and costs, because of their rightward skew. Variance estimates for each model accounted for the clustering of data at the hospital level, and data were analyzed as per the latest AHRQ statistical update.[16]

Results

The 2003 KID identified 1587 hospitalizations for HSV in infants admitted at an age of 60 days or less in the entire United States. These infants had a total hospital cost of $27,147,000. Of the cohort, 10% had a concurrent congenital anomaly. Most infants (73.5%) were admitted within 14 days of birth, and 15.5% were transferred from another hospital. Based on APR-DRG criteria, 33% of the infants were classified as having a moderate risk of death, 24% as major risk, and 12.2% as extreme risk. The majority of infants were treated at non-children's hospitals (85.3%) in urban locations (91.5%). The average LOS was 12.0 $\pm$ 0.6 days and the average total hospital cost was $17,382 $\pm$ 1269. After admission, 267 of the infants, or 16.8%, had at least 1 serious complication. Fifty infants died during the hospitalization included in the KID.

Risk Factor Analysis

Serious Complications

Univariable (Table 1) analysis identified several factors associated with higher rates of serious complications. Younger age at admission was associated with a higher risk of serious complications. This trend was greatest for infants admitted under 14 days of age, of which 20.2% had a serious complication, compared with 10.2% of the infants admitted between 29 and 60 days of age. Infants with any identified congenital anomaly had significantly higher rates of serious complication (41.1% vs. 14.8% for infants without a

2010 Society of Hospital Medicine DOI 10.1002/jhm.627
Published online in wiley InterScience (www.interscience.wiley.com).

TABLE 1. Clinical Outcomes of Infants With HSV

Patient-Level Factors	% of Cohort	% with Serious Complication	% Death
Age at presentation			
≤7 days	58.4	21.6*	4.2*
8–14 days	15.1	15.8	3.6
15–28 days	16.4	9.7	2.1
29–60 days	10.1	10.2	0
Low birth weight			
Yes	10.6	44.2*	9.0*
No	89.4	14.3	2.7
Type of insurance			
Private	47.4	15.6	2.1*
Medicaid	49.0	19.2	4.8
Self pay	3.6	17.0	0
Race			
White	52.8	17.7	3.5
Black	18.9	17.6	4.2
Other	28.3	19.2	4.5
Gender			
Female	45.4	15.7	2.2
Male	54.6	18.9	4.3
Any congenital anomaly			
Yes	10.0	41.1*	10.4*
No	90.0	14.8	2.6
Admission type			
Routine	62.3	15.9*	2.8*
Emergency room	22.2	8.8	1.1
Transfer from another hospital	15.5	38.7	9.6
APR-DRG risk			
Mild	3.0	0.3*	0*
Moderate	33.0	2.0	0.5
Major	24.0	24.7	2.3
Extreme	12.2	85.0	20.8
Hospital-level factors			
Children's hospital			
Yes	14.7	27.0	6.4
No	85.3	16.3	3.1
Teaching hospital			
Yes	68.4	21.3*	4.3*
No	31.7	8.5	1.5
Location			
Urban	91.5	18.0*	3.6
Rural	8.5	9.0	1.6
Hospital size			
Small	14.1	19.3	4.2
Medium	25.9	14.3	3.2
Large	60.0	18.1	3.3

NOTE: Values are adjusted results. Bolt values signify results statistically significant at the $p < 0.05$ level.

Abbreviations: APR-DRG, all-patient refined diagnosis-related group; HSV, herpes simplex virus.

*Significant differences between groups of factors by Wald test, $P < 0.01$.

congenital anomaly). Similar findings were seen with low birth weight infants. Infants who were transferred prior to the hospitalization captured in the KID had a higher complication rate (38.7%) than infants admitted as a routine admission (15.9%) or via the emergency room (8.8%). Among hospital-level factors, infants admitted to children's or teaching hospitals had higher rates of serious complications, although only the difference between teaching and nonteaching hospitals reached statistical significance (Table 1).

Many of these factors were independently associated with increased complication rates in multivariable analysis (Table 2). Infants under 7 days of age on admission (odds ratio [OR], 2.68; 95% confidence interval [CI], 1.11–2.47), low birth weight (OR, 5.17; 95% CI, 2.98–8.98), and the concurrent presence of a congenital anomaly (OR, 3.09; 95% CI, 1.80–5.33) were associated with higher odds of a serious complication. Site of care lost its statistical significance once our models adjusted for differences in illness severity. Insurance status, gender, and race were not associated with a change in complication rates for these infants.

Death

Risk factors for higher mortality rates followed similar trends as those for the risk of a serious complication. Younger age at admission, low birth weight status, the presence of a serious complication, admission from another hospital, and treatment at a children's hospital or teaching hospital were all associated with higher mortality rates. In multivariable analysis, the concurrent presence of a congenital anomaly was associated with higher odds of death (OR, 4.26; 95% CI, 1.76–10.3). The cause of increased death in infants with congenital anomalies appeared to be a higher rate of serious complications, as including serious complications in the multivariable regression model resulted in the association between congenital anomalies and death losing statistical significance (OR in revised model 1.95; 95% CI, 0.63–6.05). Site of care again was not associated with differences in mortality after controlling for patient case-mix.

Concurrent Congenital Anomalies

Based on the higher complication and mortality rates seen in infants with HSV who had a concurrent congenital anomaly, we then investigated how the presence of specific congenital anomalies influenced clinical outcomes, LOS, and total hospital costs with HSV disease. Using the congenital anomaly groups listed in the Appendix, we found that congenital heart disease, central nervous system anomalies, pulmonary anomalies, and gastrointestinal anomalies were each associated with either higher rates of serious complications, longer LOS, or higher total hospital costs compared to infants without congenital anomalies (Table 3). Serious complications occurred most commonly in patients with central nervous system anomalies (55.6%) and congenital heart disease (50.8%), while infants with pulmonary anomalies had the longest LOS (37.1 ± 10.0 days) and highest total hospital costs of all anomaly categories. The types of complications differed by the anomaly group: infants with cardiac and pulmonary anomalies had the highest rates of respiratory complications (45% and 40%, respectively), whereas those with central nervous system anomalies had the highest rates of cardiac complications (51%). Each

2010 Society of Hospital Medicine DOI 10.1002/jhm.627
Published online in wiley InterScience (www.interscience.wiley.com).

TABLE 2. Multivariable Model of Risk Factors Associated With Differences in Serious Complications or Mortality in Infants With HSV

	Serious Complication		Mortality	
Risk Factor	**Odds Ratio**	**95% CI**	**Odds Ratio**	**95% CI**
Age at admission				
≤7 days	**2.68**	**1.11–2.47**	1.63	0.34–7.73
8–14 days	1.22	0.40–3.73	2.15	0.36–12.9
14–28 days	0.87	0.32–2.37	Reference*	
29–60 days	Reference			
Racial/ethnic status				
White	Reference		Reference	
Black	0.90	0.45–1.82	1.30	0.43–3.89
Other	0.99	0.57–1.70	1.19	0.48–2.99
Treatment at children's hospital	2.33	0.83–6.18	2.59	0.65–10.2
Treatment at teaching hospital	1.71	0.94–3.12	1.86	0.56–6.25
Female gender	0.96	0.63–1.48	**0.28**	**0.10–0.82**
Medicaid insurance	1.51	0.91–2.50	1.69	0.63–4.53
Transferred from another hospital	**3.76**	**2.03–6.98**	**3.47**	**1.42–8.46**
Transferred to another hospital	1.35	0.67–2.73	†	
Presence of a congenital anomaly	**3.09**	**1.80–5.33**	**4.26**	**1.76–10.3**
Low birth weight infant	**5.17**	**2.98–8.98**	**5.33**	**1.90–15.0**

NOTE: Values are for adjusted results. Bold values signify results statistically significant at the $p < 0.05$ level.

Abbreviations: CI, confidence interval; HSV, herpes simplex virus.

*No infant admitted between 29 and 60 days of age died in this cohort.

†All infants died before being transferred to another hospital.

TABLE 3. Impact of Congenital Anomalies on the Clinical Outcomes and Health Resource Use of Infants Hospitalized With HSV

	Number*	% With Serious Complication	LOS (days)	Total Hospital Costs (2003 dollars)
No congenital anomaly	1391	14.8	11.3 ± 0.6	15,118 ± 1158
Type of congenital anomaly				
Congenital heart disease	73	50.8‡	23.5 ± 4.6†	46,760 ± 9340‡
Central nervous system anomaly	31	55.6‡	15.4 ± 3.0	23,962 ± 5037†
Head/neck anomaly	13	40.6	11.1 ± 4.6	14,132 ± 7860
Pulmonary anomaly	13	34.1	37.1 ± 10.0†	67,234 ± 21,002†
Gastrointestinal anomaly	20	33.5	21.6 ± 4.9†	41,207 ± 13,878
Genitourinary anomaly	19	24.1	11.0 ± 2.5	10,906 ± 1890‡
Musculoskeletal anomaly	§	§	§	§
Genetic anomaly	18	10.2	12.2 ± 2.4	15,990 ± 3808

NOTE: All reported values are mean ± standard errors of the mean.

Abbreviations: HSV, herpes simplex virus; KID, Kid's Inpatient Database; LOS, length of stay.

*Numbers of patients are national estimates derived from identified children in the KID.

†Statistically different from infants without congenital anomalies, $P < 0.05$.

‡Statistically different from infants without congenital anomalies, $P < 0.01$.

§Specific values could not be reported because the number of identified infants with musculoskeletal anomalies was below 10 observations.[5]

anomaly class had a similar rate of neurological complications, between 30% and 40%.

Site of Care

Finally, we examined the LOS and costs of receiving care at a children's hospital. The data shown in Tables 1 and 2 suggest that receiving treatment at a children's hospital does not result in improved clinical outcomes for infants admitted with HSV. One potential advantage, though, is improved efficiency of care, which would result in a shorter LOS or lower costs. Using negative binomial multivariable regression models to account for differences in patient characteristics, regional variation, and insurance status, treatment at a children's hospital was associated with an 18% shorter LOS (95% CI, 1%–34%) compared to non-children's hospitals after accounting for the generally sicker infants treated at children's hospitals. Children's hospitals, though, were more expensive than non-children's hospitals (increase of $642

2010 Society of Hospital Medicine DOI 10.1002/jhm.627
Published online in wiley InterScience (www.interscience.wiley.com).

per day; 95% CI, $232–1052). These results remained consistent when we omitted transferred patients from the model, instead of controlling for them in the analysis.

Conclusions

There has been little prior information to guide practitioners and parents about factors that potentially influence clinical outcome of infants hospitalized with HSV in non-children's hospitals, although over 80% of infants are managed at non-children's hospitals. These studies also did not have the power to characterize the risk of poor clinical outcome associated with rarer clinical factors.[1,2,6] This study, using nationally representative data, found that these rarer clinical factors and site of care may influence the outcomes of infants hospitalized with HSV, albeit in different methods. Younger age at admission and a coexisting congenital anomaly remained statistically significant predictors of worse clinical outcomes after controlling for various patient and hospital factors. Not all congenital anomalies increased the risk of death or serious complications; rather, anomalies that affected either the cardiopulmonary system or the central nervous system appeared to result in the highest increases in risk. This study also found that treatment of infants with HSV at a children's hospital was associated with a 28% shorter LOS after accounting for the sicker patients cared for by children's hospitals. This finding is in contrast to prior studies of common pediatric conditions, where there were no differences in the LOS between children's and non-children's hospitals,[17,18] and severe sepsis, where children's hospitals had longer LOSs.[19] These results confirm the importance of specific risk factors in predicting the likelihood that an infant admitted with HSV may have a poor clinical outcome. Also, these results emphasize the differences in outcomes that may occur at different types of hospitals.

This study is the first to find that certain congenital anomalies or conditions may be associated with worse clinical outcomes from HSV. There is little information in the literature to explain these findings. Those anomalies that affect the cardiopulmonary or central nervous system may either worsen the symptoms of HSV or predispose infants to have a serious complication, such as shock or respiratory failure. This finding would be similar to the increased risk of serious complications seen in infants with congenital heart disease who contract respiratory syncytial virus[20] or infants with genetic syndromes who undergo heart surgery.[21] Alternatively, because we do not have information on do-not-resuscitate status, the presence of one of these congenital anomalies may result in more withdrawal of care when an infant is infected with HSV and has a serious complication; the LOS of these children may not reflect these decisions because the decision to withdrawal care may only occur after the child's condition worsens significantly, which may happen any time during the disease course. However, this theory is less likely because we failed to find similar results with other congenital anomalies such as genetic or chromosomal syndromes. Further examination of these infants and their overall response to insults such as HSV is needed to understand how these anomalies influence the outcomes of a serious, unrelated illness.

Age upon admission was another important predictor of poor outcomes when analyzed in univariable or multivariable analysis. This result is consistent with prior work,[1–4] which suggests that younger children are more likely to be hospitalized with either congenitally acquired HSV or systemic disease. The information contained in the KID does not allow us to determine whether young age is a risk factor for poor outcome irrespective of the clinical presentation of HSV, or whether age serves as a proxy for the appearance of more severe clinical disease. This effect of age remained present even after controlling for the higher risk of a serious complication and death in low birth weight infants. There are limited data that suggest that premature birth is an independent risk factor for worse outcomes associated with perinatal or congenital infection; 1 previous case study of *Enterobacter sakazakii* infections found a higher fatality rate for premature infants compared to term infants.[22] This study supports these findings.

This study found that treatment at a children's hospital resulted in a 28% shorter LOS without a statistically significant difference in clinical outcomes after controlling for case-mix differences. This finding is in contrast to prior studies of common pediatric conditions[17,18] and severe sepsis.[19] There are several potential explanations for the difference in findings. For common pediatric conditions, there may be fewer variations in treatment style and less need for new diagnostic modalities that are more available at academic centers. For HSV disease, though, children's hospitals may also be more likely than non-children's hospitals to perform polymerase-chain reaction (PCR) testing for the diagnosis of perinatally acquired HSV, correctly identify the disorder, or receive the test results in a timely fashion. Pediatric subspecialists, such as infectious disease physicians or neurologists, are also likely to be more available at children's hospitals than at other centers. While the role of subspecialty consultation in improving outcomes for neonates with HSV is not known, improved outcomes at children's hospitals has been described for other serious conditions such as splenic injuries.[23] Children's hospitals had higher daily costs than non-children's hospitals, as has been found in other work.[17,19] Children's hospitals may be treating sicker patients, for whom we are unable to adequately adjust for their illness severity with hospital administrative data.[17,19] Also, there may be a greater use of medical tests and treatments that increase the costs of care. These costs do not include indirect costs to the families such as loss of work and travel costs. In light of the shorter LOS in children's hospitals, policy makers will need to balance the potentially higher daily costs of care with more efficient management of the disease process.

Because this study used hospital administrative records, there are a few limitations. We used ICD-9CM diagnosis

2010 Society of Hospital Medicine DOI 10.1002/jhm.627
Published online in wiley InterScience (www.interscience.wiley.com).

codes to identify patients, congenital anomalies, and complications. The diagnosis of some infants with HSV or less significant congenital anomalies could have been missed because clinicians either overlooked the disease or did not make the diagnosis before discharge. This form of spectrum bias would likely miss the infants with the least severe disease and make it more difficult to find the results that we found in this study.[24] Prior work successfully used and validated similar ICD-9CM codes to identify HSV cases among the different types of hospitals included in the KID.[6–11] Our study design estimated 1587 cases of neonatal HSV in 2003. A prospective study of maternal serologic and virologic status during pregnancy estimated 480 to 2160 new cases of neonatal HSV per year.[25] Thus, while miscoding is a potential limitation to our study, the overall numbers of patients in this study were similar to past annual estimates. One potential area of miscounting, though, was the inability of the KID to link the records of 16% of the identified infants with HSV whose care was transferred between hospitals. These infants may result in misleading LOS or cost information: lower for the transferring hospital, because they only kept the child a short period of time, or lower for the accepting hospital, as some of the total hospital stay is not accounted for in the KID. We accounted for this issue in 2 ways. First, we included a variable for being transferred in the multivariable models, and found no difference in any results when we omitted these patients from the analysis. Second, we performed a univariable analysis stratified by transfer status, which did not differ substantially from our main model for most variables. Accurate linkage of all the hospital records for an infant's hospital course, likely only through a mandatory reporting system for infant HSV, would help confirm the associations we identified in this study.

In conclusion, infants with congenital anomalies should be closely monitored for the development of serious complications associated with HSV, particularly those infants with congenital heart disease, pulmonary anomalies, or central nervous system anomalies. Closer investigation of the care practices that children's hospitals use in the management of infants with HSV is needed to improve the efficiency of care delivered to these infants, as HSV disease remains a significant public health problem.

Address for correspondence and reprint requests:
Scott A. Lorch, MD, MSCE, Center for Outcomes Research, The Children's Hospital of Philadelphia, 3535 Market Street, Suite 1029, Philadelphia, PA 19104; Telephone: 215-590-1714; Fax: 215-590-2378; E-mail: lorch@email.chop.edu Received 30 October 2008; revision received 6 August 2009; accepted 15 September 2009.

References

1. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics*. 2001;108:223–229.
2. Whitley RJ, Kimberlin DW, Roizman B. Herpes simplex viruses. *Clin Infect Dis*. 1998;26:541–553.
3. Arvin AM, Whitley RJ, Gutierrez KM. Herpes simplex virus infections. In: Remington JS, Wilson CB, Baker CJ, editors. *Infectious Diseases of the Fetus and Newborn Infant*. 5th ed. Philadelphia, PA: W.B. Saunders; 2001. p 425–446.
4. Whitley RJ, Corey L, Arvin A, et al. Changing presentation of herpes simplex virus infection in neonates. *J Infect Dis*. 1988;158:109–116.
5. Design of the HCUP Kids' Inpatient Database (KID), 2003. Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; 2003. Revised January 30, 2006. Available at: http://www.hcup-us.ahrq.gov/db/nation/kid/reports/KID_2003_Design_Edited_013006.pdf. Accessed October 2009.
6. Whitley R, Davis EA, Suppapanya N. Incidence of neonatal herpes simplex virus infections in a managed-care population. *Sex Transm Dis*. 2007;34:704–708.
7. Mark KE, Kim HN, Wald A, et al. Targeted prenatal herpes simplex virus testing: can we identify women at risk of transmission to the neonate. *Am J Obstet Gynecol*. 2006;194:408–414.
8. Szucs TD, Berger K, Fisman DN, et al. The estimated economic burden of genital herpes in the united states. *BMC Infect Dis*. 2001;1:5.
9. Yasmeen S, Romano PS, Schembri ME, et al. Accuracy of obstetric diagnoses and procedures in hospital discharge data. *Am J Obstet Gynecol*. 2006;194:992–1001.
10. Gutierrez KM, Falkovitz Halpern MS, Maldonado Y, et al. The epidemiology of neonatal herpes simplex virus infections in California from 1985 to 1995. *J Infect Dis*. 1999;180:199–202.
11. Tao G, Kassler WJ, Rein DB. Medical care expenditures for genital herpes in the United States. *Sex Transm Dis*. 2000;27:32–38.
12. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348:1546–1554.
13. Shwartz M, Iezzoni LI, Moskowitz MA, et al. The importance of comorbidities in explaining differences in patient costs. *Med Care*. 1996;34:767–782.
14. Yoon PW, Olney RS, Khoury MJ, et al. Contribution of birth defects and genetic diseases to pediatric hospitalizations. A population-based study. *Arch Pediatr Adolesc Med*. 1997;151:1096–1103.
15. Silber JH, Gleeson SP, Zhao H. The influence of chronic disease on resource utilization in common acute pediatric conditions. Financial concerns for children's hospitals. *Arch Pediatr Adolesc Med*. 1999;153:169–179.
16. Health Care Cost and Utility Project. Calculating Kids' Inpatient Database (KID) Variances. December 16, 2005. Methods Series Report # 2005-5. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.hcup-us.ahrq.gov/db/nation/kid/reports/CalculatingKIDVariances.pdf. Accessed October 2009.
17. Merenstein D, Egleston B, Diener-West M. Lengths of stay and costs associated with children's hospitals. *Pediatrics*. 2005;115:839–844.
18. Srivastava R, Homer CJ. Length of stay for common pediatric conditions: teaching versus nonteaching hospitals. *Pediatrics*. 2003;112:278–281.
19. Odetola FO, Gebremariam A, Freed GL. Patient and hospital correlates of clinical outcomes and resource utilization in severe pediatric sepsis. *Pediatrics*. 2007;119:487–494.
20. Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. *J Pediatr*. 2003;143:S112–S117.
21. Gaynor JW, Wernovsky G, Jarvik GP, et al. Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. *J Thorac Cardiovasc Surg*. 2007;133:1344–1353, 1353, e1341–e1343.
22. Lai KK. *Enterobacter sakazakii* infections among neonates, infants, children, and adults. Case reports and a review of the literature. *Medicine*. 2001;80:113–122.
23. Bowman SM, Zimmerman FJ, Christakis DA, et al. Hospital characteristics associated with the management of pediatric splenic injuries. *JAMA*. 2005;294:2611–2617.
24. Mulherin SA, Miller WC. Spectrum bias or spectrum effect? Subgroup variation in diagnostic test evaluation. *Ann Intern Med*. 2002;137:598–602.
25. Brown ZA, Wald A, Morrow RA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA*. 2003;289:203–209.

2010 Society of Hospital Medicine DOI 10.1002/jhm.627
Published online in wiley InterScience (www.interscience.wiley.com).