Neonatal Herpes Simplex Virus Disease

Updates and Continued Challenges

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KEYWORDS

• Neonatal herpes • Antiviral agents • Herpes simplex virus
• Mother-to-child transmission • HSV-1 • HSV-2

KEY POINTS

- Early recognition and prompt initiation of intravenous acyclovir can aid in reducing the morbidity and mortality in infants with neonatal herpes simplex virus (HSV) disease.
- The introduction of polymerase chain reaction has improved diagnosis of neonatal HSV disease significantly, although viral culture remains the gold standard for detection of HSV in mucocutaneous lesions and in surface swabs, pending data comparing these 2 testing modalities.
- Rapid diagnostic tests at time of delivery may prove beneficial in detecting asymptomatic shedding of HSV in the maternal genital track to prevent transmission from mother to child.
- Efforts to find a prophylactic and therapeutic vaccine for both HSV type 1 and HSV type 2 are ongoing.
- Although new antiviral agents continue to be studied for the treatment of HSV infections, acyclovir remains the current drug of choice for the treatment of neonatal HSV disease.

INTRODUCTION

Over the past 40 years, significant advancements have been made in the diagnosis and management of neonatal herpes simplex virus (HSV) disease. Despite these advancements, neonatal HSV disease continues to be associated with high rates of morbidity and mortality. In the early 2000s, approximately 1500 infants out of an estimated 4 million births were diagnosed with neonatal HSV disease each year (approximately 3.75 per 10,000 births).[1] The incidence rate has continued to rise over the past

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Clin Perinatol 48 (2021) 263–274
https://doi.org/10.1016/j.clp.2021.03.003
perinatology.theclinics.com

several years, with the last reported incidence rate in 2015 of 5.3 infants per 10,000 births.[2] This rarity should not preclude clinicians from evaluating any infant with suspicion of neonatal HSV disease. Early recognition and prompt initiation of acyclovir have been imperative to improving outcomes in infants.[3–7] Reduction of morbidity and mortality rates and prevention of mother-to-child transmission through vaccination or other preventative measures are continuing goals. This article highlights some of the significant advancements made over the past 40 years in the diagnosis and management of neonatal HSV disease and identifies areas where current research is seeking to continue to improve outcomes and to reduce the incidence of the disease. Specific challenges that hinder improvement also are addressed.

CLASSIFICATIONS OF NEONATAL HERPES SIMPLEX VIRUS DISEASE

Neonatal HSV disease is diagnosed primarily in infants between day 10 and day 19 of age but disease has been recognized in infants up to 42 days of age.[8,9] Patients can be classified into 3 groups: (1) skin, eye, and mouth (SEM); (2) central nervous system (CNS) disease; and (3) and disseminated disease (**Table 1**). Isolated SEM disease is the most common presentation, affecting approximately 45% of those with neonatal HSV,[10] and is defined as disease that remains localized to the skin or mucosal surfaces. Infants diagnosed with SEM disease usually present for care between day 10 and day 12 of life.[11,12] Infants with CNS disease may present with irritability, seizures, temperature instability, lethargy, poor feeding, and/or skin involvement and account for approximately 30% of all neonates affected. Infants with CNS disease typically develop symptoms between day 16 and day 19 of life.[10–12] The least common, but potentially most devastating in terms of mortality, manifestation of neonatal HSV disease is disseminated disease (25% of all infections).[10] Presentation of disseminated neonatal HSV disease may be confused with bacterial sepsis or a metabolic disorder because of an infant's ill appearance and multiorgan involvement, including hepatic, pulmonary, and/or adrenal. Infants with disseminated infections may have CNS and/or mucocutaneous involvement in addition to multisystem organ involvement. Infants with disseminated disease develop symptoms between day 10 and day 12 of life.[11,12]

TRANSMISSION

Transmission of HSV to an infant occurs primarily during the perinatal period (85%) by exposure to HSV (type 1 [HSV-1] or type 2 [HSV-2]) in the birth canal, but an infant also can be exposed postnatally (10%) by direct contact to the virus through either orolabial or other cutaneous lesions or, less commonly, via an in utero exposure (5%).[13] Congenitally infected infants typically have a very severe presentation, including skin findings indicative of previous in utero infection (eg, scarring and hypo/hyperpigmented lesions), active skin lesions, microcephaly, chorioretinitis, and/or cutis aplasia.[13,14]

The risk of perinatal HSV transmission has been linked to several factors, including the timing of infection present in the pregnant woman (first-episode primary, first-episode nonprimary, or recurrent infection, as determined by maternal antibody status and virus type present in the genital tract), the use of fetal scalp electrodes, mode of delivery (vaginal vs cesarean delivery), and duration of rupture of membranes.[9,10] An infant is most at risk of perinatal acquisition of HSV infection when there is maternal primary genital HSV infection because there is inadequate time for protective immunoglobulins against HSV to be passed transplacentally to the infant. A first-episode nonprimary genital infection poses a somewhat lesser risk to an infant because the mother has HSV IgG antibodies to 1 type of HSV that provide some cross-protection to her

Table 1
Disease classifications of neonatal herpes simplex virus disease

Disease Classification	Percentage of Those Diagnosed	Typical Age at Presentation (d)	Common Clinical Presentation	Diagnosis	Treatment
SEM	45	10–12	Vesicular lesions or ulcerations on eye or mucous membranes	Skin/mucosal culture/PCR +, CSF PCR –, blood PCR ±, ALT normal	Intravenous acyclovir (60 mg/kg/d divided 3 times/d) for 14 d Followed by oral acyclovir (300 mg/m^2/dose 3 times/d) to complete a 6-mo suppressive course
CNS	30	16–19	Irritability, seizures, temperature instability, lethargy, poor feeding	Skin/mucosal culture/PCR ±, CSF PCR +[a], blood PCR ±, ALT normal	Intravenous acyclovir (60 mg/kg/d divided 3 times/d) for at least 21 d, pending negative CSF PCR near the end of therapy Followed by oral acyclovir (300 mg/m^2/dose 3 times/d) to complete a 6-mo suppressive course
Disseminated	25	10–12	Respiratory failure, encephalitis, hepatic failure, hypoperfusion, Disseminated intravascular coagulation	Skin/mucosal culture/PCR ±, CSF PCR ±, blood PCR ±, ALT elevated[b]	Intravenous acyclovir (60 mg/kg/d divided 3 times/d) for at least 21 d pending negative CSF PCR (if CSF initially was positive) near the end of therapy Followed by oral acyclovir (300 mg/m^2/dose 3 times/d) to complete a 6-mo suppressive course

[a] Neonates with a negative CSF PCR but who otherwise appear to have CNS involvement (abnormal CSF indices, presented with or developed seizures, or has abnormal neuroimaging or EEG) should be treated as CNS disease.
[b] In the setting of a positive HSV PCR from skin/mucosal swab, blood, or CSF or HSV isolated from viral culture of skin or mucosal swab.
"+" refers to a positive test result.
"-" refers to a negative test result.
"±" refers to either a positive or negative test result.

newly acquired HSV type (eg, a pregnant mother previously had HSV-2 and newly acquires HSV-1 near delivery). Recurrent genital HSV infection, which is the most common form of HSV genital infection in pregnancy, refers to the reactivation of a previously acquired HSV type (as determined by existing maternal antibodies).[9,13] Determining the risk of mother-to-child transmission continues to be difficult because of the inability to detect asymptomatic shedding at time of delivery.

Historically, HSV-2 was associated with genital herpes and HSV-1 with orolabial infections, but over the past 2 decades HSV-1 has become the predominate cause of genital infections in Europe and the United States. The reasoning behind the increase in HSV-1 genital infections is secondary to changing sexual practices, with an increase in oral-genital contact and a lower incidence of HSV-1 orolabial infections during childhood.[15] Sacral ganglia reactivation of HSV-1 is less common than HSV-2. Therefore, HSV-1 may be associated with an increased risk of neonatal transmission, because, when present, HSV-1 genital lesions are more likely to represent a first-episode primary or a first-episode nonprimary infection in the pregnant woman, both of which are associated with a 10-fold to 30-fold increased risk of transmission to the neonate compared with a recurrent episode.[16]

DISCUSSION

Current Diagnostic Recommendations

The recommendations provided by the American Academy of Pediatrics Committee on Infectious Diseases for evaluating an infant with suspected neonatal HSV disease have continued to evolve. The introduction of new diagnostic tests, increasing knowledge of the pathogenicity and epidemiology of HSV, and disease presentation in neonates have resulted in revised recommendations for evaluation and management of neonates with known or suspected HSV infection. The current recommendations for diagnostic evaluation of infants with suspected HSV infection include (1) viral culture and polymerase chain reaction (PCR) from any mucocutaneous lesion concerning for HSV; (2) viral culture and PCR of swabs of conjunctiva, nasopharyngeal mucosa, oral mucosa, and anal mucosa (often collectively referred to as surface swabs); (3) cerebrospinal fluid (CSF) HSV PCR; (4) whole-blood HSV PCR; and (5) an alanine aminotransferase (ALT) level.[17] Infants with suspected HSV infection should empirically receive intravenous acyclovir, 20 mg/kg/dose every 8 hours, while awaiting the results of the recommended HSV studies. If a lumbar puncture is unable to be performed due to clinical instability in an infant undergoing HSV evaluation or a lumbar puncture was attempted but CSF was unable to be obtained, empiric acyclovir should not be withheld. In such cases, a lumbar puncture should be performed as early as possible to obtain CSF indices and evaluate the CSF for HSV DNA.

The introduction of PCR has revolutionized the process of diagnosing neonatal HSV disease, especially CNS disease. Prior to the availability of PCR, the diagnosis of CNS disease was dependent on viral culture and invasive measures, such as brain biopsy.[18,19] In the mid-1990s, studies evaluating the sensitivity and specificity of HSV PCR in CSF were performed and demonstrated the utility of the diagnostic test in detecting HSV DNA in the CSF of infants; prior to the availability of molecular testing, many neonates without obvious CNS symptoms likely were managed as if they had SEM disease.[20] A negative CSF PCR, however, does not eliminate CNS involvement, especially if the CSF indices, neuroimaging, or electroencephalogram (EEG) monitoring is abnormal, or if the patient has or develops seizures.[20]

PCR also has been used in the detection of HSV DNA in blood as an additional tool for diagnosis of neonatal HSV infection.[21] Detection of HSV DNA in the blood of

neonates indicates infection but does not correlate with classification of disease; neonates may be viremic (and hence DNAemic) with isolated SEM or CNS disease. A positive HSV blood PCR result may be helpful to detect the presence of HSV DNA in neonates who may not have other diagnostic or clinical evidence of infection.[22–24]

The current recommendation for testing mucocutaneous lesions and surface swabs (specimens from mouth, nasopharynx, conjunctiva, and anus) is to perform both viral culture and molecular testing on these specimens because the sensitivity and specificity of PCR have not yet been established in infants. PCR has replaced viral culture in many institutions, however, due to the unavailability of viral culture facilities[25] as well as the more rapid turnaround time for molecular testing results. PCR test results typically are reported within 24 hours of sample collection whereas a viral culture may take between 2 days and 5 days to be reported.[9] Cultures also are more likely to be negative during the later stages (ulceration and crusting) of skin lesions whereas PCR testing is more likely to detect HSV DNA in more mature lesions where viral burden may be reduced.[26] Additional studies are needed to evaluate the sensitivity of PCR versus culture for skin and mucous membrane specimens in neonates.

Treatment

Over the past 40 years, treatment of neonatal herpes has improved significantly, with a corresponding reduction in morbidity and mortality. Prior to the use of antiviral agents for treatment of neonatal HSV disease, the mortality rate ranged from 50% to 85% in CNS and disseminated disease, respectively.[1] An older antiviral, vidarabine, proved effective in randomized controlled trials in the late 1970s.[3,4] In the 1980s, acyclovir, a nucleoside analog, was evaluated for the treatment of neonatal HSV disease and subsequently has become the mainstay of treatment.[6,27] Currently, high-dose acyclovir (60 mg/kg/d divided every 8 hours) reduces mortality to 4% in those with CNS disease and to 30% with disseminated disease.[27] Further reduction in mortality also can be achieved by initiating high-dose acyclovir within the first day of hospitalization rather than delaying to day 2 or day 3 while awaiting confirmatory test results.[7]

Duration of therapy is a minimum of 21 days of intravenous therapy in those with CNS and disseminated disease and 14 days for SEM disease.[28] Prior to discontinuing therapy at 21 days in neonates with an initial positive CSF HSV PCR, a repeat lumbar puncture is recommended to document clearance of viral DNA. If HSV DNA still is detected, the infant should receive an additional 7 days of weight-adjusted intravenous acyclovir and have a repeat lumbar puncture performed at the end of the fourth week of therapy to document clearance of HSV DNA. The extension of therapy for an additional 7 days followed by a repeat lumbar puncture should continue until clearance of viral DNA from the CSF is demonstrated.[29] Neonates who are receiving treatment with intravenous acyclovir should be hospitalized for the duration of their therapy to monitor for adverse effects of acyclovir including neutropenia and renal toxicity, which is reversible, as well as other clinical complications.[27] Following the completion of intravenous acyclovir, infants are transitioned to oral suppressive therapy with acyclovir for a 6-month course. This recommendation is based on the findings of a randomized, placebo-controlled study that infants who received oral suppressive acyclovir therapy had improved neurologic outcomes and fewer skin recurrences than infants who did not receive suppressive therapy.[30]

Other oral nucleoside analogs, valacyclovir and famciclovir, are available for use in HSV infections, specifically genital lesions, but have not been studied in neonatal HSV disease. Valacyclovir, the prodrug of acyclovir, is an oral agent that has improved bioavailability compared with oral acyclovir, but its pharmacokinetic profile in neonates is not yet known. The pharmacokinetics of valacyclovir have been evaluated

down to 1 month of age, but variability in drug exposure in very young infants has limited dosing recommendations to infants 3 months and older.[31] Additional studies evaluating the pharmacokinetics of valacyclovir in neonates are needed prior to any recommendations being made on its use.

Two additional parenteral antiviral agents, cidofovir and foscarnet, are associated with significant toxicity and typically are reserved for the treatment of acyclovir-resistant HSV infections in immunocompromised patients.[32,33] Resistance of HSV to acyclovir to date is reported mainly in immunocompromised patients and not frequently in neonates[28]; therefore, these antiviral agents rarely are used in the neonatal population. Newer antiviral agents currently in development, brincidofovir and pritelivir, have been evaluated for the use in HSV disease. Brincidofovir, an orally bioavailable lipid acyclic nucleotide phosphonate, poses a possibility for use in HSV infections because its intracellular conversion to cidofovir diminishes the renal toxicity associated with the administration of cidofovir. Unlike cidofovir, however, brincidofovir was noted to cause significant gastrointestinal disturbances in stem cell transplant patients, and this has limited its further development.[33,34] Pritelivir is a helicase-primase inhibitor that offers a novel approach to preventing HSV replication and provides promise in treating HSV infections. One study evaluated its use in genital infections and noted a decrease in viral shedding and symptomatic lesions in those receiving higher doses of the novel antiviral agent.[35] Currently, no studies have evaluated its use in neonates, but it may pose a future option for use in pregnant women or seropositive partners in hopes of decreasing asymptomatic shedding of the virus and transmission to the neonate.

Combination therapies also have been considered for the treatment of severe HSV infections, with the addition of another antiviral agent to acyclovir in an effort to further reduce mortality.[28] This approach has not yet been addressed in neonates but is a possible future consideration that will require the accumulation of pharmacokinetic data.

How Can Neonatal Herpes Simplex Virus Disease Be Prevented?

In order to reduce mother-to-child transmission of HSV infection, the American College of Obstetricians and Gynecologists (ACOG) recommends cesarean delivery in all women noted to have active genital lesions or prodromal symptoms at time of labor, even if rupture of membranes already has occurred.[36] Cesarean delivery is not routinely recommended to reduce peripartum transmission in women with a history of recurrent genital herpes without active lesions at onset of labor, although, in order to account for the possible risk of prolonged viral shedding, it may be considered in women who have primary or nonprimary first-episode genital infection at any point during the third trimester.[36]

ACOG also recommends that suppressive antiviral therapy be started at 36 weeks' gestation in pregnant women who have a prior history of HSV genital lesions.[36] This therapy aids in reduction of active genital lesions at time of delivery in women with a prior history of genital herpes. Yet antenatal suppressive therapy does not completely prevent asymptomatic shedding at time of delivery and it also does not prevent transmission from HSV infections acquired late in pregnancy.[13,37] HSV infections have occurred in neonates born to women receiving antiviral suppressive therapy.[38]

Identification of pregnant women who are asymptomatically shedding HSV at the time of delivery would be beneficial in preventing mother-to-child transmission. Obtaining prenatal or perinatal genital cultures from pregnant women does not predict which women will be asymptomatically shedding at time of delivery.[37,39] The

Step 1: Obstetrician to collect a swab of maternal genital lesion and send for culture, HSV PCR, and HSV typing. Maternal serology to also be sent for HSV-1 and HSV-2 to determine type of maternal HSV infection.

First-Episode Primary: genital lesion positive for HSV-1 or HSV-2 **AND** maternal antibody negative for both HSV-1 or HSV-2

First-Episode NonPrimary: genital lesion positive for HSV-1 **AND** maternal antibody negative for HSV-1 but positive for HSV-2

OR

genital lesion positive for HSV-2 **AND** maternal antibody negative for HSV-2 but positive for HSV-1

Recurrent: genital lesion positive for HSV-1 **AND** maternal antibody positive for HSV-1

OR

genital lesion positive for HSV-2 **AND** maternal antibody positive for HSV-2

Step 2: While awaiting maternal testing of genital lesion and serology, determine if mother had a prior history of genital lesions.

A: If mother reports prior history of HSV: 1) obtain swabs for HSV cultures AND PCR from conjunctiva, nasopharynx, mouth, and anus on infant at 24 hours of life **PLUS** 2) HSV blood PCR. Do not automatically start IV acyclovir.

1. If any above return positive, finish evaluation of infant with LP for CSF studies including HSV PCR and obtain serum ALT. Start IV acyclovir 20 mg/kg/dose every 8 hours and continue based on disease classification.
2. If testing on infant remains negative, educate parents on neonatal HSV disease and arrange for close follow up.

B: If mother reports **no** prior history of HSV: 1) obtain swabs for HSV cultures AND PCR from conjunctiva, nasopharynx, mouth, and anus on infant at 24 hours of life **PLUS** 2) HSV blood PCR **PLUS** 3) perform an LP for CSF to send for cell count, glucose, protein, and HSV PCR **PLUS** 4) obtain a serum ALT **PLUS** 5) start IV acyclovir 20 mg/kg/dose every 8 hours.

1. If mother's genital lesion is determined to be a recurrent infection and all neonatal testing remains negative, stop IV acyclovir, educate family on neonatal HSV disease, and arrange for close follow up.
2. If mother's genital lesion is determined to be a recurrent infection and the neonatal surface culture/PCR is positive, but CSF indices are normal, CSF and blood PCR are negative, ALT is normal, and infant remains asymptomatic, treat preemptively with IV acyclovir for a total of 10 days.
3. If mother's genital lesion is determined to be a recurrent infection and neonate is symptomatic, surface culture/PCR is positive, CSF indices are abnormal, CSF and/or blood PCR are positive, and/or ALT is abnormal, continue IV acyclovir for 14–21 days, with the duration being based on disease classification.
4. If mother's genital lesion is determined to be a first-episode primary/first-episode nonprimary and the neonatal surface culture/PCR is positive but the CSF indices are normal, CSF and blood PCR are negative, ALT is normal, and infant remains asymptomatic, treat preemptively with IV acyclovir for a total of 10 days.
5. If mother's genital lesion is determined to be a first-episode primary/first-episode nonprimary and baby is symptomatic, surface culture/PCR is positive, CSF indices are abnormal, CSF and/or blood PCR are positive, and/or ALT is abnormal, continue IV acyclovir for 14–21 days, with the duration being based on disease classification.

Fig. 1. Steps to managing infants born to mothers with active genital lesions at delivery.

turnaround time from specimen collection to result for both culture and PCR testing precludes both from being practical informants of delivery modality. As a result, culture and PCR are not performed routinely at time of labor to assess for asymptomatic shedding. The introduction of a rapid, point-of-care molecular diagnostic test designed to screen for asymptomatic shedding of HSV at the onset of labor would be valuable in determining mode of delivery, benefit of intrapartum antiviral therapy, and in consideration of neonatal antiviral prophylaxis.[13,40] One multicenter clinical trial (ClinicalTrials Identifier: NCT01878383) is evaluating the use of a point-of-care PCR diagnostic in pregnant women at onset of labor; the results of this study currently are pending publication.

When evaluating the risk of transmission to an infant, relying on history to determine a maternal history of genital HSV infection is ineffective because a majority of women with infants who have neonatal HSV disease are unaware of having had a prior genital HSV infection.[37,41] The use of serology at time of delivery in women with active genital lesions may assist with classification as a first-episode primary, first-episode nonprimary, or recurrent infection. Serology performed at prenatal appointments could identify seronegative pregnant women who might benefit from counseling on strategies to prevent exposure during the third trimester, because this period of gestation poses the highest risk of mother-to-child transmission. Serology also could aid in counseling seropositive women to recognize the subtle symptoms of a reactivation,[41] and perhaps knowledge of seropositivity might decrease the use of fetal scalp electrodes.[10] The programmatic complexities of serologic assessments of pregnant women and their partners during pregnancy and the interpretation of reactive HSV-1 serology in a person who likely had HSV-1 disease as a child, however, are challenging.

The American Academy of Pediatrics published guidance in 2013 with recommendations for the evaluation and management of infants born to women with active genital lesions at the time of delivery (**Fig. 1**). This document bases the assessment of an infant's risk for developing HSV disease on classification of maternal genital infection as a primary, first-episode nonprimary, or recurrent episode and provides guidance for diagnostics and antiviral management.[9]

Vaccine Development

A vaccine is the most effective way to prevent mother-to-child transmission of HSV. A preventative vaccine that prevents acquisition of HSV-1 and HSV-2 in a seronegative woman and a therapeutic vaccine that decreases the likelihood of viral shedding in those who are seropositive each would have a substantial impact on the incidence of neonatal HSV infection and disease. One recent therapeutic vaccine demonstrated reduction in viral shedding and duration of symptomatic lesions, but these reductions were temporary.[42] Another recent therapeutic vaccine candidate being studied, HSV529, has had promising response in seronegative individuals, but continued efforts are being made to improve its immunogenicity.[43] Vaccine research remains an area of interest to both obstetricians and neonatologists, with several candidate vaccines under evaluation.

SUMMARY

Although understanding of neonatal HSV disease has grown exponentially over the past 40 years, with gains in diagnostics, treatment, and prevention, a rising incidence rate and continued poor outcomes in affected neonates are concerning. The need for further advances in point-of-care diagnostics and vaccination that could be applied to the prevention of mother-to-child transmission of HSV as well as efforts to optimize management to decrease the morbidity and mortality of infants with neonatal HSV disease continues to be a high priority.

CLINICS CARE POINTS

- Early detection is key to improving the morbidity and mortality of neonatal HSV disease.
- Culture remains the gold standard currently for evaluation of mucocutaneous lesions and surface swabs in neonates while the sensitivity of PCR in the detection of HSV DNA for these specimens continues to be evaluated.

- PCR has improved diagnosis of neonatal HSV CNS disease vastly. Neonatal HSV CNS infection may be diagnosed based on clinical presentation or other laboratory parameters, even if the CSF HSV PCR is negative.
- A blood PCR to detect HSV DNA is a helpful adjunct to detecting viremia in neonates without notable signs and symptoms of HSV infection.
- Mother-to-child transmission of HSV is highly dependent on timing and classification of maternal infection.
- Intravenous acyclovir is the mainstay of treatment of neonatal HSV disease.
- Despite multiple vaccine research trials, no vaccine has yet proved beneficial.

Best practices

What is the current practice for Neonatal Herpes Simplex Virus Disease?

Best Practice/Guideline/Care Path Objective(s) For Neonates Suspected of Having HSV Disease:

- Promptly evaluate any infant with suspected HSV disease with the following diagnostic tests: (1) viral culture and PCR on "surface swabs" and any mucocutaneous lesion if present, (2) CSF HSV PCR, (3) whole blood HSV PCR, and (4) serum ALT level.
- Initiate IV acyclovir 20 mg/kg/dose every 8 hours as soon as possible while awaiting results of diagnostic tests.
- In an infant suspected of having neonatal HSV disease, do not delay starting IV acyclovir therapy if unable to obtain CSF for HSV PCR testing. A lumbar puncture should be repeated or performed as soon as clinically able.
- Duration of IV acyclovir is dependent upon disease classification- 14 days for SEM disease and a minimum of 21 days for CNS and disseminated disease.
- A repeat lumbar puncture should be performed in all infants with an initial positive CSF HSV PCR near the end of 21 days of IV acyclovir to evaluate for clearance of viral DNA; continued PCR-positivity from CSF necessitates continuation of IV acyclovir for at least another 7 days, with another repeat lumbar puncture near the end of that extension of parenteral therapy (consultation with a pediatric infectious diseases specialist is advised in this situation).
- Upon completion of treatment course with IV acyclovir, all infants should be transitioned to suppressive therapy with oral acyclovir for 6 months to improve neurodevelopmental outcomes and reduce skin recurrences.

What changes in current practice are likely to improve outcomes?

- Have a heightened awareness of neonatal HSV in order to identify any infants who should be evaluated for neonatal HSV disease.
- Begin IV acyclovir without delay in such neonates.

Is there a Clinical Algorithm? If so, please include

See Fig. 1.

Bibliographic Source(s): [1,9,12,13,27,31,37,41]

DISCLOSURE

SHJ reports prior consulting fees from Bayer, outside the scope of this work.

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