Diagnosis and Management of Neonatal Herpes Simplex Infection in the Emergency Department

Sriram Ramgopal, MD, Paria M. Wilson, MD, MEd,†‡ and Todd A. Florin, MD, MSCE**

Abstract: Neonatal herpes simplex virus infection (HSV) is rare in neonates, with an estimated global incidence of 10 per 100,000 live births. Neonatal HSV is challenging to diagnose due to often vague signs and symptoms. Untreated, the mortality of some HSV subtypes exceeds 80%. Overtesting and overtreatment can result in prolonged hospitalizations and expose neonates to medication toxicity. In contrast, prompt evaluation and use of empiric antiviral therapy before the results of definitive testing can improve outcomes for infants with HSV. A wide degree of practice variation exists with respect to testing and treatment for neonatal HSV, and more research is required to safely risk-stratify this population. This review presents the epidemiology, risk factors, presenting features, and emergency department management of neonatal HSV infection.

Key Words: herpes, HSV, neonates, febrile infant

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TARGET AUDIENCE

This CME activity is intended for health care providers in emergency department, urgent care, and hospital settings that administer medical care to young infants.

LEARNING OBJECTIVES

After completion of this CME activity, the reader should be better able to:

1. Evaluate a child with suspected neonatal HSV.
2. Determine diagnostic testing required for an infant with suspected neonatal HSV.
3. Assess risks and benefits of empiric treatment for neonatal HSV.

For the emergency department (ED) provider, neonatal herpes simplex virus (HSV) infection is challenging to identify on the basis of history, clinical and laboratory evaluation. Neonatal HSV results in significant mortality, as high as 85% in patients without therapy.[1] Prompt evaluation and use of empiric antiviral therapy before the results of definitive testing can substantially improve outcomes.[1,2] In this review, we will discuss key aspects of the emergent recognition and treatment of infants with suspected neonatal HSV in the ED.

VIROLOGY

HSV-1 and HSV-2, which typically cause oral and genital lesions in older children and adults, can both cause neonatal HSV infection.[3,4] Some recent changes in epidemiology suggest that HSV-1 may cause a greater proportion of genital disease in the United States.[5] Herpes simplex virus is a DNA virus that is lytic in epidermal cells and latent in neuronal cells, allowing for persistence of infection for the duration of the host lifetime and periodic reactivation.[6]

EPIDEMIOLOGY

Estimates of HSV incidence vary widely by study and geographic region (Table 1). The global incidence of neonatal HSV from the years 2010–2015 is approximately 10 cases per 100,000 live births.[16] However, these findings are extrapolated from the literature, the majority of which is derived from Western nations. A national surveillance program for neonatal HSV does not exist with the United States. In one analysis using the Healthcare Cost and Utilization Project Kids' Inpatient Database in 2006, the estimated incidence of neonatal HSV in the United States was 9.6 per 100,000 births. This rate was higher in the Midwest (12.9 per 100,000) and in black patients (13.8 per 100,000).[14] Among infants evaluated for bacterial meningitis, the incidence of neonatal HSV is approximately 0.4%.[4,19]

TRANSMISSION AND HISTORICAL FACTORS

Neonatal HSV is most commonly acquired via vertical transmission, particularly during late pregnancy. The Centers for Disease Control (CDC) estimated the prevalence of HSV-1 and HSV-2 in the general population as 38% and 12%, respectively for the years 2015 and 2016.[20] A high viral load is associated with transmission. As such, a maternal history of HSV infection, maternal history of having sexual partners with genital herpes, and the occurrence of symptomatic first episodes of genital herpes during pregnancy or delivery are associated with neonatal disease.[21] Approximately one third of women are seronegative for HSV in the United States. Herpes simplex virus seropositivity occurs less frequently in women with fewer lifetime sexual partners.[22] However, because the risk of maternal-fetal transmission is higher in those with first episodes of infection at the time of labor, such previously seronegative women have a higher risk of transmission in the event of HSV acquisition during pregnancy. Among women with recurrent genital herpes, a higher likelihood of symptom recurrence occurs during pregnancy.[23] In 1 large prospective study by Brown et al, 2% of 7,046 pregnant women with serial HSV serologies performed during pregnancy demonstrated HSV seroconversion.[24] Of these, only one third had symptoms consistent with herpes infection. Nine women acquired genital HSV infection without seroconversion near labor onset and had vaginal delivery: of these, 4 infants had neonatal HSV.

*Assistant Professor for Pediatrics, Division of Emergency Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States of America, †Assistant Professor for Pediatrics, Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati, Ohio, United States of America, and ‡Assistant Professor for Pediatrics, Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America.

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Reprints: Sriram Ramgopal, MD, Division of Pediatric Emergency Medicine Department of Pediatrics Ann and Robert H. Lurie Children's Hospital of Chicago 225 E Chicago Ave Box 62 Chicago, IL 60611 (e-mail: sramgopal@luriechildrens.org).

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TABLE 1. Studies Evaluating the Incidence of Neonatal HSV

Author, Year	Region and Time Period	Data Source	Incidence (Per Live Births)
Tookey and Peckham, 1996[7]	British Isles, 1986–1991	Surveillance data	1.65/100,000
Gutierrez et al, 1999[8]	California, 1985–1995	Retrospective, government-based discharge data	11.3–11.7/100,000
Kropp et al, 2006[9]	Canada, 2000–2003	Prospective, active solicitations from pediatricians	5.9 births per 100,000
Whitley et al, 2007[10]	US managed-care population; 1997–2002	Administrative	0.08% of discharged neonates
Mahnert et al, 2007[11]	Single center study; 1999–2003	Hospital	5/100,000
Xu et al, 2007[12]	US managed-care population; 1997–2002	Administrative	12.9/100,000
Morris et al, 2008[13]	California, 1995–2003	Retrospective, government-based discharge data	12.1/100,000
Flagg and Weinstock, 2011[14]	United States, 2006	Retrospective, KIDS Inpatient Database	9.6/100,000 Higher incidence in Midwest (12.9/100,000) and in black patients (13.8/100,000) and Medicaid enrollees (15.1/100,000)
Jones et al, 2014[15]	Australia, 1997–2011	Surveillance data	3.27/100,000
Looker et al, 2017[16]	Global; 2010–2015	Extrapolation from published data and birth rates	Suspected incidence: 10/100,000
Mahant et al, 2018[17]	Multistate (10–12 states); 2009–2015	Medicaid claims data	4.5/100,000, rising annually
Lao et al, 2019[18]	New York City; 2006–2015	Surveillance and administrative	9.9/100,000 (surveillance); 12.1/100,000 (administrative)

The association of neonatal HSV and invasive monitoring or trauma to the scalp as might occur in instrumental deliveries, has also been reported in multiple case reports and observational studies.[25–29] In 1 prospective evaluation, the odds of HSV transmission was 6.8 (95% confidence interval, 1.4–32.0) if a scalp monitor was used.[25] Beyond these, additional risk factors associated with vertical transmission include fever during pregnancy, HSV isolation from the cervix, delivery before 38 weeks, and younger maternal age.[25]

In women with clinical or subclinical genital herpes infection, delivery by cesarean section may be an important modifiable approach to prevent vertical transmission. In 1 prospective study of 202 women with HSV isolated during labor, 10 had neonates with HSV infection, which included 1 of 85 infants delivered by cesarean section and 9 of 117 delivered vaginally. These results strongly suggest that HSV transmission could be reduced, though not eliminated, by cesarean section delivery.[25] Other prospective trials have demonstrated a role for antivirals in the prevention of vertical transmission, though the risk of vertical transmission is not eliminated entirely.[30–34] Though it crosses the placenta, acyclovir has not been shown to have an association with birth defects in children of exposed mothers.[35]

The ability of history and physical examination to identify neonates with neonatal HSV is limited. Case reports[36] and studies from the CDC note that most (69%) mothers of infected neonates did not have a known history of genital herpes and reported being asymptomatic at the time of delivery.[37] The advent of DNA-based diagnostic assays for herpes (in comparison to culture-based methods) similarly identified that larger proportions of asymptomatic women were carriers of HSV DNA despite culture negativity.[38] Recent acquisition of genital herpes in asymptomatic women has a higher rate of transmission compared with those with asymptomatic reactivation of HSV.[27]

A minority of cases are transmitted through other means. In-utero transmission may occur with primary or reactivation of herpes infections. This typically results in congenital malformations involving the skin, eye, and central nervous system (CNS). Nearly all such affected infants (>90%) demonstrate skin lesions.[39] Postpartum transmission may occur via contact with caregivers with recently acquired infection, such as cold sores.[40–42]

CLINICAL ASSESSMENT

The diagnosis of neonatal HSV relies on nonspecific signs and symptoms. Neonatal meningitis is more common in infants younger than 21 days, particularly during weeks 2 to 3 of life, though cases can occur in the second month of life.[3,4,19] Guidelines from the American Academy of Pediatrics (AAP) divide clinical manifestations of neonatal HSV into 3 types[1]: disseminated disease, in which multiple organs are involved including the lungs or liver (25% of cases), and frequently the CNS[2]; Localized CNS disease, in which the viral infection is predominantly manifested with neurologic findings, though skin, eyes, or mouth involvement may occur in 30% of cases[3]; localized skin, eye, and mouth disease (SEM, 45% of cases), in which there is no visceral or CNS involvement.[43] These classifications generally correspond to disease severity. Mortality is highest among those with disseminated disease.[1,44] In general, infants with a history of prematurity have more severe disease with higher mortality, with a greater proportion having disseminated disease.[45,46]

The hallmark of HSV infection is the presence of skin vesicles on a shallow, erythematous base that typically appear in isolation or in clusters. The majority of patients with SEM disease present within the first 10 to 12 days of life, this may be as soon as the first 24 hours in those with in utero exposure.[47] Skin vesicles may be noted at sites of previous scalp electrodes,[28] with a potential correlation noted with higher vesicle quantity and presence of neurologic disease.[44]

The diagnosis of neonatal HSV in patients without skin vesicles is a greater challenge. Approximately 30% to 40% of patients

with CNS or disseminated disease do not have vesicles. In the ED, HSV is typically considered in young infants presenting with fever or hypothermia.[4,19,48–51] However, a substantial proportion of patients with neonatal HSV are afebrile and do not have hypothermia.[47,48] In 1 multicenter evaluation of 112 cases of neonatal CNS HSV by Cruz et al,[4] 5.2% were hypothermic at presentation, 30.9% were febrile, and the remainder (63.9%) were euthermic. These numbers were not statistically different when compared with 25,421 HSV-uninfected control patients. As such, the absence of temperature instability is an unreliable sign to assess for the risk of disease.

Several studies have attempted to identify other features which may be used to better identify patients with neonatal HSV with the goal of focused testing and empiric antiviral therapy (Table 2). Skin vesicles, temperature instability, and events concerning for seizures should certainly raise concern for HSV infection. However, for a large proportion of patients with disease, symptoms can be more nonspecific and include respiratory disease, conjunctivitis, or behavioral or feeding changes. In 1 series of 32 patients reported by Long et al,[3] 50% (16/32) came to attention with nonspecific complaints, such as fever, hypothermia, poor feeding, changes in activity level, or apnea in the absence of neurologic, mucous membrane, or cutaneous findings. Of these, 94% had CNS disease. Thus, a high index of suspicion is required in the assessment of potential cases of HSV infection.

DIAGNOSIS

A number of diagnostic tests can raise suspicion for HSV infections, though no single test is diagnostic. Previous case series have identified abnormalities of platelet counts, white blood cell counts, and liver enzymes in association with neonatal HSV (Table 2). However, among studies typically performed in EDs with rapid turnaround time, no single test demonstrates adequate sensitivity or specificity for HSV infection. Of note, clinical prediction models which attempt to risk stratify febrile infants into high- and low-risk groups for serious or invasive bacterial infections are not specifically designed to identify HSV and should not be used for this purpose.[53–57]

The value of cell counts from CSF evaluation is frequently raised in clinical practice. Several studies have attempted to identify the role of CSF cytology in the diagnosis of neonatal HSV. In a study comparing 10 patients with neonatal HSV meningitis to other neonates diagnosed with bacterial meningitis, a higher rate HSV was noted among febrile infants with CSF pleocytosis and mononuclear predominance, though the results of this study must be interpreted in the context of the relatively small number of cases.[19] In the series reported by Long, CSF leukocytes were predominantly mononuclear in 26 of 27 cases where CSF results were interpretable. Interestingly, of 15 patients with CNS HSV disease, 4 (27%) of 15 did not have any CSF pleocytosis (<9 cells/mm^3).[3] Similar rates of normal CSF evaluations have been obtained in older patients with herpes encephalitis.[58,59] As such, although CSF pleocytosis, and in particular monocytosis, may raise suspicion for disease, the absence of CSF leukocytosis does not rule out the presence of CNS HSV infection.

Definitive diagnosis of HSV relies on culture or DNA amplification assays, which are generally not available on a point-of-care basis from the ED. Polymerase chain reaction (PCR) assays are preferable, as they demonstrate higher sensitivity to cultures.[60] Newer real-time PCR modalities may allow for significant reductions in test

TABLE 2. Summary of Clinical and Laboratory Features Associated With HSV

Author, Year	Source, (n)	Clinical Features	Laboratory Findings
Whitley, 1980[52]	Case series among infants enrolled in vidarabine trial N = 56	Skin vesicles (71%) CNS symptoms (9%) Organ dysfunction (9%)	
Kimberlin et al, 2001[47]	Infants enrolled in 2 acyclovir trials N = 186	Skin vesicles (68%) Lethargy (38%) Fever (39%) Conjunctivitis (19%) Seizure (50%) Pneumonia (13%)	DIC (11%)
Caviness et al, 2008[48]	Single-center retrospective study (case-control) N = 40 cases	Respiratory distress (73%) Hypothermia (27%) Jaundice (23%) Seizure (36%)	Thrombocytopenia (53%) Elevated liver enzymes (AST 73%, ALT 47%)
Caviness et al, 2008[19]	Single-center retrospective study (case-control) N = 10 cases	Fever (30%) Hypothermia (with sepsis-like syndrome) (20%)	CSF with mononuclear pleocytosis (10%)
Long et al, 2011[3]	Single-center retrospective (case series) N = 32	Skin lesions (28%) Corneal clouding (3%) Fever (53%) Seizures (19%) Nonspecific (50%) Hypothermia (13%) Anterior fontanelle fullness (3%) Poor feeding (29%) Irritability (10%)	Bands (16%) Neutrophil predominance (9%) Leukocytosis or leukopenia (<10%) Thrombocytopenia (6%) Thrombocytosis (34%) Elevated ALT (20%)
Cruz et al, 2018[4]	Multi-center retrospective (case-control) N = 112 cases	Hypothermia (5%) Fever (31%)	

DIC, disseminated intravascular coagulation; AST, aspartate aminotransferase; ALT, alanine transaminase; CSF, cerebrospinal fluid.

performance times.[61] In patients for whom HSV is suspected, guidelines from the AAP recommend performance of the following[1]: swab specimens from the mouth, nasopharynx, conjunctivae, and anus ("surface specimens") for culture or PCR[2]; skin vesicles specimens for culture or PCR[3]; CSF sample for HSV PCR[4]; whole blood sample for HSV PCR; and[5] whole blood sample measurement of alanine transaminase.[43] The Tzank smear is no longer recommended. Unfortunately, among those infants who do undergo testing in the ED, the majority only have testing performed on CSF, leading to incomplete testing according to the above guidelines.[4] In a study of 21 patients, CNS-only testing missed 6 (29%) patients with disseminated disease for whom serum PCR was the only positive HSV test.[62] Techniques for rapid diagnosis, such as direct fluorescent antibody stains from vesicles or enzyme immune assay for HSV antigen are specific but are not sensitive when compared with culture.[43]

TREATMENT AND PROGNOSIS

The nucleoside agents acyclovir and vidarabine are used in management of neonatal HSV,[63] and function by inhibiting HSV DNA polymerase and viral DNA synthesis. In the first randomized controlled trial evaluating the efficacy of vidarabine versus placebo among 56 infants with HSV infection, vidarabine therapy resulted in a significantly lower mortality rate (85% vs 57%) in those with CNS or disseminated disease ($P = 0.014$).[1] Long-term follow-up of infants treated with vidarabine demonstrated that one third of treated infants had normal neurologic development after a 2-year follow-up period.[64] There is conflicting evidence on the superiority of vidarabine to acyclovir in reducing mortality and morbidity among neonates with HSV.[65,66]

In practice, acyclovir is preferred to vidarabine for neonatal HSV. Although adverse events associated with acyclovir are common, they are generally not severe. In a study of 89 infants younger than 120 days with HSV receiving acyclovir, clinical adverse events, including hypotension, seizures, and renal failure, occurred in 15% of patients.[67] Laboratory adverse events, including sodium or potassium abnormalities, elevated creatinine or blood urea nitrogen, or derangements of the complete blood count including neutropenia, leukopenia, and thrombocytopenia, occurred in 42% of patients. Only 9% had major laboratory adverse events, including severe electrolyte disturbances or evidence of renal injury.

Only parenteral dosing of acyclovir is recommended for infected neonates. Trials using high-dose acyclovir (60 mg/kg per day, typically divided into doses every 8 hours) support a reduced mortality rate and borderline improvement in morbidity in those receiving higher-dose compared with lower-dose regimens.[68] The rate of acyclovir clearance increases with neonatal maturation. A population-based pharmacokinetic analysis suggests the following regimen for empiric acyclovir dosing in suspected cases: 20 mg/kg per dose every 12 hours in infants with a postmenstrual age of 30 weeks or less, 20 mg/kg per dose every 8 hours in infants with a postmenstrual age of 30 to 35 weeks, and 20 mg/kg per dose every 6 hours in infants with a postmenstrual age 36 to 41 weeks.[69] Currently, only the 20 mg/kg dosing every 8 hours is recommended by the AAP.[43] A 14-day regimen is used for infants with SEM disease, and a 21-day treatment is used for infants with CNS and disseminated disease, with a transition to long-term oral therapy after completion of intravenous therapy.

CLINICAL PATHWAYS FOR NEONATAL HSV

Currently, substantial variation exists in rates of HSV testing among at-risk neonates evaluated in the ED, partially related to the difficulty with recognition of this rare disease. In a multicenter study of infants 60 days or younger, who were evaluated for bacterial meningitis, rates of CNS HSV testing ranged from 14% to 72%.[4] A number of investigators have identified characteristics of infants tested for HSV infection (Table 3). Although some of these reasons are evidence-based, others, such as testing concurrently for enterovirus, do not represent best practices.[72]

The ED provider must manage the delicate balance of accurately identifying all potential cases of neonatal HSV while simultaneously avoiding overtesting and overtreating the vast majority of patients who do not have disease. Overtesting and treating

TABLE 3. Factors Associated With Testing for HSV

Author, Year	Study (n)	Factors Associated With Testing (Adjusted Odds Ratio, 95% Confidence Interval; or Percent)	Factors Not Associated With Testing
Davis et al, 2008[70]	Case control (171)	Seizure (8.3, 1.7–41.0) CSF Enteroviral PCR sent (4.7, 1.4–15.8) AST/ALT sent (5.6, 2.7–11.8)	Elevated CSF WBC/RBC
McGuire et al, 2012[51]	Nested case control (570)	Interfacility transport (7.27, 5.30–9.98) Enterovirus testing sent (7.27, 5.30–9.98) Hypothermia (1.46, 1.17–1.83) Seizures (13.75, 5.60–33.76) Tachypnea (3.67, 2.32–5.80) Hypotension (6.89, 5.68–8.37) Vesicular rash (18.70, 1.28–273.68)	CSF mononuclear pleocytosis Method of delivery
Benidir et al, 2013[71]	Survey (158)	Positive maternal history (>50%)	Wellness of child (34%) Skin changes (37%) Worrisome neurologic symptoms (37%)
Swartz et al, 2019[72]	Case control (536)	Age ≤28 days (5.31, 2.91–9.68) Seizure (29.56, 4.46–195.92) History of maternal vaginal lesions (15.60, 5.14–47.35) Postnatal HSV contact (15.32, 4.45–52.72) Vesicular lesions (8.03, 1.88–34.33) Febrile 1.75 (1.03–2.99) CSF pleocytosis (3.10, 1.78–5.39) Enteroviral PCR sent (6.54, 3.80–11.25)	Season Poor tone Focal source of infection Bulging fontanelle Thrombocytosis Elevated CSF protein

WBC, white blood cell; RBC, red blood cell; CSF, cerebrospinal fluid; ALT, alanine transaminase; AST aspartate transaminase.

carries the burden of excessive resource utilization, exposure of infants to medication adverse effects and unnecessary procedures, and undue parental anxiety. In multicenter studies, infants undergoing HSV evaluation had longer hospital lengths of stay.[73,74] In contrast, undertesting can be associated with substantially worsened morbidity and mortality. In a multicenter study utilizing administrative data among 41 hospitals included in the Pediatric Health Information System, delayed administration of acyclovir longer than 1 day after hospitalization among neonates with HSV was associated with an increased odds of death after adjustment for age (adjusted odds ratio, 2.63; 95% confidence interval, 1.36–5.08).[2]

There is wide interest in tools to better risk-stratify patients into low and high-risk groups for neonatal HSV. The rarity of HSV disease compounds challenges toward the development of risk-stratification models. Long et al described a model in which all neonates younger than 21 days were tested and empirically treated for HSV, a method which would have a high sensitivity but low specificity.[3] In another model developed by Byington et al,[75] empiric testing and treatment was recommended for infants younger than 42 days with findings of a vesicular rash, seizures, clinical sepsis, or abnormal CSF findings. A recent algorithm developed at Cincinnati Children's Hospital Medical Center for infants 0 to 28 days of age incorporates historical and physical examination findings with CSF parameters to stratify infants into high- and low-risk groups.[76] High-risk infants undergo HSV testing based on the AAP guidelines and empiric acyclovir therapy. Lower-risk infants younger than 21 days may require only CSF PCR evaluation without empiric treatment, whereas those 22 to 28 days may require no evaluation at all. Such evidence-based guidelines may help to reduce variations in care, limit adverse effects of empiric antiviral therapy, and optimize resource utilization. None of these models have been externally validated, and the applicability of these pathways to other institutions will likely depend on laboratory turnaround times and local incidence of neonatal HSV infections. However, as rapid PCR testing becomes more widely available, broader use of this diagnostic assay may allow for shortened treatment courses of empiric acyclovir and reduced hospitalizations.[77]

CONCLUSIONS

As a rare condition with nonspecific signs and symptoms but with significant morbidity and mortality, neonatal HSV is a challenging condition to diagnose and treat requiring a high index of suspicion. Prompt initiation of therapy can improve both survival and morbidity. Currently, though care can be optimized to reduce variation and unnecessary testing and treatment, any strategy in the ED to correctly identify all patients at-risk of this condition will necessarily have poor specificity. Future research is required to better identify patients at risk of disease to better optimize care for this subset of patients while minimizing empiric hospitalization or antiviral medication for others without disease.

REFERENCES

1. Whitley RJ, Nahmias AJ, Soong SJ, et al. Vidarabine therapy of neonatal herpes simplex virus infection. *Pediatrics*. 1980;66:495–501.
2. Shah SS, Aronson PL, Mohamad Z, et al. Delayed acyclovir therapy and death among neonates with herpes simplex virus infection. *Pediatrics*. 2011;128:1153–1160.
3. Long SS, Pool TE, Vodzak J, et al. Herpes simplex virus infection in young infants during 2 decades of empiric acyclovir therapy. *Pediatr Infect Dis J*. 2011;30:556–561.
4. Cruz AT, Freedman SB, Kulik DM, et al. Herpes simplex virus infection in infants undergoing meningitis evaluation. *Pediatrics*. 2018;141.
5. Bernstein DI, Bellamy AR, Hook EW, et al. Epidemiology, clinical presentation, and antibody response to primary infection with herpes simplex virus type 1 and type 2 in young women. *Clin Infect Dis*. 2013;56:344–351.
6. Ryan KJ, Ahmad N, Weissman S, et al. *Sherris Medical Microbiology, Seventh Edition*. McGraw-Hill Education; 2018.
7. Tookey P, Peckham CS. Neonatal herpes simplex virus infection in the British Isles. *Paediatr Perinat Epidemiol*. 1996;10:432–442.
8. 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.
9. Kropp RY, Wong T, Cormier L, et al. Neonatal herpes simplex virus infections in Canada: results of a 3-year national prospective study. *Pediatrics*. 2006;117:1955–1962.
10. 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.
11. Mahnert N, Roberts SW, Laibl VR, et al. The incidence of neonatal herpes infection. *Am J Obstet Gynecol*. 2007;196.
12. Xu F, Gee JM, Naleway A, et al. Incidence of neonatal herpes simplex virus infections in two managed care organizations: implications for surveillance. *Sex Transm Dis*. 2008;35:592–598.
13. Morris SR, Bauer HM, Samuel MC, et al. Neonatal herpes morbidity and mortality in California, 1995–2003. *Sex Transm Dis*. 2008;35:14–18.
14. Flagg EW, Weinstock H. Incidence of neonatal herpes simplex virus infections in the United States, 2006. *Pediatrics*. 2011;127.
15. Jones CA, Raynes-Greenow C, Isaacs D. Population-based surveillance of neonatal herpes simplex virus infection in Australia, 1997–2011. *Clin Infect Dis*. 2014;59:525–531.
16. Looker KJ, Magaret AS, May MT, et al. First estimates of the global and regional incidence of neonatal herpes infection. *Lancet Glob Heal*. 2017;5:e300–e309.
17. Mahant S, Hall M, Schondelmeyer AC, et al. Neonatal herpes simplex virus infection among Medicaid-enrolled children: 2009–2015. *Pediatrics*. 2019;143.
18. Lao S, Flagg EW, Schillinger JA. Incidence and characteristics of neonatal herpes: comparison of two population-based data sources, New York City, 2006–2015. *Sex Transm Dis*. 2019;46:125–131.
19. Caviness AC, Demmler GJ, Almendarez Y, et al. The prevalence of neonatal herpes simplex virus infection compared with serious bacterial illness in hospitalized neonates. *J Pediatr*. 2008;153:164–169.
20. McQuillan G, Kruszon-Moran D, Flagg EW, et al. Prevalence of herpes simplex virus type 1 and type 2 in persons aged 14-49: United States, 2015–2016. *NCHS Data Brief*. 2018;1–8.
21. Sullivan-Bolyai J, Hull HF, Wilson C, et al. Neonatal herpes simplex virus infection in King County, Washington. Increasing incidence and epidemiologic correlates. *JAMA*. 1983;250:3059–3062.
22. Patton ME, Bernstein K, Liu G, et al. Seroprevalence of herpes simplex virus types 1 and 2 among pregnant women and sexually active, nonpregnant women in the United States. *Clin Infect Dis*. 2018;67:1535–1542.
23. Vontver LA, Hickok DE, Brown Z, et al. Recurrent genital herpes simplex virus infection in pregnancy: infant outcome and frequency of asymptomatic recurrences. *Am J Obstet Gynecol*. 1982;143:75–84.
24. Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med*. 1997;337:509–515.
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.

26. Amann ST, Fagnant RJ, Chartrand SA, et al. Herpes simplex infection associated with short-term use of a fetal scalp electrode. A case report. *J Reprod Med*. 1992;37:372–374.
27. Brown ZA, Benedetti J, Ashley R, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. *N Engl J Med*. 1991;324:1247–1252.
28. Goldkrand JW. Intrapartum inoculation of herpes simplex virus by fetal scalp electrode. *Obstet Gynecol*. 1982;59:263–265.
29. Kohelet D, Katz N, Sadan O, et al. Herpes simplex virus infection after vacuum-assisted vaginally delivered infants of asymptomatic mothers. *J Perinatol*. 2004;24:147–149.
30. Kabra NS, Thabane L. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. *Obstet Gynecol*. 2004; 103:1004–1005.
31. Pinninti SG, Angara R, Feja KN, et al. Neonatal herpes disease following maternal antenatal antiviral suppressive therapy: a multicenter case series. *J Pediatr*. 2012;161.
32. Scott LL, Hollier LM, McIntire D, et al. Acyclovir suppression to prevent recurrent genital herpes at delivery. *Infect Dis Obstet Gynecol*. 2002;10: 71–77.
33. Watts DH, Brown ZA, Money D, et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. *Am J Obstet Gynecol*. 2003;188:836–843.
34. Sheffield JS, Hill JB, Hollier LM, et al. Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. *Obstet Gynecol*. 2006;108:141–147.
35. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the international acyclovir pregnancy registry, 1984–1999. *Birth Defects Res A Clin Mol Teratol*. 2004;70:201–207.
36. Yeager AS, Arvin AM. Reasons for the absence of a history of recurrent genital infections in mothers of neonates infected with herpes simplex virus. *Pediatrics*. 1984;73:188–193.
37. Stone KM, Brooks CA, Guinan ME, et al. National surveillance for neonatal herpes simplex virus infections. *Sex Transm Dis*. 16:152–156.
38. Cone RW, Hobson AC, Brown Z, et al. Frequent detection of genital herpes simplex virus DNA by polymerase chain reaction among pregnant women. *JAMA*. 1994;272:792–796.
39. Hutto C, Arvin A, Jacobs R, et al. Intrauterine herpes simplex virus infections. *J Pediatr*. 1987;110:97–101.
40. Marquez L, Levy ML, Munoz FM, et al. A report of three cases and review of intrauterine herpes simplex virus infection. *Pediatr Infect Dis J*. 2011;30:153–157.
41. Pichler M, Staffler A, Bonometti N, et al. Premature newborns with fatal intrauterine herpes simplex virus-1 infection: first report of twins and review of the literature. *J Eur Acad Dermatol Venereol*. 2015;29: 1216–1220.
42. Isenring E, Fehr J, Gültekin N, et al. Infectious disease profiles of Syrian and Eritrean migrants presenting in Europe: a systematic review. *Travel Med Infect Dis*. 2018;25:65–76.
43. Kimberlin DW, Brady MT, Long SS, Jackson MA. Red Book 2018: Report of the Committee on Infectious Diseases. In: Red Book Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2018.
44. Whitley R, Alford C, Caddell G, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. *N Engl J Med*. 1991;324:450–454.
45. Kylat RI, Addams J, Sobonya RE. Fatal disseminated herpes simplex in a very premature neonate. *Autops Case Rep*. 2018;8:e2018050.
46. O'Riordan DP, Golden WC, Aucott SW. Herpes simplex virus infections in preterm infants. *Pediatrics*. 2006;118:e1612–e1620.
47. 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.
48. 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;27:425–430.
49. Kasmire KE, Vega C, Bennett NJ, et al. Hypothermia: a sign of sepsis in young infants in the emergency department? *Pediatr Emerg Care*. 2018.
50. Wood JK, Halvorson EE, Auriemma JR, et al. Clinical characteristics and health outcomes of neonates reporting to the emergency department with hypothermia. *Hosp Pediatr*. 2018;8:458–464.
51. McGuire JL, Zorc J, Licht D, et al. Herpes simplex testing in neonates in the emergency department. *Pediatr Emerg Care*. 2012;28:949–955.
52. Whitley RJ, Nahmias AJ, Visintine AM, et al. The natural history of herpes simplex virus infection of mother and newborn. *Pediatrics*. 1980;66:489–494.
53. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993;329: 1437–1441.
54. Jaskiewicz JA, McCarthy CA, Richardson AC, et al. Febrile infants at low risk for serious bacterial infection—an appraisal of the Rochester criteria and implications for management. Febrile infant collaborative study group. *Pediatrics*. 1994;94:390–396.
55. Kuppermann N, Dayan PS, Levine DA, et al. A clinical prediction rule for stratifying febrile infants 60 days and younger at risk for serious bacterial infections. *JAMA Pediatr*. 2019;173:342–351.
56. Gomez B, Mintegi S, Bressan S, et al. Validation of the "step-by-step" approach in the management of young febrile infants. *Pediatrics*. 2016; 138:e20154381.
57. Aronson PL, Shabanova V, Shapiro ED, et al. A prediction model to identify febrile infants ≤60 days at low risk of invasive bacterial infection. *Pediatrics*. 2019;144.
58. Saraya AW, Wacharapluesadee S, Petcharat S, et al. Normocellular CSF in herpes simplex encephalitis. *BMC Res Notes*. 2016;9.
59. Muttalib F, Papenburg J. Absence of pleocytosis alone is insufficient to exclude encephalitis caused by herpes simplex virus in children. *J Clin Microbiol*. 2014;52:1022–1022.
60. Strick LB, Wald A. Diagnostics for herpes simplex virus: is PCR the new gold standard? *Mol Diagn Ther*. 2006;10:17–28.
61. Navidad J, Pfotenhauer B, Leigh N, et al. Clinical evaluation and cost analysis of a trioplex real-time PCR assay for the detection and differentiation of herpes simplex virus 1 and 2 in cutaneous and mucocutaneous lesions. *J Med Microbiol*. 2019;68:748–754.
62. Cantey JB, Mejías A, Wallihan R, et al. Use of blood polymerase chain reaction testing for diagnosis of herpes simplex virus infection. *J Pediatr*. 2012;161:357–361.
63. Rangel M, Falkenberg M. An overview of the marine natural products in clinical trials and on the market. *J Coast Life Med*. 2015;3:421–428.
64. Whitley RJ, Yeager A, Kartus P, et al. Neonatal herpes simplex virus infection: follow-up evaluation of vidarabine therapy. *Pediatrics*. 1983;72:778–785.
65. Sköldenberg B, Forsgren M, Alestig K, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. *Lancet*. 1984;2:707–711.
66. Whitley R, Arvin A, Prober C, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. Infectious diseases collaborative antiviral study group. *N Engl J Med*. 1991;324:444–449.
67. Ericson JE, Gostelow M, Autmizguine J, et al. Safety of high-dose acyclovir in infants with suspected and confirmed neonatal herpes simplex virus infections. *Pediatr Infect Dis J*. 2017;36:369–373.

68. Kimberlin DW, Lin CY, Jacobs RF, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics*. 2001;108:230–238.

69. Sampson MR, Bloom BT, Lenfestey RW, et al. Population pharmacokinetics of intravenous acyclovir in preterm and term infants. *Pediatr Infect Dis J*. 2014;33:42–49.

70. Davis KL, Shah SS, Frank G, et al. Why are young infants tested for herpes simplex virus? *Pediatr Emerg Care*. 2008;24:673–678.

71. Benidir A, Lim R, Salvadori M, et al. Current practice patterns regarding diagnostic investigations and empiric use of acyclovir by Canadian pediatric emergency physicians in febrile neonates. *Pediatr Emerg Care*. 2013;29:273–278.

72. Swartz S, Hadjiev J, Kolinski J, et al. Factors associated with HSV PCR CSF testing and empiric acyclovir therapy in young febrile infants. *Clin Pediatr (Phila)*. 2019;58:1194–1200.

73. Aronson PL, Cruz AT, Freedman SB, et al. Association of Herpes Simplex Virus Testing with hospital length of stay for infants ≤60 days of age undergoing evaluation for meningitis. *J Hosp Med*. 2019;14:492–495.

74. Shah SS, Volk J, Mohamad Z, et al. Herpes simplex virus testing and hospital length of stay in neonates and young infants. *J Pediatr*. 2010;156:738–743.

75. Byington CL, Reynolds CC, Korgenski K, et al. Costs and infant outcomes after implementation of a care process model for febrile infants. *Pediatrics*. 2012;130:e16–e24.

76. Brower LH, Wilson PM, Murtagh Kurowski E, et al. Using quality improvement to implement a standardized approach to neonatal herpes simplex virus. *Pediatrics*. 2019;144.

77. Van TT, Mongkolrattanothai K, Arevalo M, et al. Impact of a rapid herpes simplex virus PCR assay on duration of acyclovir therapy. *J Clin Microbiol*. 2017;55:1557–1565.