Herpes PCR Testing and Empiric Acyclovir Use Beyond the Neonatal Period

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**KEY WORDS**
herpes simplex virus, meningoencephalitis, acyclovir, empiricism, diagnosis, clinical medicine

**ABBRVIATIONS**
APR—All Patient Refined
CNS—central nervous system
CSF—cerebrospinal fluid
DRG—diagnosis-related group
HSV—herpes simplex virus
ICD—International Classification of Diseases, Ninth Revision
LOS—length of stay
PHIS—Pediatric Health Information System
WBC—white blood cell

Dr Gaensbauer participated in conceptualization and design of the study, extracted and analyzed data, and drafted the initial manuscript; Ms Birkholz carried out initial data extraction and data analysis, and reviewed and revised the manuscript; Ms Pfannenstein participated in conceptualization and design of the study, performed initial analysis of data, and reviewed and revised the manuscript; Dr Todd, senior author, participated in conceptualization and design of the study, extracted and analyzed data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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**WHAT’S KNOWN ON THIS SUBJECT:** Herpes encephalitis outside the neonatal period is typically severe and recognizable to clinicians. Excessive testing for herpes encephalitis is associated with increased medical costs and hospital length of stay, and risks patient harm.

**WHAT THIS STUDY ADDS:** Herpes testing and empirical acyclovir treatment in older and less unwell patients has been increasing in US pediatric hospitals over the past decade, which may reflect a more fundamental problem in current approaches to clinical decision-making.

**BACKGROUND:** Diagnostic strategies based on empirical testing and treatment to identify herpes simplex virus (HSV) infection in neonates may not be appropriate for older children in whom the most common presentation of severe infection is encephalitis, a rare and clinically recognizable condition.

**METHODS:** Use of acyclovir in infants and children in 6 common non-HSV infection–related diagnosis-related groups was characterized between 1999 and 2012 at 15 US pediatric hospitals by using the Pediatric Health Information System database. Characteristics of non-neonatal patients at 1 institution tested for HSV encephalitis over a 6.5-year period were then analyzed to identify factors associated with potentially unnecessary testing and treatment.

**RESULTS:** Acyclovir use increased from 7.6% to 15.6% (P < .001) from 1999 to 2012. Much of this increase came in infants 30 to 60 days of age (82.7% increase, P < .001) and in patients with milder disease severity (44.8% increase, P < .001). Length of stay was increased by 2 days for children treated with acyclovir (P < .001). At our institution, 1394 HSV cerebrospinal fluid polymerase chain reactions were performed in children >30 days old, with only 3 positive results (0.2%). Comparison of the 3 subjects with positive testing and 55 with negative testing revealed that all cases, but only 4% (95% confidence interval 1.2%–14.0%) of noncases had clinical characteristics typical of HSV encephalitis.

**CONCLUSIONS:** Strategies for diagnosis and empirical treatment of suspected HSV encephalitis beyond the neonatal period have trended toward the approach common for neonates without evidence of an increase in disease incidence. This may result in increased medical costs and risk to patients. Pediatrics 2014;134:e651–e656
Herpes simplex virus (HSV) encephalitis in children is a potentially devastating, yet, fortunately, very uncommon disease in nonneonates, occurring in approximately 1 per 1 million children and adolescents per year.1 Diagnostic strategies for HSV encephalitis must therefore identify cases rapidly and uniformly, while avoiding excessive or inefficient clinical practices. Empirical diagnostic and therapeutic approaches in newborn infants, in whom presentation of HSV disease can be subtle, may not be appropriate for older children, in whom the disease typically has more overt manifestations. At our institution, we have noted a trend over the past decade toward increased testing and empirical therapy for HSV disease in these age groups.

Overtesting and treating for HSV results in inappropriate use of health care resources, as well as potential adverse events related to unnecessary treatment with acyclovir. In nonneonates, acyclovir is associated with increases in serum creatinine and glomerular filtration rate in older children, particularly when coadministered with other nephrotoxic medications, such as antibiotics.3,4 Furthermore, shifts in the factors influencing HSV diagnostic and empirical treatment decisions may represent a more fundamental problem in the current practice of pediatrics.

To better define this phenomenon, a 2-part study was undertaken. The first part aimed to define trends in HSV empirical treatment at US pediatric hospitals by using the Pediatric Health Information System (PHIS) database, and the second part examined the characteristics of patients tested for HSV at our own institution.

METHODS

Data Extraction From PHIS Database

Patient demographic and utilization data were extracted from the PHIS database.

The PHIS hospitals are (currently) 44 of the largest and most advanced children’s hospitals in America. The database collects demographic, diagnostic, procedural, and utilization data on >6 million pediatric subjects, representing a wide geographic distribution in the United States. The study population was made up of pediatric inpatients in the PHIS database discharged between January 1, 1999, and December 31, 2012. Only the 15 participating hospitals for which complete data were available for the entire study period were included. The dataset was designed to include all neonates with systemic HSV infection and all older children with central nervous system (CNS) involvement, by using final discharge International Classification of Diseases, Ninth Revision (ICD-9) diagnoses. Included diagnoses and corresponding ICD-9 codes are presented in Supplemental Table 3. To avoid missing late neonatal HSV infections, the broader ICD-9 criteria were used up to 60 days of age. Subsequent admissions in qualifying subjects were excluded to avoid double-counting.

To analyze trends in acyclovir use in nonneonates, we first identified 6 nonneonatal patient refined—diagnosis-related groups (APR-DRGs; 3M Health Information Systems, Salt Lake City, UT) in the dataset in which acyclovir was prescribed >5% of the time: nervous system infection (diagnosis-related groups [DRG] 50) and viral meningitis (51), septicemia/disseminated infection (720), fever (722), viral illness (723), and other infection/parasitic disease (724). Data on demographics, acyclovir use, days of hospitalization, severity score, and outcomes during the 14-year study period were then assessed for each of these groups. Cases with accompanying varicella ICD-9 codes (052.0–2, 7–9) were excluded.

Testing and Treatment of Nonneonatal HSV at a Single Institution

All HSV PCR tests sent on cerebrospinal fluid (CSF) at Children’s Hospital Colorado between January 1, 2007, and June 30, 2013, were identified from a laboratory database. Medical records from all patients >30 days old with positive tests and from 55 randomly selected subjects >30 days old with negative tests were reviewed to obtain demographic, clinical, radiologic, and laboratory characteristics, and to identify use and duration of acyclovir. The number of negative tests selected for review was based on an initial objective of developing clinical prediction rules, which was subsequently abandoned because of low numbers of positives. The medical chart reviewer (J.G.) was not blind to HSV test results. Specific findings on neurologic examination were not collected to avoid subjectivity in documentation and interpretation, although altered mental status was assessed if clearly stated in the medical record by the attending provider. Subjects with known diagnoses of immune compromising conditions (HIV, malignancy) were excluded.

The initial objective was to analyze the predictive value of a clinical assessment of typical signs and symptoms of HSV encephalitis: presence of fever (by history or as documented at presentation), seizures, and altered mental status, and CSF white blood cell (WBC) count >5 WBC/cm3.5 However, the low number of positive cases (2) prevented robust statistical analysis of predictive value. We therefore concentrated on a descriptive analysis of the cohort with negative tests, to explore the clinical characteristics that led to HSV testing, and to identify factors leading to potentially unnecessary testing.

Ethics Committee Approvals

This study was approved by the Organizational Research Risk and Quality Improvement Review Panel at Children’s Hospital Colorado as delegated by the Colorado Multiple Institutional Review Board.

Statistical Analysis

Trends in herpes cases and acyclovir use over time in nonherpes DRGs were
analyzed by linear regression and analysis of variance, and association between time periods and acyclovir use was assessed by using χ² tests. Analysis of characteristics of tested subjects at our institution was descriptive.

RESULTS

Acyclovir Use in PHIS Hospitals

During the 14-year study period, 743 cases of invasive HSV infection occurred at the 15 reporting hospitals, 357 (48%) cases in subjects <30 days old and 386 (52%) in children ≥30 days old. There was no significant change in HSV cases over time in either age group (P = .770 and P = .734 by analysis of variance, Fig 1). In contrast, during the same period, use of acyclovir for the combined non-HSV DRGs increased significantly from 7.6% in 1999 to 15.6% in 2012 (R² = 0.909; P < .001, Fig 1).

To further explore the changes in acyclovir use among the PHIS hospitals over the 14-year study period, rates of acyclovir in the first 7 years were compared with rates in the second 7 years (Table 1). For all children in the combined non-herpes DRGs, acyclovir usage increased from 10.8% to 14.5%, an overall increase of 34.3% (P < .001). Individual significant overall increases occurred in all 6 DRGs with the greatest percentage changes in viral meningitis (120.6%), fever (69.2%), and septicemia (53.1%). Significant increases (P < .001) occurred in children aged 0 to 29 days (80.9%), 30 to 59 days (82.7%), and 60 days to <1 year (43.1%). Lesser changes were noted in older children (≥1 year to <5 years [−14.5%, P = .007] and ≥5 years to <13 years [5.8%, P = 2]). Of interest, the increase in acyclovir usage occurred only in children with severity scores <3 (44.8%, P < .001). Additionally, hospital LOS was significantly higher by an average of 2.1 days (5.85 vs 3.76 days, P < .001) in those children who received acyclovir in these non-herpes DRGs as compared with those who did not, an association that remained significant after adjustment for year of discharge, severity, and patient age.

Herpes Testing at Children’s Hospital Colorado

From 2007 to mid-2013, 3006 HSV PCR tests were sent on CSF samples at Children’s Hospital Colorado. Of these, 1394 (46%) were sent on children <30 days old, and only 3 (0.22%) yielded a positive result in this age group, with 2 children, ages 11 and 13 months, diagnosed with HSV encephalitis. The third positive occurred in a 13-year-old diagnosed with a spontaneously resolving HSV meningitis, in whom the result returned after discharge without HSV treatment from the hospital.

Characteristics of 55 Subjects With Negative HSV Testing

Subjects with negative HSV CSF PCR testing ranged in age from 1 month to 16 years and 4 months, with a median age of 20 months (Table 2). Fever (temperature ≥38.0°C) by history or at the time of HSV testing was present in 58% of subjects. Forty-two percent had either a history of or observed seizure activity, and 16% had altered mental status by history or at the time of testing. Half of all HSV PCR tests were sent on subjects without CSF pleocytosis (CSF WBC count <5/cm³). Fifty-six percent of subjects were tested for enterovirus, although only 3 (9%) of 32 were positive. The vast majority (98%) of subjects were admitted to the hospital and 73% underwent an MRI within the first 48 hours of presentation. Temporal lobe abnormalities were not noted in any scan. Sixty-nine percent received empirical acyclovir before test results, with a median duration of empirical treatment of 3 days.

Predictive Value of Assessment for Typical Clinical Presentation

Both cases of HSV encephalitis in our series met our predefined criteria for “typical” HSV clinical presentation. Conversely, only 4% (95% confidence interval 1%–14%) of negative subjects met these criteria, that is, 96% of HSV testing...
was performed on patients who did not have the clinical features typical of HSV infection.

**DISCUSSION**

This study characterizes increasing trends nationwide in empirical treatment of presumed HSV encephalitis in children outside the neonatal period and with less-severe presentations. At our own institution, testing and empirical treatment in patients who lacked clinical and laboratory findings typical of HSV encephalitis was common. Perinatally acquired HSV disease in newborns is relatively common, and can be subtle yet devastating. Thus, many clinicians adopt a conservative, empirical approach to HSV testing and treatment in this age group. However, this may not be an appropriate approach in older children, in whom HSV is typically more readily apparent than in a neonate. In a series of 113 children and adults with HSV encephalitis before the introduction of PCR-based diagnostics, a prodrome of malaise, headache, and nausea/vomiting was typical, and fever occurred in 90% of subjects. Progressive alteration in mentation occurred in 71% and seizure activity occurred in 67%; all cases had identifiable focal abnormalities on clinical, computed tomography, or EEG findings. The introduction of CSF PCR led to the understanding that less-severe forms of HSV CNS disease do exist, although these cases typically lack only the classic severe focal encephalitis syndrome: fever (94% to 96% of cases) and altered mental status to some degree remain near universal findings in reports of “milder” disease. In a series of 16 children, all cases presented with fever and all had clear evidence of CNS involvement. Isolated cases of truly milder CNS disease in children have been reported only very rarely.

**TABLE 1** Changes in Acyclovir Use Among Hospitalized Children With Non-HSV Diagnoses, PHIS Database, 1999–2012

<table>
<thead>
<tr>
<th>Category</th>
<th>Time Period</th>
<th>Percentage Change From 1999–2005 Period</th>
<th>P Value^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>4103/38 115 (10.8%)</td>
<td>6323/43 663 (14.5%)</td>
<td>34.3</td>
</tr>
<tr>
<td>APR-DRG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Meningitis (DRG 51)</td>
<td>990/7868 (12.6%)</td>
<td>1341/4830 (27.8%)</td>
<td>120.6</td>
</tr>
<tr>
<td>Fever (DRG 722)</td>
<td>853/13 687 (6.5%)</td>
<td>1633/14 887 (11.0%)</td>
<td>69.2</td>
</tr>
<tr>
<td>Septicemia (DRG 720)</td>
<td>448/4688 (9.6%)</td>
<td>735/5012 (14.7%)</td>
<td>53.1</td>
</tr>
<tr>
<td>Other infection (DRG 724)</td>
<td>831/6781 (12.3%)</td>
<td>1113/7148 (15.6%)</td>
<td>26.8</td>
</tr>
<tr>
<td>CNS Infection (DRG 50)</td>
<td>778/1794 (43.4%)</td>
<td>785/1658 (47.8%)</td>
<td>10.1</td>
</tr>
<tr>
<td>Viral illness (DRG 723)</td>
<td>165/3295 (4.9%)</td>
<td>708/10 128 (7.0%)</td>
<td>42.9</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–29 d</td>
<td>1402/7812 (17.9%)</td>
<td>2459/8532 (28.8%)</td>
<td>60.9</td>
</tr>
<tr>
<td>30–59 d</td>
<td>648/6204 (10.4%)</td>
<td>1352/7151 (19.0%)</td>
<td>82.7</td>
</tr>
<tr>
<td>60 d to &lt;1 y</td>
<td>360/6200 (5.8%)</td>
<td>546/6608 (8.3%)</td>
<td>43.1</td>
</tr>
<tr>
<td>≥1 y to &lt;5 y</td>
<td>548/7200 (7.6%)</td>
<td>591/9052 (6.5%)</td>
<td>14.5</td>
</tr>
<tr>
<td>≥5 y to &lt;13 y</td>
<td>791/7716 (10.3%)</td>
<td>866/7959 (10.9%)</td>
<td>5.8</td>
</tr>
<tr>
<td>≥13 y to &lt;18 y</td>
<td>354/2883 (11.9%)</td>
<td>499/4361 (11.4%)</td>
<td>4.2</td>
</tr>
<tr>
<td>Severity score^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>313/32 753 (9.6%)</td>
<td>4945/35 491 (13.9%)</td>
<td>44.8</td>
</tr>
<tr>
<td>3–4</td>
<td>969/5362 (18.1%)</td>
<td>1578/8172 (16.9%)</td>
<td>−6.6</td>
</tr>
</tbody>
</table>

^a 2x test. ^b APR-DRG Severity Score: 1 = mild; 2 = moderate; 3 = major; 4 = extreme.

**TABLE 2** Herpes PCR Testing From CSF, 2006–2012, and Clinical and Laboratory Characteristics of Selected Subjects

<table>
<thead>
<tr>
<th>PCR Result</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All herpesvirus PCR testing from CSF: 2006–2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>14</td>
<td>2992</td>
</tr>
<tr>
<td>Age ≥30 d</td>
<td>11</td>
<td>1598</td>
</tr>
<tr>
<td>Age &gt;30 d</td>
<td>3</td>
<td>1384</td>
</tr>
</tbody>
</table>

**Clinical and laboratory characteristics of subjects age >30 days selected for chart review**

<table>
<thead>
<tr>
<th>Positive HSV PCR, n = 3^a</th>
<th>Negative HSV PCR, n = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final diagnosis of HSV encephalitis</td>
<td>2</td>
</tr>
<tr>
<td>Fever, n (%)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Seizures, n (%)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Altered mental status, n (%)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>CSF pleocytosis, n (%)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Median CSF WBC/cm^3^b (range)</td>
<td>830 (90–1770)</td>
</tr>
<tr>
<td>“Typical” clinical syndrome^b</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Enteroviral PCR testing</td>
<td>0</td>
</tr>
<tr>
<td>Admission to hospital</td>
<td>2 (100)</td>
</tr>
<tr>
<td>MRI within first 48 h</td>
<td>2 (100)</td>
</tr>
</tbody>
</table>

^a One subject with a positive test was diagnosed with HSV meninigitis and not included in further descriptive analysis. ^b “Typical” clinical syndrome: fever, altered mental status, seizures and CSF pleocytosis (WBC >5/cm^3).
CSF is abnormal in virtually all patients with HSV encephalitis. Of 18 patients with HSV-positive CSF described by Domingues et al, none had a CSF WBC/cm³ count <5. In the pediatric series from Toronto, 15 (94%) of 16 patients had a WBC count >5 in the CSF; 1 subject, a 14-year-old girl, presented with fever and status epilepticus, and had a CSF WBC count of 3. In the mild case reported by DeVincenzo and Thorne, only 1 WBC/cm³ was noted on an initial tap, but 3 days later increased to 11. Two adult patients were reported with 0 WBCs in CSF at presentation; however, both subjects were immunosuppressed (chronic steroid therapy, AIDS).

Our own series, although characterized by a very low number of cases, is consistent with these observations that HSV encephalitis in children is a rare and clearly recognizable clinical syndrome. Both cases of HSV encephalitis presented with fever, seizures, altered mental status, and CSF pleocytosis (90 and 1770 WBC/cm³ respectively). They both had focal abnormalities on MRI and EEG. The third HSV-positive test at CHC during the study period came from a 13-year-old who presented with meningismus without fever, and was discharged from the hospital without acyclovir therapy before the test result being reported. This case is consistent with an HSV meningitis, which is typically benign and self-limited, and does not typically require treatment (and thus is not a case that depends on a urgent virologic diagnosis).

Nearly 1400 negative HSV PCRs were performed on CSF on a broad spectrum of patients, strong evidence against the significant incidence of milder or more subtle forms of HSV CNS infection. Our findings complement a study of pediatric acyclovir use in the United Kingdom, in which the investigators found 27% of acyclovir courses were unjustified by the clinical presentation. However, relative to their findings, our practice is significantly less discriminatory: only 54% of our tested subjects had fever, and half had no CSF pleocytosis.

Initiatives designed to reduce reliance on laboratory testing in clinically low-risk patients have the potential to significantly reduce medical costs and adverse events. In an analysis of hospital expenditures in infants tested for HSV compared with infants not tested, Shah et al found an unadjusted difference in cost of nearly $1750 and a 39% increase in LOS among infants 29 to 56 days old. This is consistent with our findings in the PHIS database of an increase in LOS of an average of 2 days among patients receiving acyclovir for nonherpes DRGs. Furthermore, at our institution, nearly three-quarters of patients with negative testing underwent an MRI, demonstrating the potential for unnecessary clinical suspicions to lead to increased expenditures beyond increases in LOS. These figures also do not account for potential harm to patients from acyclovir-induced nephrotoxicity, which has been reported to occur in up to 35% of acyclovir courses in pediatrics, with renal failure occurring in almost 4%.

Several potential limitations in our study must be acknowledged. Data from the PHIS network may have been misclassified or inputted incorrectly, although this is unlikely to have a major effect on our conclusions given the large dataset. In the review of testing at our institution, the very low number of cases of HSV encephalitis limits our ability to describe potential variability in clinical presentation of pediatric HSV encephalitis. The large number of negatives, however, is instructive as to the very low frequency of this disease. Last, the more detailed review of testing comes from a single center, and although increases in acyclovir use were observed throughout the 15 PHIS hospitals, it is possible that alternate explanations for this shift at other centers exist.

Our findings confirm increasing testing and empirical therapy for suspected HSV at our institution and strongly suggest that this is occurring in pediatric hospitals across the United States. Based on our findings, future work will explore further the factors (such as hospital “culture,” perceptions of risk, and the seniority and experience of providers) associated with clinical decision-making within our hospital, and develop more specific educational and systemic interventions aimed at improving our approach to the diagnosis and empirical treatment. Our data suggest that many unnecessary tests could be avoided by simple interventions, such as delaying an HSV PCR until CSF cell counts have been reviewed (and confirmed as abnormal) by ordering providers; a measure that could have reduced testing in our series by up to 50%. In patients who are clinically unwell, but still unlikely to have HSV, a more nuanced approach to influencing clinical decision-making will be required to more comprehensively reduce testing.

Finally, our observations are consistent with a broader phenomenon in medical practice described as “creeping empiricism.” Empiricism as a dominant influence in clinical practice is not a new notion; the problem, with both contemporary and historical examples, was clearly described in an editorial nearly 30 years ago. However, given near-exponential increases in medical costs, the burden to society of inappropriate or excessive empirical practice may never have been greater than in the present era. Furthermore, adverse events related to unnecessary tests or treatment run counter to the major reemphasis on patient safety. There is no shortage of conditions for which creeping empiricism influences clinical practice, often to the detriment of both the individual patient and to a society dependent on finite health care resources. Although this phenomenon is by no means limited to pediatrics, examples in our own specialty might include routine voiding...
cystourethrogram after initial febrile urinary tract infection,18 steroid use for bronchiolitis,19 tonsillectomy for recurrent throat infections,20 universal school-based forward bend screening for scoliosis,21 and antibiotic treatment of inner ear effusion.22 Our data add testing and treatment of HSV encephalitis in older children to this list. In fact, the word herpes is derived from the Greek word meaning “to creep,” so perhaps in more ways than one, this condition is an ideal paradigm to highlight an emerging problem of creeping empiricism in clinical medicine.

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