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Neonatal Herpes Simplex Virus Infection Evaluation and Management Clinical Pathway

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Rationale:

This clinical pathway was developed by a consensus group of Johns Hopkins All Children's Hospital (JHACH) physicians, advanced practice providers, nurses, and pharmacists to standardize the management of children hospitalized for neonatal herpes simplex virus (NHSV) infection. It addresses the following:

- To provide American Academy of Pediatrics (AAP) supported guidelines for the evaluation and management of newborn infants exposed to maternal genital herpes lesions
- To streamline the evaluation & management approach of infants with suspected herpes infection during the Neonatal Intensive Care Unit (NICU) stay

Background / Published Data and Levels of Evidence:

Prevalence and associated morbidity:
NHSV infection affects approximately 1,500 infants yearly (incidence of 1 in 3,200 deliveries). A recent study from a United States (U.S.) multistate Medicaid population of > 2 million births identified an incidence rate of 4.5 infants per 10,000 live births with a yearly disease incidence increase of 56% from 2009 to 2015 (from 3.4 to 5.3 per 10,000 live births).[1,2] Intrapartum acquisition accounts for > 85% of cases. Of mothers who are seropositive for herpes simplex virus (HSV), the majority are unaware of their infection, have no evidence of genital lesions at the time of delivery, no previous history of genital herpes nor a partner having admitted to a history of herpes.[3]

Despite its relatively low prevalence, NHSV causes serious morbidity and mortality with a risk for long-term permanent sequelae among affected infants. Strong clinical suspicion, timely diagnosis, and early antiviral treatment are critical to improving outcomes.[4,5]

Subtypes of HSV:
HSV is a member of the Herpesviridae family of viruses and shares the biological properties of latency and reactivation causing recurrent infections. HSV is typed into HSV type 1 (HSV-1) and HSV type 2 (HSV-2) using serologic and molecular techniques. The deoxyribonucleic acid (DNA) of HSV-1 and HSV-2 contain many homologous sequences distributed over the entire genome of both types, which produce unique immunoglobulin G (IgG) and antigenically similar polypeptides. This cross-reactivity between HSV-1 and HSV-2 glycoproteins is why many commercially available serologic assays cannot reliably distinguish between HSV-1 and HSV-2 antibodies.[6]

Historically, HSV-2 has been associated with genital herpes and HSV-1 with oro-labial infection. However, in recent years, HSV-1 has become the predominant cause of genital infection. The increased incidence is believed to be secondary to less frequent acquisition of HSV-1 in childhood and to changing sexual practices with more frequent oro-genital contact.[7-9]
Genital HSV-1 does not reactivate as often as HSV-2 and places the infant at a higher risk of infection.[10-12] The reason is that when present in a pregnant woman, HSV-1 genital lesions are more likely to represent a first-episode primary or a first-episode nonprimary infection (see below). Both conditions are associated with a 10-fold to 30-fold increased risk of transmission to the neonate compared with a recurrent episode.[13]

Classification of Maternal HSV infection:
Correct classification of the maternal infection into primary, non-primary, or recurrent and the type HSV (HSV-1 / HSV-2) are key components of accurate diagnosis and optimal treatment approach. The classification is accomplished when clinical evaluation is correlated with virus isolation, polymerase chain reaction (PCR), and serologic testing using a type-specific assay.[14]

Maternal infection is classified as follows:

1. *Primary first episode*: The mother contracts a new HSV-1 or HSV-2 infection with genital lesions without serum HSV antibodies.
2. *Nonprimary first episode*: The mother has HSV-1 or HSV-2 genital lesions with antibodies present only against the opposite virus type. The risk of perinatal transmission of this new HSV is probably as high as if it were a primary infection.
3. *Recurrent episodes*: The mother has a recurrence of genital lesions and appropriate and adequate HSV antibodies to the infecting type of HSV.[15]

Transmission:
The majority of NHSV are acquired peripartum (~85%), with in-utero infection accounting for < 5% of cases and postnatal infection the remaining, ~10%.[17]

Peripartum transmission risk factors:
Several HSV transmission risk factors have been identified with the most significant being the type of maternal infection (primary, non-primary, or recurrent) and their antibody status.

Infants born to mothers with *primary first episode* at the time of delivery are at greatest risk of NHSV infection, with transmission rates up to 60%. This is mainly because of the risk of viral shedding and the absence of maternal seroconversion, which is protective for the newborn.

Infants born to mothers with *non-primary first episode* are at high but slightly lower risk of NHSV infection because the mother has HSV antibodies to a type of HSV that provide some cross-protection to her newly acquired HSV type (e.g., a pregnant mother previously had HSV-2 and newly acquired HSV-1 near delivery) the transmission has been reported at up to 45%.[12,18-20]

Infants born to mothers with *recurrent infections* have the lowest transmission risk at less than 2% due to lower viral loads, lower concentration and duration of viral shedding during reactivation, and the presence of passively acquired, type-specific HSV antibodies in the infant.[12,15,18,21]

In-utero infection acquired trans-placentally or trans-cervically accounts for < 5% of cases and has been reported to result in pregnancy complications including preterm birth and/or intrauterine growth restriction.[3,22-24]

The type of HSV is another reported risk factor for NHSV with a trend toward a greater proportion of NHSV infections due to HSV-1 in the past few years and a higher rate of HSV-1 transmission from mother to infant when HSV-1 is isolated at delivery versus HSV-2.[21,25]

Other risk factors include 1) the mode of delivery (cesarean section delivery reduces the risk of NHSV compared to vaginal delivery but does not eliminate the risk for newborns)[12,15,25]; 2) the duration of rupture of membranes; 3) the integrity of cutaneous barrier (use of fetal scalp electrodes and other instrumentation); 4) preterm delivery; and 5) teen mother

Table 1. Interpretation of Maternal HSV Diagnostic Tests[16]

Primary episode	Recurrent episode	Nonprimary first episode
Primary HSV-1	Recurrent HSV-1	Nonprimary HSV-1 first episode
▪ Positive PCR HSV-1 ▪ Negative PCR HSV-2 ▪ Negative HSV-1 and 2 IgG	▪ Positive PCR HSV-1 ▪ Negative PCR HSV-2 ▪ Positive HSV-1 IgG ▪ Negative HSV-2 IgG	▪ Positive PCR HSV-1 ▪ Negative PCR HSV-2 ▪ Negative HSV-1 IgG ▪ Positive HSV-2 IgG
Primary HSV-2	Recurrent HSV-2	Nonprimary HSV-2 first episode
▪ Negative PCR HSV-1 ▪ Positive PCR HSV-2 ▪ Negative HSV-1 and 2 IgG	▪ Negative PCR HSV-1 ▪ Positive PCR HSV-2 ▪ Negative HSV-1 IgG ▪ Positive HSV-2 IgG	▪ Negative PCR HSV-1 ▪ Positive PCR HSV-2 ▪ Positive HSV-1 IgG ▪ Negative HSV-2 IgG

Neonatal presentation:

Infections typically present in the first 4 weeks of life but can present for the first time up to 6 weeks after birth.

In the absence of typical skin lesions, signs, and symptoms of NHSV infection are often non-specific nor pathognomonic for the infection[28], and a high index of suspicion is paramount to early diagnosis. In one study reporting the results of HSV testing of all neonates up to 21 days of age being evaluated for sepsis, 31% had mucocutaneous involvement, 19% had seizures, and 50% had nonspecific symptoms (usually fever). Fever was only present in 53% of infants, hypothermia in 13%, poor feeding in 29%, and irritable but consolable in 10%; 76% did not appear ill or toxic.[29] Another more recent multicenter retrospective study of > 25,000 infants < 60 days old with a median age of 28 days who underwent lumbar puncture for evaluation of fever or other clinical concerns presenting to an emergency department setting with signs of CNS infection showed that testing for HSV was performed in 35% of patients and HSV infection was identified in 1.2% of those tested (39% had skin, eye, and mouth disease, 32% had CNS disease and 29% had disseminated disease).[30] Other studies show a similar distribution.[6] According to their data, HSV prevalence peaked in the second week of life and declined substantially in the second month of life.

Classification: (NHSV is classified into 3 main categories)
1) *Skin, eye, and mouth* (*SEM) infection*: Infection is localized to skin, eye, or mucosa (mouth or rectum) only. Lesions can be vesicular or ulcerative. Preterm infants may present with atypical lesions given the immaturity of their skin. SEM infection accounts for ~45% of NHSV.

2) *Central nervous system (CNS) disease*: Manifests as irritability, seizures, temperature instability, lethargy, or poor feeding. Early in HSV CNS disease, these signs and symptoms may not be present. Laboratory evaluation may reveal cerebrospinal fluid (CSF) pleocytosis, and/or positive CSF HSV PCR. CNS infection accounts for ~30% of NHSV.

3) *Disseminated disease*: Involves one or more organ systems, and could result in respiratory failure, encephalitis, hepatic failure, myocarditis, hypoperfusion, or disseminated intravascular coagulation. Often its initial presentation is with nonspecific signs and symptoms of neonatal sepsis. Disseminated disease accounts for ~25% of NHSV.

Infants with disseminated disease are more likely to present early (within the first 14 days of life), while the presentation of patients with CNS and SEM peak in the second and third weeks of life.[16]

Evaluation for suspected HSV infection:
As signs and symptoms of HSV infection in neonates vary widely and are not specific nor pathognomonic for the infection, the decision to initiate an HSV evaluation remains at the discretion of the neonatologist. Infants who may qualify for such an evaluation include but are not limited to those with a seizure of unknown etiology, skin vesicles suggestive of herpes, elevated transaminases (greater than twice the upper limit of normal for gestational and postmenstrual age) that are not explained by a different more probable etiology, thrombocytopenia or unexplained fever.

Clinical Management:

A. *Specimens to collect on any infant being worked up for possible NHSV:*

1) *Skin or mucous membranes vesicles*: Intact vesicles should be popped for a swab of the vesicle base and sent for HSV PCR with HSV culture being a second option.[31] At JHACH, only the PCR is performed. At other institutions staffed by JHACH Neonatologists, the choice between ordering an HSV culture or an HSV PCR on these specimens will depend upon which test will offer the fastest results, but the PCR is preferred over culture due to improved sensitivity and generally quicker results.

2) *Blood: HSV DNA PCR is the test of choice.*[31] A positive PCR is NOT necessarily evidence of disseminated disease since some patients with clinical SEM disease may have a positive blood PCR without involvement of other organ systems.

3) *CSF: HSV DNA PCR is the test of choice.*

   CSF Meningitis-Encephalitis Panel (MEP) typically results quicker than HSV PCR and has greater specificity for HSV but may not be as sensitive. *If enough CSF is obtained, send both MEP and HSV PCR.*[31] *However, if the specimen is limited, send testing for specific HSV PCR only.*

   HSV culture from the CSF has poor sensitivity and should not be ordered.

   The CSF HSV PCR remains adequately sensitive for the first 5 days after starting acyclovir therapy; *therefore, a delayed or repeated lumbar puncture will continue to provide useful diagnostic information for this period.*

   If the initial CSF HSV PCR is negative, yet neonatal HSV CNS disease is strongly suspected, the CSF PCR should be repeated during the first week of illness.[32]

   As blood in the CSF is known to decrease the sensitivity of the HSV PCR, repeat CSF testing by Interventional Radiology under ultrasound guidance is recommended if negative PCR in the face of a bloody tap and high suspicion of infection.

4) *Mucosal (surface) testing:* According to the 2021-2024 Red Book Report of the Committee on Infectious Diseases of the American Academy of Pediatrics, testing of mucosal sites for HSV infection may be performed by EITHER PCR or culture.[33] At JHACH, the PCR is the diagnostic test of choice on mucosal specimens, and HSV surface cultures are no longer being performed in the Microbiology Lab.

   Five separate swabs should be obtained from the left and right eyes, nose, mouth, and rectum placed into a single viral transport tube, and sent for HSV DNA PCR.

If HSV PCR is unavailable, five swabs from the same sites should be placed into a viral transport tube and sent for HSV culture, however, this test is now a send-out.

In the electronic medical record, the source should be specified as one of the collected sites (e.g., "oral"), and the additional 4 sites should be typed into "Other info." PCR testing of surface specimens is positive in ≥ 90% of cases and provides the greatest diagnostic yield of all methods to detect HSV, regardless of disease classification.[34]

B. *Any additional specimen testing may be obtained ONLY if requested and approved by Infectious Disease (ID)* (examples may include tracheal aspirates in intubated patients, peritoneal fluid in neonates undergoing peritoneal drainage, etc.).

C. *Additional laboratory evaluation*
   1. Complete metabolic profile (CMP) with alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
   2. Routine sepsis work-up tests (complete blood count (CBC) with differential, blood culture, urinalysis (UA), urine culture, CSF cell count, chemistry, and culture).
   3. Chest radiograph (X-ray) if respiratory symptoms.
   4. *If there are concerns for additional etiologies of late-onset sepsis, please refer to the Late-Onset Sepsis Clinical Pathway for further guidance*.

D. *Suggested testing:*
   1. Ophthalmology exam to evaluate eye involvement.
   2. Electroencephalogram (EEG) for suspected seizure activity. An abnormal EEG with lateralized periodic discharges is a characteristic finding in neonatal encephalitis. It is not sensitive or specific.
   3. Neuroimaging evaluations with magnetic resonance imaging (MRI) (preferred), computed tomography (CT) scan, or ultrasonography.[12,14,16]
   4. Neuroimaging abnormalities are more likely to be identified a week into the illness.

E. *Serological testing:*

   1. *Serology testing of the neonate* is typically not of significant clinical value in the diagnosis of NHSV; a positive immunoglobulin (Ig) G may reflect previous maternal infection with trans-placental translocation of antibodies and the IgM response is poor in neonatal HSV and has a high rate of cross-reactivity with other IgM assays. Furthermore, negative serology may occur in the first-episode maternal primary infection if the infection is early on.

   2. *Maternal serology testing*: If maternal genital lesions are present at the time of delivery, it is recommended to have the Obstetrical Team obtain lesions swabs/scraping for HSV PCR and blood for HSV-1 and HSV-2 specific antibodies. The testing should be performed upon the mother's presentation to the hospital for delivery or ideally earlier at

the Obstetrician's Office upon eruption of the genital lesion. Such testing is critical in delineating the appropriate course of action.

3. In the absence of maternal genital lesions at the time of delivery, serology testing (acute and convalescent IgG titers) may be considered and/or recommended by ID when determining the duration of antiviral therapy in cases where there is not a strong clinical suspicion for neonatal HSV infection, another plausible and more likely explanation exists for the presenting symptoms (i.e., hypoxic-ischemic encephalopathy (HIE)) and a complete work-up was not able to be obtained.

F. *Supportive measures:* Ensure proper management of fluid and electrolyte balances, nutrition, shock, respiratory support, seizures, disseminated intravascular coagulation and other coagulopathies, and antimicrobial therapy for secondary bacterial infections. Intravenous immunoglobulin (IVIG) may be considered in specific cases (i.e., myocardial dysfunction, systemic inflammatory response syndrome (SIRS)).

G. *Acyclovir dose, duration, and route:* Because of poor oral bioavailability, neonatal herpes must be treated with intravenous (IV) acyclovir. At the time of this revision (May 2024), the recommended dosing of acyclovir is the following:

For patients < 30 days post-natal age (PNA) **AND**

1. Post-menstrual age (PMA) < 30 weeks
   i) 20 mg/kg/dose Q12H

2. PMA ≥ 30 weeks
   i) 20 mg/kg/dose Q8H
   ii) Gives you an overdose warning that it exceeds the maximum daily dose of 40 mg/kg and 3 doses a day exceeds the maximum of 2 doses per day

Doses should also be adjusted for renal impairment and as the patient grows.

It is recommended to refer to the NeoFax, and check with pharmacy as acyclovir dosing and frequency may change.

Duration of treatment with acyclovir:

1. Infants born to mothers with confirmed recurrent infection who remain asymptomatic and have negative testing: Acyclovir may be discontinued unless there is compelling clinical evidence of possible HSV disease without a determination of an alternative cause (e.g., seizure with a temporal lobe EEG abnormality). Education on signs and symptoms of infection should be provided to the family before discharge.

2. Infants born to mothers with a primary HSV 1 / 2 episode OR with a non-primary first HSV 1 / 2 episode (refer to Table 1 for definitions) who remain asymptomatic with negative testing: Treat with IV acyclovir for 10 days.

3. Symptomatic newborns with positive surface or blood PCR and negative CSF PCR and no seizures or other signs of disseminated disease: Treat with IV acyclovir for 14 days.

4. Disseminated disease: The duration of IV acyclovir therapy should be a minimum of 21 days.

5. CNS disease: In patients with seizures or positive CSF HSV PCR, IV acyclovir therapy should be continued for 21 days.
   (1) For any infant whose initial CSF PCR is positive, a repeat lumbar puncture for CSF PCR should be repeated before the end of IV therapy (e.g., day 19-20) to confirm viral clearance.
   (2) If the repeat CSF PCR is positive, IV acyclovir should be continued for 7 more days, and the CSF PCR testing should be repeated weekly until negative.

Parenteral antiviral therapy should be continued until the CSF HSV DNA PCR is negative.

The lumbar punctures (LP) performed toward the end of the antiviral initial treatment are key in determining any further extended treatment and hospital stay. Hence, a qualified and experienced provider should perform the LP once. If the attempt fails, an Interventional Radiology consult should be placed. Neonates with confirmed CNS involvement should undergo an EEG evaluation.[35,36]

Other considerations:
Neonates with virologically confirmed HSV infection should undergo ophthalmologic and neuroimaging evaluations with MRI (preferred), CT, or ultrasonography.[12,14,16] Neuroimaging abnormalities are more likely to be identified a week into the illness.

Incomplete Evaluation:
If blood, CSF, or mucosal HSV studies were not performed during evaluation, we recommend consulting ID to determine the best duration of IV acyclovir. Melvin, *et al.* recently evaluated HSV viral clearance in 6 infants with disseminated disease during acyclovir treatment showing a single-phase exponential decay with a median viral half-life of 1.26 days regardless of baseline viral level at the initiation of therapy indicating there may be a long plasma half-life of HSV DNA.[37] Another small study revealed that HSV DNA remained in the serum and/or CSF from several patients for 1-2 weeks after the beginning of treatment.[38]

The CSF HSV PCR remains adequately sensitive for the first 5 days after starting acyclovir therapy; therefore, a delayed or repeated lumbar puncture will continue to provide useful diagnostic information for this period.

Monitoring during IV acyclovir therapy:
Renal function (blood urea nitrogen (BUN) and creatinine) and absolute neutrophil counts should be monitored weekly and more frequently if abnormalities are detected clinically or via laboratory evaluation.

Suppressive therapy:
Suppressive therapy with oral acyclovir is recommended for all infants surviving neonatal HSV infection of any classification (SEM, CNS, or disseminated) and who were treated with a 10-21-day course of IV acyclovir. The oral suppressive acyclovir dose is 300 mg/m^2/dose administered three times daily for 6 months after the completion of parenteral therapy for acute disease. The dose should be adjusted monthly to account for growth. The absolute neutrophil count should be assessed at 2 and 4 weeks after initiating suppressive therapy and then monthly for 6 months.

H. *The evaluation and management guidance presented in this pathway apply to 4 different infant categories:*
   1. Asymptomatic infants exposed to maternal genital herpes lesions at delivery (section I)
   2. Asymptomatic infants whose mother has a history of genital herpes but no active genital lesions at delivery (section J)
   3. Asymptomatic infants whose mother has a documented history of first-episode primary or nonprimary infections during the third trimester but no active genital lesions at delivery (section K)
   4. Infants who undergo a herpes evaluation as part of their clinical care not related to maternal herpes lesions (section L)

   Always refer to Table 1 for interpretation of maternal HSV infection classification

   In hospital settings with limited access to PCRs for HSV DNA or to type-specific serologic tests, the approach detailed in the algorithms may have limited applicability and an ID consult should be considered

I. *Evaluation of the asymptomatic infant exposed to maternal genital herpes lesions at delivery:* Infants exposed to active HSV genital lesions at delivery should NOT have delayed bathing.[39] Please refer to Figures 1 and 2 for detailed guidance on evaluation and management.

J. *Evaluation of asymptomatic infants born to mothers with a history of genital HSV infection, but no active genital lesions at delivery and no history of lesions in the third trimester of pregnancy*

Most infants whose birthing parent has a history of genital herpes but no genital lesions at delivery should be observed for signs of infection (e.g., vesicular lesions of the skin, respiratory distress, seizures, or signs of sepsis) but should not have specimens for HSV virology studies obtained and should not receive empiric parenteral acyclovir.

The only exceptions are infants born to persons with documented first-episode primary or nonprimary infections during the third trimester (see section K).

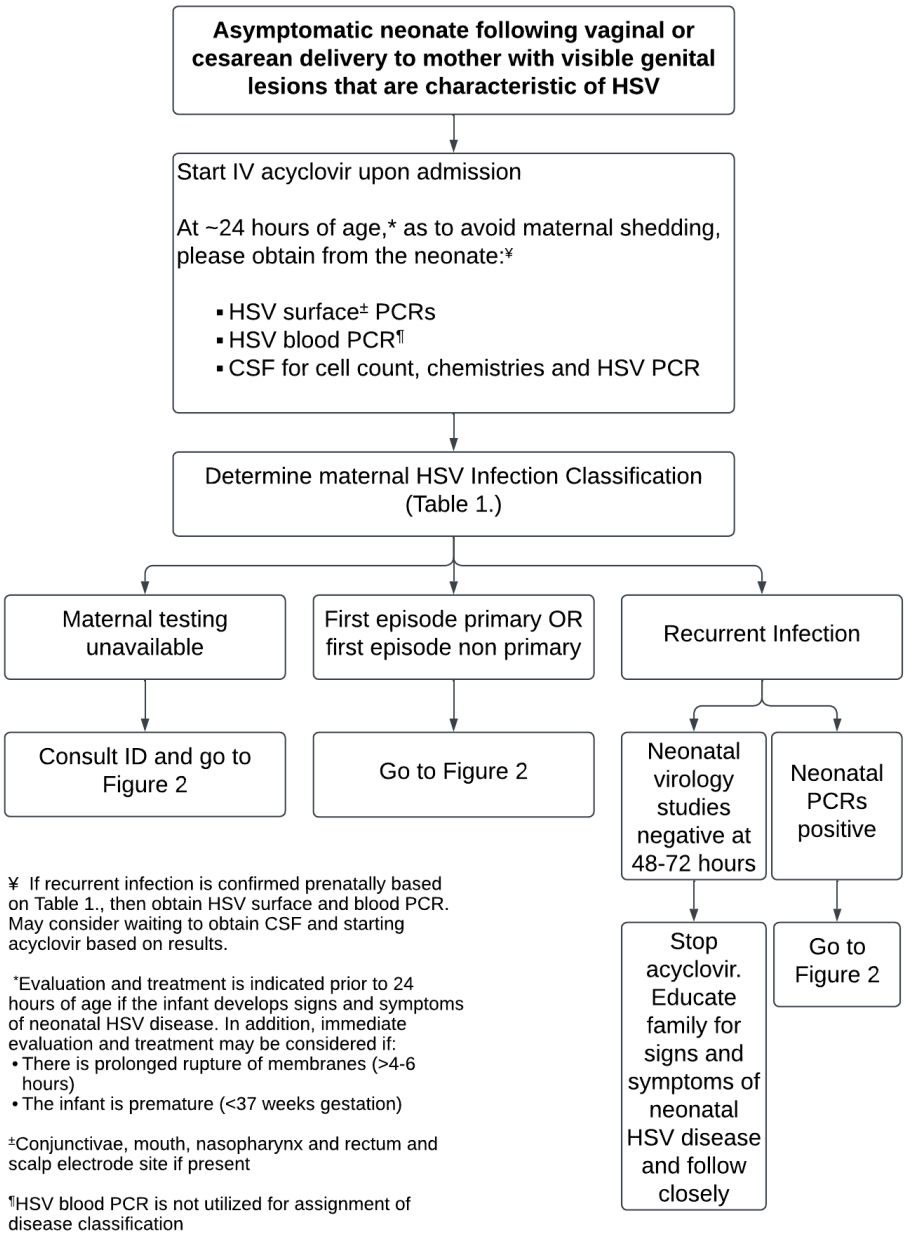
K. *Evaluation of asymptomatic infants born to mothers with a documented history of first-episode primary or nonprimary HSV infection during the third trimester and no HSV genital lesions at delivery* [40]

"These infants should have HSV surface PCR and HSV blood PCR obtained at ~24 hours of age, regardless of mode of delivery or birthing parent's receipt of antiviral suppressive therapy. The results of these tests should be responded to as outlined" in Figure 3. "The rationale for this recommendation is that the American College of Obstetricians and Gynecologists states that cesarean delivery may be offered to people with documented first-episode infections during the third trimester because of the possibility of prolonged viral shedding. Education of parents and caregivers about the signs and symptoms of neonatal HSV infection during the first 6 weeks of life is prudent." Please refer to Figure 3 for detailed guidance on evaluation and management

Asymptomatic infants whose mother has a documented history of first-episode primary or nonprimary infections during the third trimester but no active genital lesions at delivery

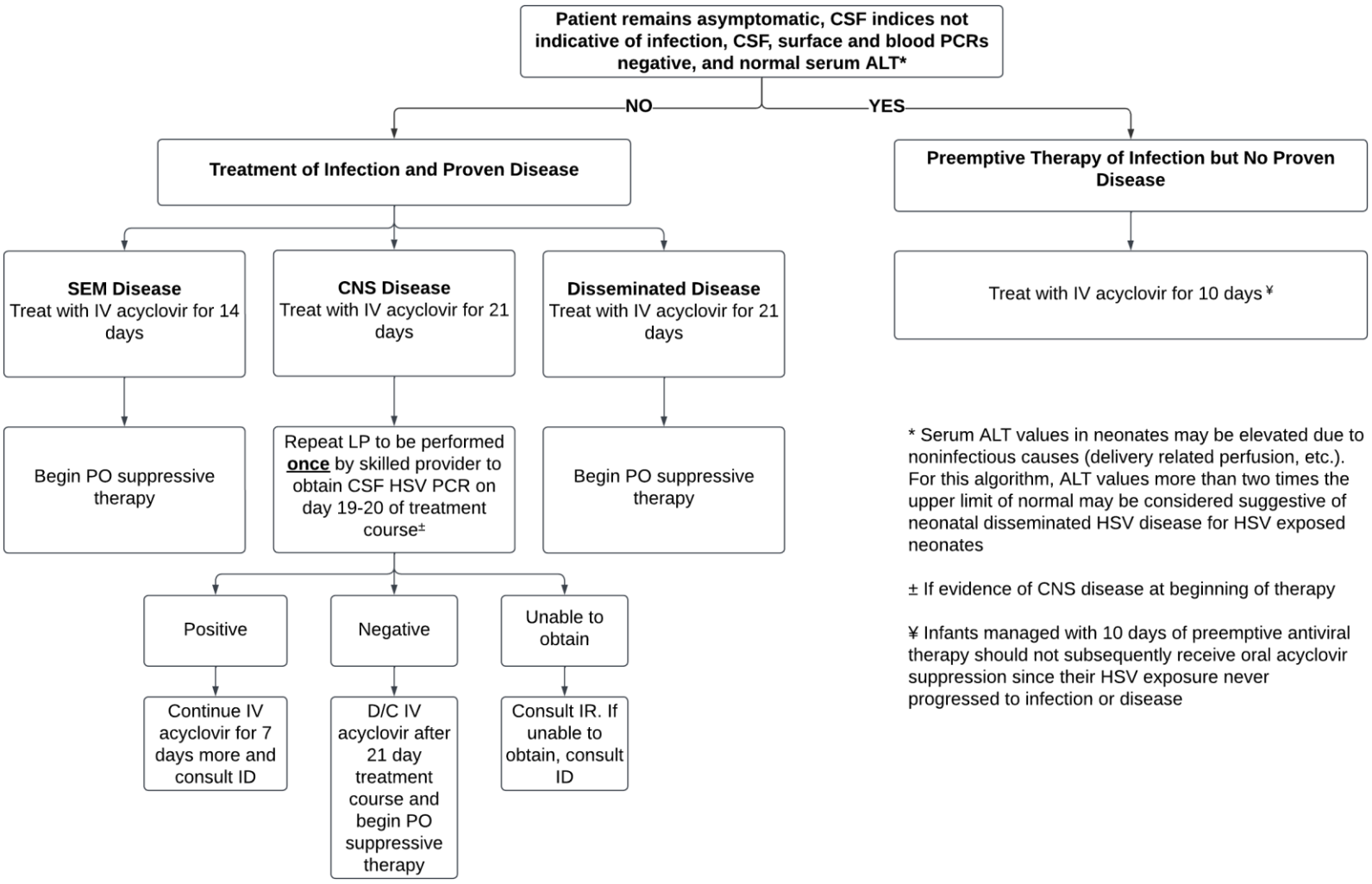
L. *Evaluation of the neonate undergoing a herpes evaluation as part of their clinical care unrelated to maternal herpes lesions.* Please refer to Figure 4 for detailed guidance on evaluation and management.

Figure 1. Algorithm for the evaluation of ASYMPTOMATIC neonates following vaginal or cesarean delivery to women with active genital herpes lesions



*Per the AAP, if at any time during the outlined evaluation, an infant develops symptoms that could indicate NHSV disease (e.g., fever, lethargy, irritability, thrombocytopenia, vesicular rash, seizures), a full diagnostic evaluation should be performed, and IV acyclovir initiated.[40]

Figure 2. Algorithm for the treatment of ASYMPTOMATIC neonates following vaginal or cesarean delivery to women with active genital herpes lesions

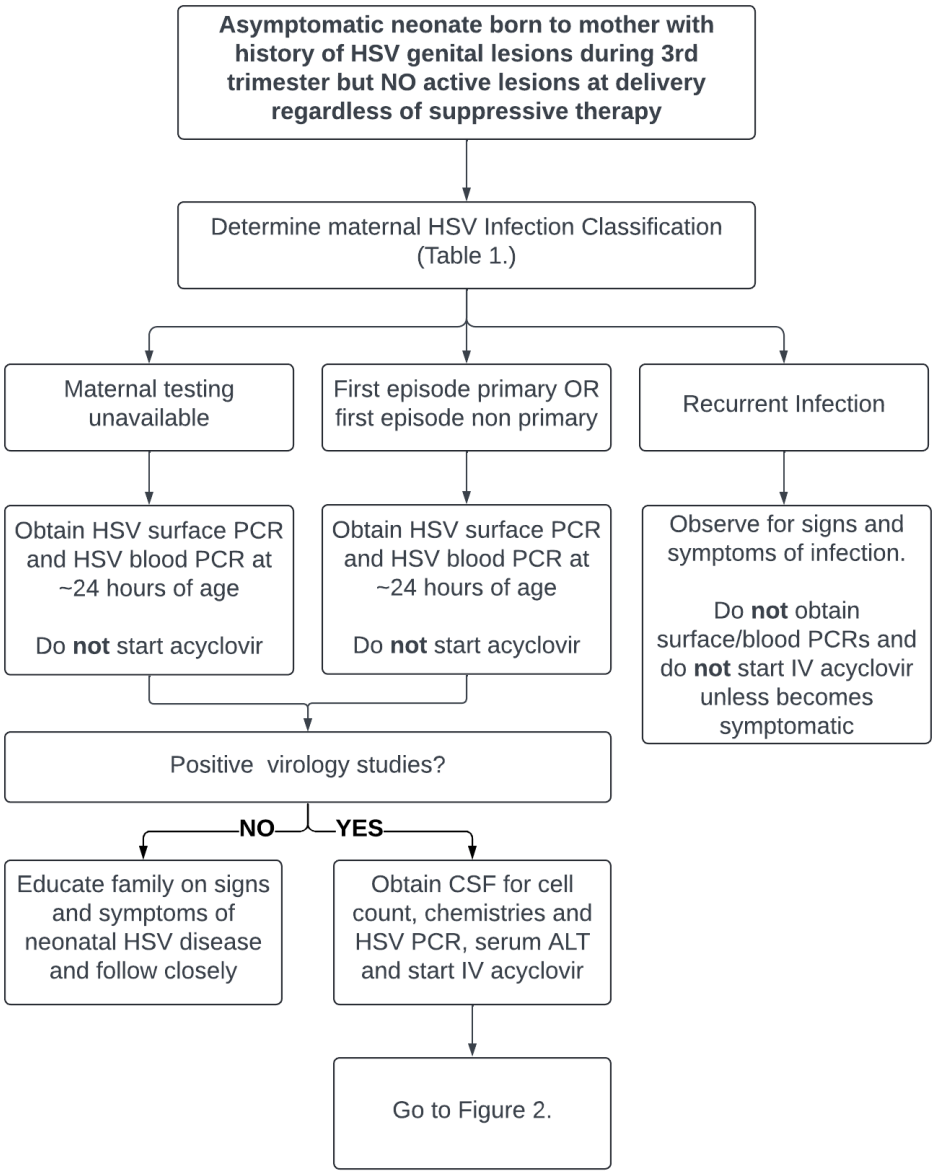


* Serum ALT values in neonates may be elevated due to noninfectious causes (delivery related perfusion, etc.). For this algorithm, ALT values more than two times the upper limit of normal may be considered suggestive of neonatal disseminated HSV disease for HSV exposed neonates

± If evidence of CNS disease at beginning of therapy

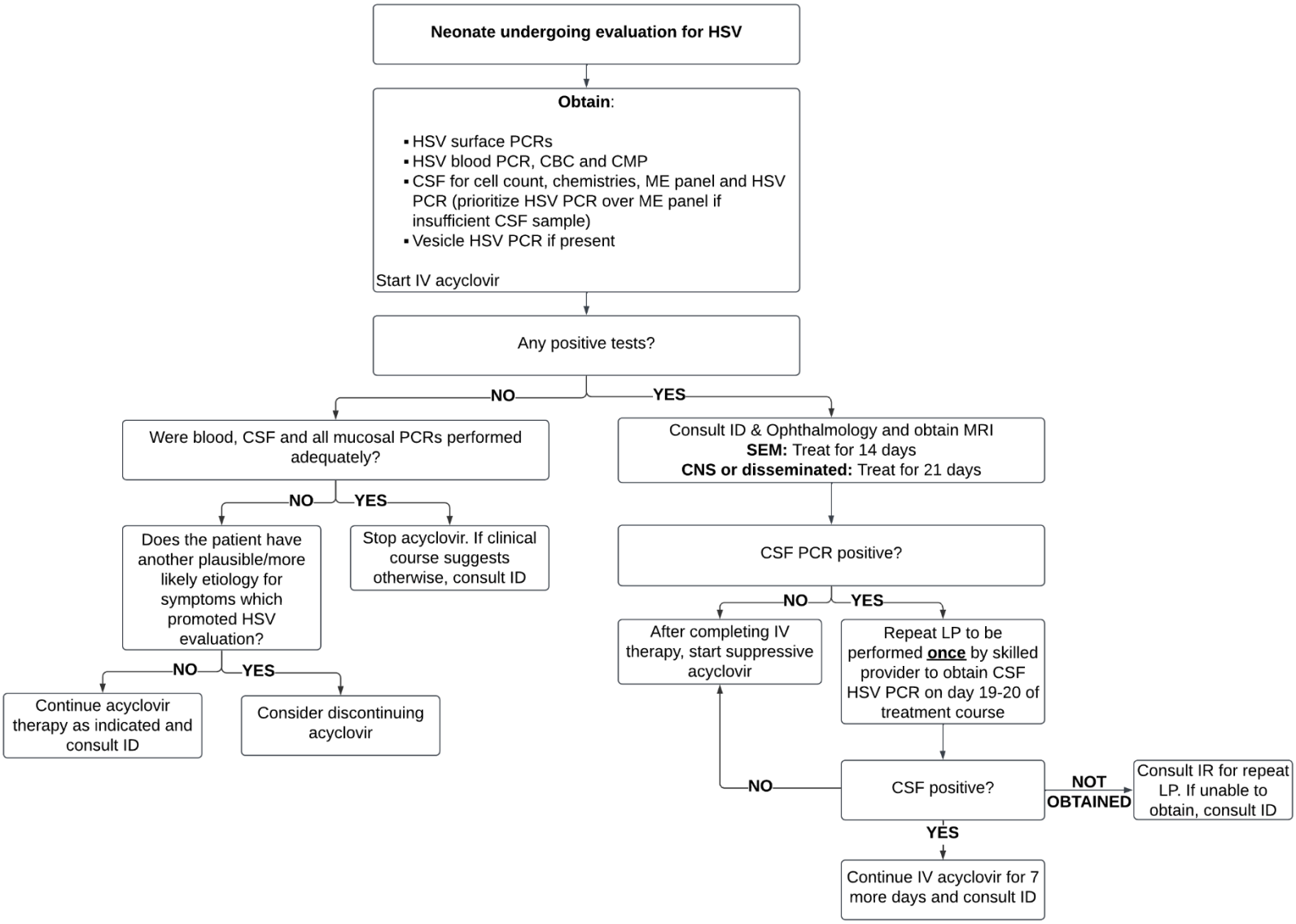
¥ Infants managed with 10 days of preemptive antiviral therapy should not subsequently receive oral acyclovir suppression since their HSV exposure never progressed to infection or disease

Figure 3. Evaluation of ASYMPTOMATIC infants born to mothers with a documented history of first-episode primary or nonprimary HSV infection during the third trimester and no HSV genital lesions at delivery



Education of parents and caregivers about the signs and symptoms of neonatal HSV infection during the first 6 weeks of life is prudent. Please educate the family on the importance of contacting their doctor if there are any signs of HSV infection including fever (100.4 ºF rectally), poor feeding, irritability, skin rash, seizures, increased work of breathing, cyanosis, apnea, jaundice, easy bleeding. All caregivers who touch the newborn should wash their hands thoroughly with soap and water beforehand. All newborns should follow up with their pediatrician within 1-3 days of discharge and at regularly defined intervals, per the pediatrician.

Figure 4. Algorithm for the evaluation of infants undergoing herpes evaluation during NICU stay



References:

1. Kimberlin DW, Baley J, et al. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics 2013;131: 383-6.
2. Mahant S, Hall M, Schondelmeyer AC, et al. Neonatal Herpes Simplex Virus Infection Among Medicaid-Enrolled Children: 2009-2015. Pediatrics 2019
3. Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med 1997;337: 509-15.
4. 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: 230-8
5. Kimberlin DW. Herpes simplex virus infections of the newborn. Semin Perinatol 2007; 31:19-25
6. Kimberlin DW. Neonatal herpes simplex infection. Clin Microbiol Rev. 2004 Jan;17(1):1-13.
7. Looker KJ, Magaret AS, May MT, Turner KME, Vickerman P, Gottlieb SL, et al. (2015) Global and Regional Estimates of Prevalent and Incident Herpes Simplex Virus Type 1 Infections in 2012. PLoS ONE 10(10): e014076
8. Lafferty WE, Downey L, Celum C, Wald A. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. *J Infect Dis* 2000; 181: 1454–7.
9. Xu F, Schillinger JA, Sternberg MR, Johnson RE, Lee FK, Nahmias AJ, *et al.* Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988–1994. *J Infect Dis* 2002; 185: 1019–24.
10. Wald A, Zeh J, Selke S, Ashley RL, Corey L. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med* 1995; 333: 770–5.
11. Engelberg R, Carrell D, Krantz E, Corey L, Wald A. Natural history of genital herpes simplex virus type 1 infection. *Sex Transm Dis* 2003; 30: 174–7.
12. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003; 289: 203–9.
13. Samies NL, James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Disease: Updates and Continued Challenges. Clin Perinatol. 2021 Jun;48(2):263-274.
14. Hensleigh PA, Andrews WW, Brown Z, Greenspoon J, Yasukawa L, Prober CG. Genital herpes during pregnancy: inability to distinguish primary and recurrent infections clinically. Obstet Gynecol. 1997 Jun;89(6):891-5.
15. Allen UD, Robinson JL, Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Prevention and management of neonatal herpes simplex virus infections. Paediatr Child Health 2014;19:201-12.
16. De Rose DU, Bompard S, Maddaloni C, Bersani I, Martini L, Santisi A, Longo D, Ronchetti MP, Dotta A, Auriti C. Neonatal herpes simplex virus infection: From the maternal infection to the child outcome. J Med Virol. 2023 Aug;95(8): e29024
17. Kimberlin DW, Whitley RJ. Neonatal Herpes: What we have learned. Sem Ped Infect Dis. 2005; 16 (1): 7-16.

18. 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; 324:1247-52.
19. Melvin AJ, Mohan KM, Vora SB, Selke S, Sullivan E, Wald A. Neonatal Herpes Simplex Virus Infection: Epidemiology and Outcomes in the Modern Era. J Pediatric Infect Dis Soc. 2022 Mar 24;11(3):94-101.
20. Scott H. James, Jeanne S. Sheffield, David W. Kimberlin, Mother-to-Child Transmission of Herpes Simplex Virus, *Journal of the Pediatric Infectious Diseases Society*, Volume 3, Issue suppl_1, September 2014, Pages S19–S23.
21. Johnston C, Magaret A, Selke S, Remington M, Corey L, Wald A. Herpes simplex virus viremia during primary genital infection. J Infect Dis 2008;198: 31-4.
22. Brown ZA, Benedetti J, Selke S, Ashley R, Watts DH, Corey L. Asymptomatic maternal shedding of herpes simplex virus at the onset of labor: relationship to preterm labor. Obstet Gynecol 1996;87: 483-8.
23. Nahmias AJ, Josey WE, Naib ZM, Freeman MG, Fernandez RJ, Wheeler JH. Perinatal risk associated with maternal genital herpes simplex virus infection. Am J Obstet Gynecol 1971;110: 825-37.
24. Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. N Engl J Med 1987; 317:1246-51.
25. Z.A. Brown, A. Wald, R.A. Morrow, *et al.* Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant JAMA, 289 (2003), pp. 203-209.
26. Brown EL, Gardella C, Malm G, Prober CG, Forsgren M, Krantz EM, Arvin AM, Yasukawa LL, Mohan K, Brown Z, Corey L, Wald A. Effect of maternal herpes simplex virus (HSV) serostatus and HSV type on risk of neonatal herpes. Acta Obstet Gynecol Scand. 2007;86(5):523-9.
27. Nahmias AJ, Josey WE, Naib ZM, Freeman MG, Fernandez RJ, Wheeler JH. Perinatal risk associated with maternal genital herpes simplex virus infection. American Journal of Obstetrics and Gynecology 1971; 10 (6): 825-837.
28. Curfman et al. J Pediatric 2016 May; 172:121-126.e1
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: 556-61.
30. Cruz AT, Freedman SB, Kulik DM, et al. Herpes Simplex Virus Infection in Infants Undergoing Meningitis Evaluation. Pediatrics 2018; 141:1688. Epub 2018 Jan 3.
31. Wald A, Huang ML, Carrell D, Selke S, Corey L. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. J Infect Dis 2003;188: 1345 -51.
32. Frenkel LM. Challenges in the diagnosis and management of neonatal herpes simplex virus encephalitis. Pediatrics 2005;115: 795-7.
33. American Academy of Pediatrics, Committee on Infectious Diseases Herpes simplex virus. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH. *Red Book: 2021-2024 Report of the Committee on Infectious Diseases*. 32th ed. American Academy of Pediatrics; 2021;407-417.

34. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 2001;108: 223-9.
35. Kimberlin DW. Neonatal herpes simplex infection. Clin Microbiol Rev 2004; 17:1-13.
36. Toth C, Harder S, Yager J. Neonatal herpes encephalitis: a case series and review of clinical presentation. Can J Neurol Sci 2003;30: 36-40.
37. Melvin AJ, Mohan KM, Schiffer JT, et al. Plasma and cerebrospinal fluid herpes simplex virus levels at diagnosis and outcome of neonatal infection. J Pediatr 2015;166: 827-33.
38. Kimura H, Futamura M, Kito H, 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.
39. Nolt D, O'Leary ST, Aucott SW; American Academy of Pediatrics, Committee on Infectious Diseases, Committee on Fetus and Newborn. Risks of infectious diseases in newborns exposed to alternative perinatal practices. Pediatrics. 2022;149(2): e2021055554
40. American Academy of Pediatrics. Report of the Committee on infectious diseases. Herpes simplex. Red Book. 2024-2027; pp467-478.
41. Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med 1997;337: 509-15.
42. 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: 230-8
43. Kimberlin DW. Herpes simplex virus infections of the newborn. Semin Perinatol 2007; 31:19-25
44. Kimberlin DW. Neonatal herpes simplex infection. Clin Microbiol Rev. 2004 Jan;17(1):1-13.
45. Looker KJ, Magaret AS, May MT, Turner KME, Vickerman P, Gottlieb SL, et al. (2015) Global and Regional Estimates of Prevalent and Incident Herpes Simplex Virus Type 1 Infections in 2012. PLoS ONE 10(10): e014076
46. Lafferty WE, Downey L, Celum C, Wald A. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. *J Infect Dis* 2000; 181: 1454–7.
47. Xu F, Schillinger JA, Sternberg MR, Johnson RE, Lee FK, Nahmias AJ, *et al.* Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988–1994. *J Infect Dis* 2002; 185: 1019–24.
48. Wald A, Zeh J, Selke S, Ashley RL, Corey L. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med* 1995; 333: 770–5.
49. Engelberg R, Carrell D, Krantz E, Corey L, Wald A. Natural history of genital herpes simplex virus type 1 infection. *Sex Transm Dis* 2003; 30: 174–7.
50. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003; 289: 203–9.
51. Samies NL, James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Disease: Updates and Continued Challenges. Clin Perinatol. 2021 Jun;48(2):263-274.

52. Hensleigh PA, Andrews WW, Brown Z, Greenspoon J, Yasukawa L, Prober CG. Genital herpes during pregnancy: inability to distinguish primary and recurrent infections clinically. Obstet Gynecol. 1997 Jun;89(6):891-5.
53. Allen UD, Robinson JL, Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Prevention and management of neonatal herpes simplex virus infections. Paediatr Child Health 2014;19:201-12.
54. De Rose DU, Bompard S, Maddaloni C, Bersani I, Martini L, Santisi A, Longo D, Ronchetti MP, Dotta A, Auriti C. Neonatal herpes simplex virus infection: From the maternal infection to the child outcome. J Med Virol. 2023 Aug;95(8): e29024
55. Kimberlin DW, Whitley RJ. Neonatal Herpes: What we have learned. Sem Ped Infect Dis. 2005; 16 (1): 7-16.
56. 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; 324:1247-52.
57. Melvin AJ, Mohan KM, Vora SB, Selke S, Sullivan E, Wald A. Neonatal Herpes Simplex Virus Infection: Epidemiology and Outcomes in the Modern Era. J Pediatric Infect Dis Soc. 2022 Mar 24;11(3):94-101.
58. Scott H. James, Jeanne S. Sheffield, David W. Kimberlin, Mother-to-Child Transmission of Herpes Simplex Virus, *Journal of the Pediatric Infectious Diseases Society*, Volume 3, Issue suppl_1, September 2014, Pages S19–S23.
59. Johnston C, Magaret A, Selke S, Remington M, Corey L, Wald A. Herpes simplex virus viremia during primary genital infection. J Infect Dis 2008;198: 31-4.
60. Brown ZA, Benedetti J, Selke S, Ashley R, Watts DH, Corey L. Asymptomatic maternal shedding of herpes simplex virus at the onset of labor: relationship to preterm labor. Obstet Gynecol 1996;87: 483-8.
61. Nahmias AJ, Josey WE, Naib ZM, Freeman MG, Fernandez RJ, Wheeler JH. Perinatal risk associated with maternal genital herpes simplex virus infection. Am J Obstet Gynecol 1971;110: 825-37.
62. Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. N Engl J Med 1987; 317:1246-51.
63. Z.A. Brown, A. Wald, R.A. Morrow, *et al.* Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant JAMA, 289 (2003), pp. 203-209.
64. Brown EL, Gardella C, Malm G, Prober CG, Forsgren M, Krantz EM, Arvin AM, Yasukawa LL, Mohan K, Brown Z, Corey L, Wald A. Effect of maternal herpes simplex virus (HSV) serostatus and HSV type on risk of neonatal herpes. Acta Obstet Gynecol Scand. 2007;86(5):523-9.
65. Nahmias AJ, Josey WE, Naib ZM, Freeman MG, Fernandez RJ, Wheeler JH. Perinatal risk associated with maternal genital herpes simplex virus infection. American Journal of Obstetrics and Gynecology 1971; 10 (6): 825-837.
66. Curfman et al. J Pediatric 2016 May; 172:121-126.e1
67. 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: 556-61.

68. Cruz AT, Freedman SB, Kulik DM, et al. Herpes Simplex Virus Infection in Infants Undergoing Meningitis Evaluation. Pediatrics 2018; 141:1688. Epub 2018 Jan 3.
69. Wald A, Huang ML, Carrell D, Selke S, Corey L. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. J Infect Dis 2003;188: 1345 -51.
70. Frenkel LM. Challenges in the diagnosis and management of neonatal herpes simplex virus encephalitis. Pediatrics 2005;115: 795-7.
71. American Academy of Pediatrics, Committee on Infectious Diseases Herpes simplex virus. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH. *Red Book: 2021-2024 Report of the Committee on Infectious Diseases*. 32th ed. American Academy of Pediatrics; 2021;407-417.
72. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 2001;108: 223-9.
73. Kimberlin DW. Neonatal herpes simplex infection. Clin Microbiol Rev 2004; 17:1-13.
74. Toth C, Harder S, Yager J. Neonatal herpes encephalitis: a case series and review of clinical presentation. Can J Neurol Sci 2003;30: 36-40.
75. Melvin AJ, Mohan KM, Schiffer JT, et al. Plasma and cerebrospinal fluid herpes simplex virus levels at diagnosis and outcome of neonatal infection. J Pediatr 2015;166: 827-33.
76. Kimura H, Futamura M, Kito H, 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.
77. Nolt D, O'Leary ST, Aucott SW; American Academy of Pediatrics, Committee on Infectious Diseases, Committee on Fetus and Newborn. Risks of infectious diseases in newborns exposed to alternative perinatal practices. Pediatrics. 2022;149(2): e2021055554
78. American Academy of Pediatrics. Report of the Committee on Infectious Diseases. Herpes simplex. Red Book. 2024-2027; pp467-478.

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Neonatal Herpes Simplex Virus Infection Evaluation and Management Clinical Pathway

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