

EDITOR'S NOTE: The following interrelated editorials by Kimberlin and Long place the findings of Caviness et al regarding herpes simplex infection in young infants into a clinical framework. The editorialists delineate their personal approach and recommendations for the empiric use of acyclovir therapy; they illustrate the variations in practice that result when there is a shortfall of evidence. These perspectives indicate the concept that there is room for guidance flavored by experience and personal weighting of risk: benefit ratios.

—William F. Balistreri, MD, Editor, *The Journal of Pediatrics*

When Should You Initiate Acyclovir Therapy in a Neonate?

In this issue of *The Journal*, Caviness et al present the results of a retrospective investigation of the prevalence of neonatal herpes simplex virus (HSV) infections among neonates admitted to Texas Children's Hospital in a 5-year period.¹ Texas Children's Hospital is a large tertiary care center with approximately 2000 neonatal admissions each year, or approximately 10 000 such admissions in the 5-year period encompassed in this report. In these 5 years, only 10 neonates with HSV disease were identified, or 2 per year on average. These raw numbers illustrate how rare neonatal HSV disease is and affirm the authors' attempt to define those babies at increased risk of neonatal herpes.

The prevalence of neonatal HSV infection in this study was 0.2% (95% CI, 0.1-0.3), which is numerically lower than the prevalence of bacterial meningitis (0.4%; 95% CI, 0.2-0.6), but is not statistically significantly different because the 95% CIs overlap. In neonates who had a cerebrospinal fluid (CSF) pleocytosis with a polymorphonuclear cell predominance, bacterial meningitis was significantly more likely than neonatal HSV disease (13.7%, 95% CI, 7.7-22.0 versus 0.0%, 95% CI, 0.0-3.6). In neonates with CSF pleocytosis and mononuclear cell predominance, however, HSV disease was not significantly more likely than bacterial meningitis (0.9% versus 0.3%, respectively, with overlapping 95% CIs). When only febrile neonates were included in these analyses, a polymorphonuclear CSF pleocytosis continued to be statistically associated with bacterial meningitis rather than neonatal HSV (14.9%, 95% CI, 7.4-25.7 versus 0.0%, 95% CI, 0.0-5.4), but a mononuclear pleocytosis was not more suggestive of neonatal HSV than bacterial meningitis (1.6%, 95% CI, 0.2-5.7 versus 0.8%, 95% CI, 0.0-4.4).

Of the 10 neonates with confirmed neonatal HSV disease, 5 had a normal temperature in the ED, 3 were febrile,

2 were hypothermic. Six neonates had skin rashes, all of which were vesicular. Alanine aspartase (AST) levels were markedly elevated in all 3 neonates with disseminated HSV disease. Thus, all subjects with neonatal HSV disease had either markedly elevated AST level with fever ($n = 1$), respiratory distress with hypothermia ($n = 2$), fever and lethargy ($n = 1$), or vesicular rash with or without fever ($n = 6$). Of the 2 neonates with fever and central nervous system (CNS) HSV disease, 1 was admitted during enteroviral season (along with 20 febrile neonates with CSF pleocytosis who had proven enteroviral disease), and 1 was admitted outside of enteroviral disease (along with 6 neonates with fever who had CSF pleocytosis and proven enteroviral disease); 1 of these 2 neonates with HSV CNS disease had a negative CSF polymerase chain reaction (PCR) result, whereas the other was positive for HSV DNA in the CSF.

In determining how the results of this study can be applied to clinical practice, several points must be made:

- 1) Neonatal herpes is a very rare disease, with only 10 cases documented from approximately 10 000 neonatal admissions in 5 years, almost 6000 of which were through the emergency department.
- 2) Abnormal CSF indices can make bacterial meningitis more likely when there is a polymorphonuclear predominance, but do not make neonatal HSV statistically more likely when there is a mononuclear predominance.

See related editorial,
p 157 and related article,
p 164

Reprint requests: David W. Kimberlin, MD, Professor of Pediatrics, Division of Pediatric Infectious Diseases, The University of Alabama at Birmingham, 1600 Seventh Ave South, CHB 303, Birmingham, AL 35233. E-mail: dkimberlin@peds.uab.edu.

J Pediatr 2008;153:155-6

0022-3476/\$ - see front matter

Copyright © 2008 Mosby Inc. All rights reserved.

10.1016/j.jpeds.2008.04.027

AST	Alanine aspartase
CNS	Central nervous system
CSF	Cerebrospinal fluid
PCR	Polymerase chain reaction

- 3) Enteroviral meningitis is 20-times more likely than HSV CNS disease in neonates admitted during enteroviral season with fever and a CSF pleocytosis.
- 4) AST (and presumably alanine aminotransferase) is elevated commonly in babies with disseminated neonatal HSV disease.
- 5) Outwardly visible signs (rash, lethargy, respiratory distress) or elevated hepatic transaminases were present in all 10 babies admitted with neonatal HSV in the 5 years at Texas Children's Hospital.

When HSV disease is suspected with a sufficiently high index of suspicion, swabs of the mouth, nasopharynx, conjunctivae, and rectum and specimens of skin vesicles, blood, and CSF should be obtained for culture ("surface cultures").² PCR assay is a sensitive method for detecting HSV DNA and is of particular value for evaluating CSF specimens from neonates with suspected HSV CNS disease,³⁻⁶ although the 1 infant in this study with neonatal CNS disease and negative CSF PCR results illustrates that this test is not infallible. Blood PCR may be of benefit in the diagnosis of neonatal HSV disease,⁵⁻¹¹ but its use should not supplant the standard work-up of such patients (eg, surface cultures and CSF PCR); no data exist to support use of serial blood PCR testing to monitor response to therapy. Radiographs and clinical manifestations can suggest HSV pneumonitis, and elevated hepatic transaminases in blood can suggest disseminated neonatal HSV disease.

Only half of all babies with neonatal herpes have CNS involvement, either categorized as CNS disease or as disseminated disease with CNS involvement.¹² Thus, negative CSF PCR results do not rule out neonatal HSV disease since by definition half of all babies with neonatal herpes would not even have a chance of being PCR-positive in CSF. When intravenous acyclovir is begun, it should be continued until the results of both the CSF PCR and the surface cultures are negative, and because herpes cultures can take 3 to 5 days to become positive, this essentially doubles the length of a typical rule-out sepsis hospitalization. Furthermore, significant neutropenia may develop in approximately 20% of babies receiving intravenous acyclovir at the recommended dose of 60 mg/kg/day administered in 3 divided daily doses.¹³ If the baby actually has a serious bacterial infection and not neonatal HSV disease (which was 23 times more likely in this study, with 4.6% of babies having a serious bacterial infection versus 0.2% having neonatal HSV), then the use of acyclovir could be harmful if the baby develops associated neutropenia.

Are there times when parenteral acyclovir should be added empirically to antibiotics when neonates are admitted for rule-out sepsis? Certainly. Evaluation for herpes and administering acyclovir is appropriate when there is a clear index of suspicion because of the presence of skin vesicles, seizures, marked elevation of hepatic transaminases, a sepsis-like picture (including hypothermia), or simply when the clinician's judgment the infant appears more ill than would be expected. A CSF pleocytosis with a mononuclear cell pre-

dominance outside of the enteroviral season also might be a time when evaluation and initiation of acyclovir are warranted. The treating physician must gather enough information (surface cultures, CSF HSV PCR) before the initiation of therapy, however, so that a rational decision can be made 4 to 5 days later to discontinue acyclovir therapy if the work-up is negative. Of course, when the infant is unstable at first evaluation, acyclovir and antibiotic therapy should be initiated, even when the work-up is not complete.

Neonatal HSV disease remains particularly challenging, even in this era of effective antiviral therapy. Some of the biggest questions relating to neonatal HSV disease currently focus on when we should use the safe and effective treatment that we have. This position is preferable to that in the 1970s, when there was no therapy for this terrible disease. Studies such as that of Caviness et al provide a valuable service by systematically reporting new data on which new judgments can be based. Although it is easy to conclude that more data are still needed, this group deserves our appreciation for their diligent contribution.

David W. Kimberlin, MD

Professor of Pediatrics
Division of Pediatric Infectious Diseases
The University of Alabama at Birmingham
Birmingham, Alabama

REFERENCES

1. Caviness AC, Demmler GJ, Almendarez Y, Selwyn BJ. The prevalence of neonatal herpes simplex viral infection compared with serious bacterial illness in hospitalized neonates. *J Pediatr* 2008;153:164-9.
2. American Academy of Pediatrics. Herpes simplex. In: Pickering LK, editor. 2006 Red book: report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006. p. 361-71.
3. Troendle-Atkins J, Demmler GJ, Buffone GJ. Rapid diagnosis of herpes simplex virus encephalitis by using the polymerase chain reaction. *J Pediatr* 1993;123:376-80.
4. Kimberlin DW, Lakeman FD, Arvin AM, Prober CG, Corey L, Powell DA, et al. Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. *J Infect Dis* 1996;174:1162-7.
5. Malm G, Forsgren M. Neonatal herpes simplex virus infections: HSV DNA in cerebrospinal fluid and serum. *Arch Dis Child Fetal Neonatal Ed* 1999;81:F24-9.
6. Kimura H, Futamura M, Kito H, Ando T, Goto M, Kuzushima K, et al. Detection of viral DNA in neonatal herpes simplex virus infections: frequent and prolonged presence in serum and cerebrospinal fluid. *J Infect Dis* 1991;164:289-93.
7. Barbi M, Binda S, Primache V, Tettamanti A, Negri C, Brambilla C. Use of Guthrie cards for the early diagnosis of neonatal herpes simplex virus disease. *Pediatr Infect Dis J* 1998;17:251-2.
8. Diamond C, Mohan K, Hobson A, Frenkel L, Corey L. Viremia in neonatal herpes simplex virus infections. *Pediatr Infect Dis J* 1999;18:487-9.
9. Kimura H, Ito Y, Futamura M, Ando Y, Yabuta Y, Hoshino Y, et al. Quantitation of viral load in neonatal herpes simplex virus infection and comparison between type 1 and type 2. *J Med Virol* 2002;67:349-53.
10. Lewensohn-Fuchs I, Osterwall P, Forsgren M, Malm G. Detection of herpes simplex virus DNA in dried blood spots making a retrospective diagnosis possible. *J Clin Virol* 2003;26:39-48.
11. Kimberlin D, Cloud G, Lakeman F, Jacobs R, Gutierrez K, Powell D, et al. Serum polymerase chain reaction (PCR) may not diagnose neonatal herpes simplex virus (HSV) disease. In: 42nd Annual Meeting of the Infectious Diseases Society of America. Boston, Massachusetts; Abstract 992; 2004.
12. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Frenkel LM, Gruber WC, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics* 2001;108:223-9.
13. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber WC, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 2001;108:230-8.