

Testing and Empiric Treatment for Neonatal Herpes Simplex Virus: Challenges and Opportunities for Improving the Value of Care

Laura Brower, MD,^a Amanda Schondelmeyer, MD, MSc,^a Paria Wilson, MD, MEd,^b Samir S. Shah, MD, MSCE^a

A 6-day-old boy presents to the emergency department with 1 day of fever and decreased intake. He has no rash, is mildly dehydrated but not ill-appearing, and has normal mental status. An evaluation for serious bacterial infection is performed, but the lumbar puncture is not successful. He receives ampicillin and gentamicin and is admitted to the inpatient unit. The resident team successfully reattempts the lumbar puncture, with 6 white blood cells and >1000 red blood cells. Herpes simplex virus testing of the cerebrospinal fluid and mucous membranes is sent, the patient is started on acyclovir, and his gentamicin is changed to cefotaxime to minimize exposure to nephrotoxic medications. On day 2 of hospitalization, the team notes that his creatinine has increased since admission. This prompts initiation of intravenous fluids and repeat laboratory testing. The parents ask about the potential impact on his future kidney function. The herpes simplex virus testing and all cultures are negative; however, discharge is delayed as repeat creatinine measurements are performed to ensure the creatinine is decreasing.

Neonatal herpes simplex virus (HSV) infections are rare, with an incidence of 9.6 per 100 000 births¹ and a prevalence of 0.2% to 0.3% in febrile neonates.² However, neonatal HSV infections are associated with high mortality and, among survivors, long-term morbidity.^{3,4} In the absence of multicenter trials and decision rules, clinicians must rely on findings from published case series, which emphasize that no combination of presenting signs and symptoms can reliably identify all neonates with HSV infection.^{5–11} The variability in presentation has given rise to multiple proposed approaches to empiric testing and treatment and, consequently, substantial variation in the factors that prompt HSV testing, sometimes without clear correlation with known risk factors.^{12–15}

It is important to address this variability in testing and treatment because nonstandardized approaches to testing for HSV are associated with longer lengths of stay and higher hospital charges.¹⁶ Aronson et al¹⁷ reviewed 35 000 emergency department visits for infants younger than 90 days with fever and found that the proportion of infants receiving acyclovir at high-utilizing hospitals was more than double the use at low-utilizing hospitals; overall 32.3% of infants 0 to 28 days and 12.4% of infants 29 to 56 days received acyclovir. Gaensbauer et al,¹⁸ using hospital discharge data, found that acyclovir use increased 60.9% and 82.7% among infants <30 and 30 to 60 days, respectively, between the time periods 1999 to 2005 and 2006 to 2012, without a corresponding increase in the number of infants diagnosed with HSV. These data highlight an opportunity to decrease acyclovir use without causing associated harm.

www.hospitalpediatrics.org

DOI:10.1542/hpeds.2015-0166

Copyright © 2016 by the American Academy of Pediatrics

Address correspondence to Laura Brower, MD, Division of Hospital Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 9016, Cincinnati, OH 45229. E-mail: laura.brower@cchmc.org

HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Dr Brower drafted the revised manuscript; Drs Schondelmeyer, Wilson, and Shah reviewed and revised the manuscript; and all authors approved the final manuscript revision as submitted.

^aDivision of Hospital Medicine, and ^bDivision of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Beyond the reasonable goal of avoiding unwarranted medication use, the risks of even short courses of acyclovir must also be considered. Extravasation injury, related to acyclovir's alkaline pH, can cause edema, erythema, pruritus, pain, and skin breakdown,¹⁹⁻²¹ particularly in neonates,²² which can lead to disfiguring injuries. The nephrotoxic side effects of acyclovir, thought to be caused by deposition of acyclovir crystals in the kidney,^{23,24} can occur with brief exposure.²⁵ Nephrotoxic medication-related acute kidney injury, which increases the immediate cost of care through need for laboratory monitoring and administration of supplemental intravenous fluids, can also cause long-term harm for patients who have the injury early in life.²⁶

No consensus exists on which neonates should be tested for HSV infection and which should be empirically treated with acyclovir. Experts in the field have argued for varied approaches.^{2,27-29} The lack of agreement among experts likely contributes to the practice variation in diagnosis and management of neonatal HSV, which was reflected in a recent survey of emergency medicine and hospital medicine physicians at our institution. We found variability in factors that prompted testing for HSV (Fig 1) and type of testing performed when considering HSV (Fig 2). The decision to

start empiric acyclovir also varied, with 46% treating all who were tested for HSV and 54% treating only those with certain high-risk clinical or laboratory features. Realizing the extent of our local practice variation, we set out to standardize our practice.

One proposed strategy is to universally test and begin empiric acyclovir for all neonates younger than 21 days. Although this approach ensures that virtually all infants with perinatally acquired HSV would receive empiric acyclovir, many infants without HSV would unnecessarily be exposed to the risks of acyclovir. The approach of testing only those with high-risk features is also not satisfying, given the multiple forms of disease presentation, the possibility of nonspecific symptoms at initial presentation, and the consequences of substantial delays in therapy for those infected. Recognition of HSV in a neonate with a vesicular rash and ill appearance is simple, but identifying the neonate with early isolated central nervous system (CNS) disease is less clear-cut. In the case series of 32 patients with HSV by Long et al,²⁹ 3 patients presented only with fever and had no cerebrospinal fluid (CSF) pleocytosis, but were ultimately diagnosed with HSV CNS disease. The small size of existing case series makes it difficult to know how many infants ultimately

diagnosed with HSV present with nonspecific symptoms. Given the association between increased mortality and delay in initiation of acyclovir,³⁰ waiting for these neonates to worsen and declare themselves before appropriate testing causes unacceptable delay.

A novel option could balance the potential harms of acyclovir with significant delays in diagnosis. At our institution, we have developed hospital-wide consensus based on existing data and our desire to balance benefits and risks of HSV testing and empiric treatment. This reflects provider consensus on empirically treating only those with high-risk clinical and laboratory features. In the approach we are currently implementing at our hospital, all patients younger than 21 days being evaluated for serious bacterial infection will have CSF HSV polymerase chain reaction (PCR) testing performed, but only those with high-risk presenting features (eg, vesicles, ill appearance) or abnormal CSF parameters³¹ will undergo more extensive testing³² and receive empiric acyclovir therapy. The intended result will be that not every patient tested for HSV will begin empiric acyclovir (although all patients meeting high-risk criteria will receive acyclovir), but, with a rapid HSV PCR turnaround time (15 hours, on average), significant delays in acyclovir

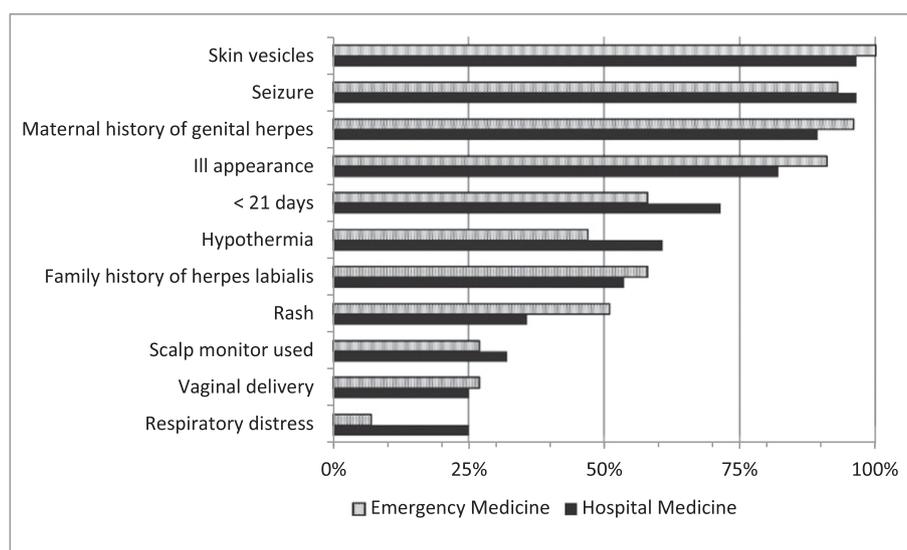


FIGURE 1 Survey results to identify factors that prompt testing for herpes simplex virus in infants undergoing evaluation for serious infection.

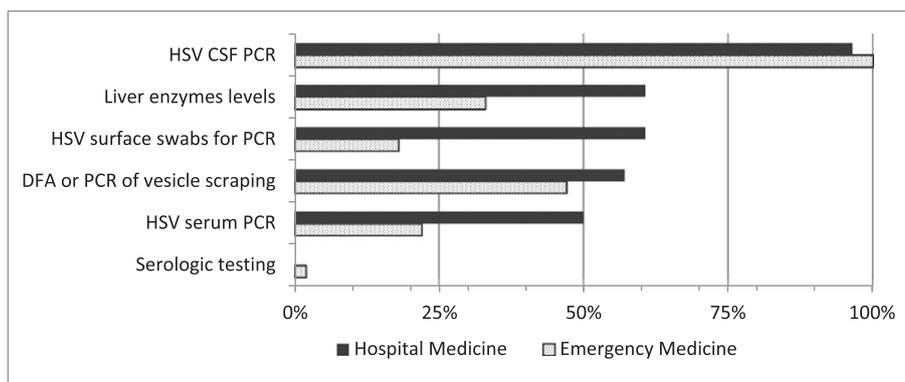


FIGURE 2 Survey results that identify typical laboratory evaluation for neonatal HSV. DFA, direct fluorescent antibody.

initiation will be avoided. By tracking all infants younger than 60 days, we intend to decrease overuse in lower-risk and older infants, while providing appropriate testing and therapy to those younger infants at higher risk. Our goal is to improve frontline collaboration with all parties invested in decision-making around management of neonatal HSV.

There are several trade-offs with our proposed approach, particularly for infants younger than 21 days without high-risk clinical or laboratory factors. In this age group, the inclusion of serum HSV PCR testing would ensure identification of infants with disseminated HSV who present with nonspecific symptoms and lack CNS involvement. However, given our aim to limit testing in those deemed to be lower risk, we targeted our testing to isolated CNS disease, as this disease is more often described to present with a paucity of symptoms. Furthermore, approximately two-thirds of infants with disseminated HSV will have CNS involvement,³³ minimizing the number of infants who would be “missed” by this approach. Another potential trade-off is the reliance on PCR testing rather than culture. The sensitivity of HSV PCR tests may vary, depending on primers used and the site of the test. Our laboratory has performed test validation and the results are available in a timely manner. Although surface cultures of skin could potentially increase the sensitivity of our approach in identifying infants with perinatally acquired HSV, trade-offs include increased costs,

including discharge delays of HSV-negative infants awaiting culture results.

Having reached consensus, our next aim is to standardize our local practice and disseminate lessons learned after outcome analysis. Recognizing that this is a rare disease and that single-center implementation is unlikely to demonstrate benefit for those infants with HSV, we will also examine outcomes in infants without the disease. Specifically, for infants at low clinical risk, especially those 30 to 60 days of age, we hope these will include decreased acyclovir use and HSV PCR testing. As others have noted, “‘Just to be safe’ is often used as a reason to test and treat our vulnerable children. Paradoxically, this maxim might be undermining the patient safety movement. The time has come to repurpose this powerful phrase as justification for safely doing less.”³⁴ Although neonatal HSV infection is rare, exposure to testing and treatment is all too common in patients at very low clinical risk; this is only 1 example of many scenarios that fall into the morass of practice variability. Widespread practice variation, especially in disease states of rare prevalence that preclude large-scale trials, has the potential to expose patients to over- or undertesting, and makes meaningful study of outcomes challenging. For this reason, standardizing practice in areas in which evidence is lacking is just as important as standardizing practice in which there is clinical certainty. We respectfully suggest a shift from simple reflection to a focus on purposeful actions

to make the system better, and then sharing that experience so we can learn from one another’s successes and failures.

REFERENCES

1. Flagg EW, Weinstock H. Incidence of neonatal herpes simplex virus infections in the United States, 2006. *Pediatrics*. 2011;127(1). Available at: www.pediatrics.org/cgi/content/full/127/1/e1
2. Caviness AC, Demmler GJ, Almendarez Y, Selwyn BJ. The prevalence of neonatal herpes simplex virus infection compared with serious bacterial illness in hospitalized neonates. *J Pediatr*. 2008; 153(2):164–169
3. Whitley R, Arvin A, Prober C, et al; The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. *N Engl J Med*. 1991;324(7):450–454
4. Kimberlin DW, Lin CY, Jacobs RF, et al; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics*. 2001;108(2):230–238
5. Kimberlin DW, Lin CY, Jacobs RF, et al; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics*. 2001; 108(2):223–229

6. Caviness AC, Demmler GJ, Selwyn BJ. Clinical and laboratory features of neonatal herpes simplex virus infection: a case-control study. *Pediatr Infect Dis J*. 2008;27(5):425–430
7. Batra D, Davies P, Manktelow BN, Smith C. The incidence and presentation of neonatal herpes in a single UK tertiary centre, 2006-2013. *Arch Dis Child*. 2014; 99(10):916–921
8. Fidler KJ, Pierce CM, Cubitt WD, Novelli V, Peters MJ. Could neonatal disseminated herpes simplex virus infections be treated earlier? *J Infect*. 2004;49(2): 141–146
9. Handel S, Klingler EJ, Washburn K, Blank S, Schillinger JA. Population-based surveillance for neonatal herpes in New York City, April 2006-September 2010. *Sex Transm Dis*. 2011;38(8):705–711
10. Kotzbauer D, Andresen D, Doelling N, Shore S. Clinical and laboratory characteristics of central nervous system herpes simplex virus infection in neonates and young infants. *Pediatr Infect Dis J*. 2014;33(11):1187–1189
11. Kotzbauer D, Frank G, Dong W, Shore S. Clinical and laboratory characteristics of disseminated herpes simplex virus infection in neonates. *Hosp Pediatr*. 2014; 4(3):167–171
12. Benidir A, Lim R, Salvadori M, Sangha G, Poonai N. Current practice patterns regarding diagnostic investigations and empiric use of acyclovir by Canadian pediatric emergency physicians in febrile neonates. *Pediatr Emerg Care*. 2013;29(3):273–278
13. Davis KL, Shah SS, Frank G, Eppes SC. Why are young infants tested for herpes simplex virus? *Pediatr Emerg Care*. 2008; 24(10):673–678
14. Cohen DM, Lorch SA, King RL, Hodinka RL, Cohn KA, Shah SS. Factors influencing the decision to test young infants for herpes simplex virus infection. *Pediatr Infect Dis J*. 2007; 26(12):1156–1158
15. McGuire JL, Zorc J, Licht D, Hodinka RL, Shah SS. Herpes simplex testing in neonates in the emergency department. *Pediatr Emerg Care*. 2012;28(10): 949–955
16. Shah SS, Volk J, Mohamad Z, Hodinka RL, Zorc JJ. Herpes simplex virus testing and hospital length of stay in neonates and young infants. *J Pediatr*. 2010;156(5): 738–743
17. Aronson PL, Thurm C, Alpern ER, et al; Febrile Young Infant Research Collaborative. Variation in care of the febrile young infant <90 days in US pediatric emergency departments. *Pediatrics*. 2014;134(4):667–677
18. Gaensbauer JT, Birkholz M, Pfannenstern K, Todd JK. Herpes PCR testing and empiric acyclovir use beyond the neonatal period. *Pediatrics*. 2014;134(3). Available at: www.pediatrics.org/cgi/content/full/134/3/e651
19. Le A, Patel S. Extravasation of noncytotoxic drugs: a review of the literature. *Ann Pharmacother*. 2014; 48(7):870–886
20. Laskin OL, Longstreth JA, Saral R, de Miranda P, Keeney R, Lietman PS. Pharmacokinetics and tolerance of acyclovir, a new anti-herpesvirus agent, in humans. *Antimicrob Agents Chemother*. 1982;21(3):393–398
21. De Souza BA, Shibu M. Painless acyclovir extravasation injury in a diabetic. *Br J Plast Surg*. 2002;55(3):264
22. Paquette V, McGloin R, Northway T, Dezorzi P, Singh A, Carr R. Describing Intravenous Extravasation in Children (DIVE Study). *Can J Hosp Pharm*. 2011; 64(5):340–345
23. Schreiber R, Wolpin J, Koren G. Determinants of aciclovir-induced nephrotoxicity in children. *Paediatr Drugs*. 2008;10(2):135–139
24. Jones CA, Walker KS, Badawi N. Antiviral agents for treatment of herpes simplex virus infection in neonates. *Cochrane Database Syst Rev*. 2009;(3):CD004206
25. Rao S, Abzug MJ, Carosone-Link P, et al. Intravenous acyclovir and renal dysfunction in children: a matched case control study. *J Pediatr*. 2015;166(6): 1462–1468.e1–e4
26. Askenazi DJ, Feig DI, Graham NM, Hui-Stickle S, Goldstein SL. 3-5 year longitudinal follow-up of pediatric patients after acute renal failure. *Kidney Int*. 2006;69(1):184–189
27. Kimberlin DW. When should you initiate acyclovir therapy in a neonate? *J Pediatr*. 2008;153(2):155–156
28. Long SS. In defense of empiric acyclovir therapy in certain neonates. *J Pediatr*. 2008;153(2):157–158
29. Long SS, Pool TE, Vodzak J, Daskalaki I, Gould JM. Herpes simplex virus infection in young infants during 2 decades of empiric acyclovir therapy. *Pediatr Infect Dis J*. 2011;30(7):556–561
30. Shah SS, Aronson PL, Mohamad Z, Lorch SA. Delayed acyclovir therapy and death among neonates with herpes simplex virus infection. *Pediatrics*. 2011;128(6): 1153–1160
31. Kestenbaum LA, Ebberson J, Zorc JJ, Hodinka RL, Shah SS. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. *Pediatrics*. 2010;125(2): 257–264
32. American Academy of Pediatrics. Herpes simplex. In: Pickering LKBC, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. American Academy of Pediatrics; 2012: 398–408
33. James SH, Kimberlin DW. Neonatal herpes simplex virus infection: epidemiology and treatment. *Clin Perinatol*. 2015;42(1):47–59, viii
34. Schroeder AR, Harris SJ, Newman TB. Safely doing less: a missing component of the patient safety dialogue. *Pediatrics*. 2011;128(6). Available at: www.pediatrics.org/cgi/content/full/128/6/e1596

Testing and Empiric Treatment for Neonatal Herpes Simplex Virus: Challenges and Opportunities for Improving the Value of Care

Laura Brower, Amanda Schondelmeyer, Paria Wilson and Samir S. Shah

Hospital Pediatrics 2016;6;108

DOI: 10.1542/hpeds.2015-0166 originally published online January 1, 2016;

Updated Information & Services	including high resolution figures, can be found at: http://hosppeds.aappublications.org/content/6/2/108
Supplementary Material	Supplementary material can be found at:
References	This article cites 29 articles, 8 of which you can access for free at: http://hosppeds.aappublications.org/content/6/2/108#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Fetus/Newborn Infant http://www.hosppeds.aappublications.org/cgi/collection/fetus:newborn_infant_sub Infectious Disease http://www.hosppeds.aappublications.org/cgi/collection/infectious_diseases_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.hosppeds.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.hosppeds.aappublications.org/site/misc/reprints.xhtml

Hospital Pediatrics®

AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Testing and Empiric Treatment for Neonatal Herpes Simplex Virus: Challenges and Opportunities for Improving the Value of Care

Laura Brower, Amanda Schondelmeyer, Paria Wilson and Samir S. Shah

Hospital Pediatrics 2016;6;108

DOI: 10.1542/hpeds.2015-0166 originally published online January 1, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hosppeds.aappublications.org/content/6/2/108>

Hospital Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Hospital Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

