JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Neonatal Herpes Simplex Virus Clinical Pathway

JOHNS HOPKINS
All Children's Hospital

Johns Hopkins All Children's Hospital

Neonatal Herpes Simplex Virus (HSV) Clinical Pathway

Table of Contents

Updated January 16th, 2020
Owner: Juan Dumois, MD

Johns Hopkins All Children's Hospital

Neonatal Herpes Simplex Virus (HSV) Clinical Pathway

Rationale

This protocol was agreed upon by a consensus group of JHACH physicians to standardize the management of neonates outside of the neonatal intensive care unit (NICU) who are being evaluated for Herpes Simplex Virus. It addresses the following clinical questions or problems:

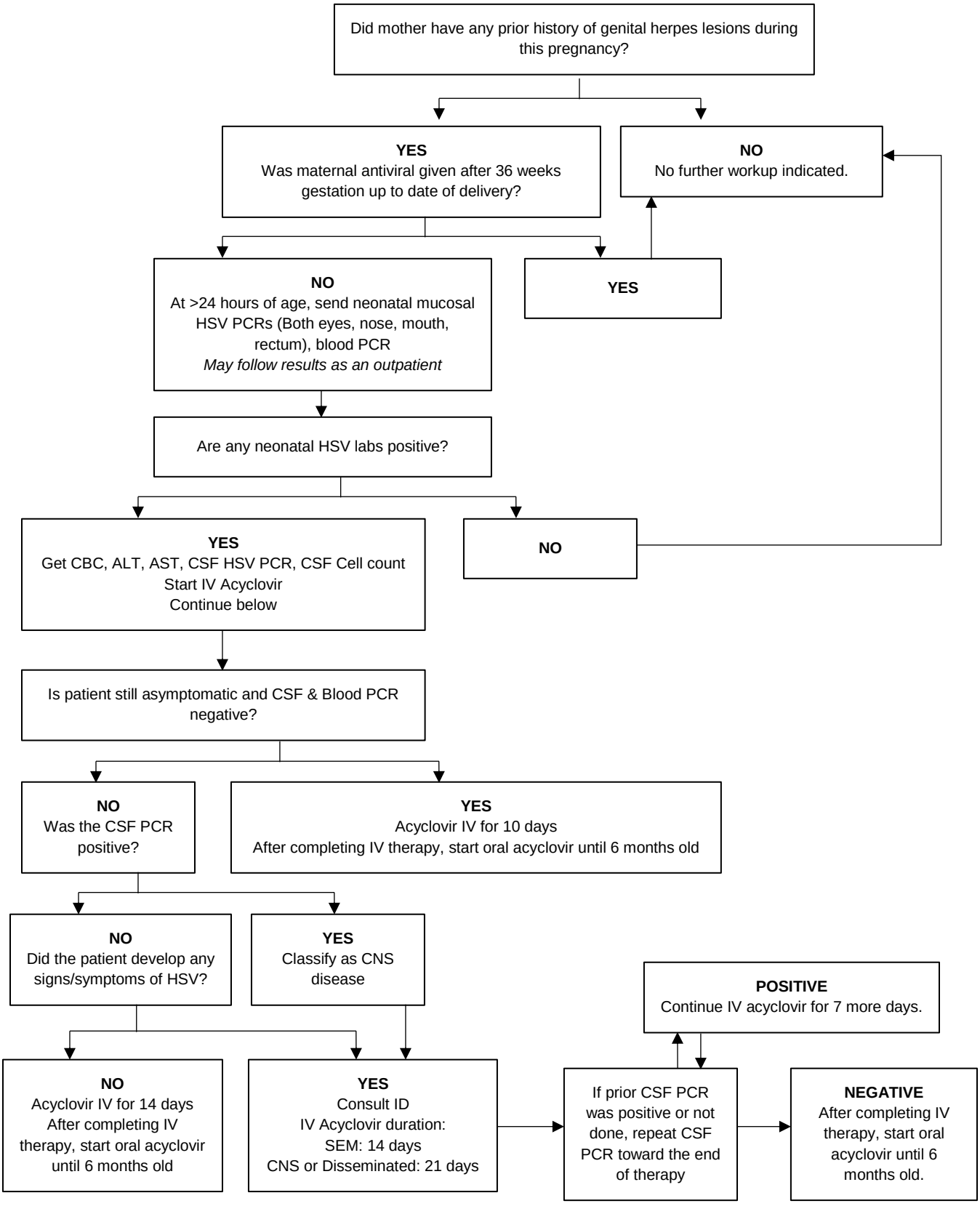
1. Evaluation of the asymptomatic neonate with maternal history of HSV
2. Evaluation of the symptomatic neonate with concern for HSV
3. When are HSV CSF studies best obtained?
4. When is it appropriate to empirically treat neonates for HSV while awaiting results?
5. Duration of treatment

(For HSV evaluation of NICU patients, please refer to the Johns Hopkins All Children's Hospital NICU Neonatal HSV Clinical Pathway)

Johns Hopkins All Children's Hospital

Asymptomatic Neonate, Maternal Genital HSV Lesions NOT Present At Delivery

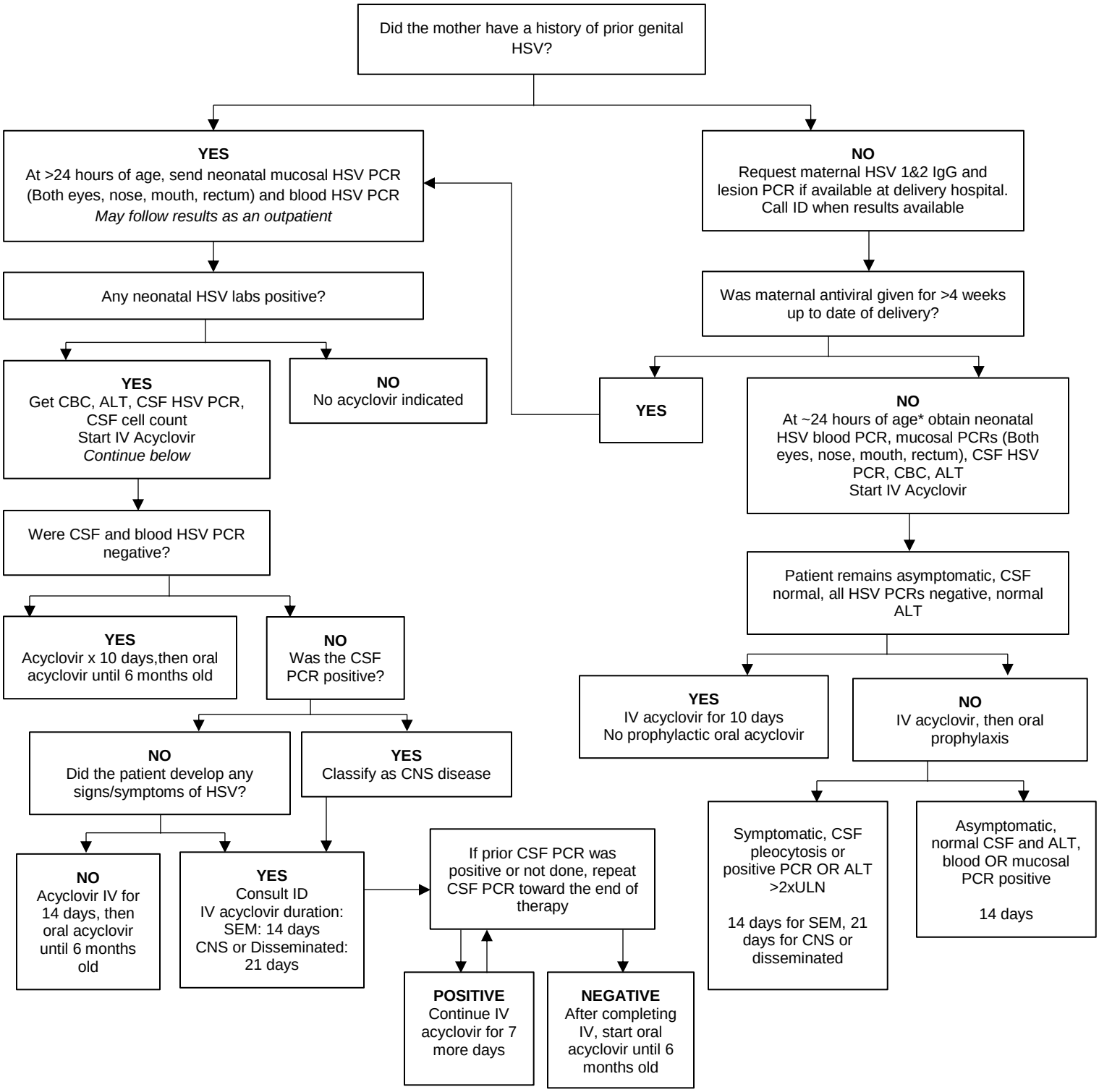
(Figure 1)



Johns Hopkins All Children's Hospital

Asymptomatic Neonate, Maternal Genital HSV Lesions WERE Present At Delivery

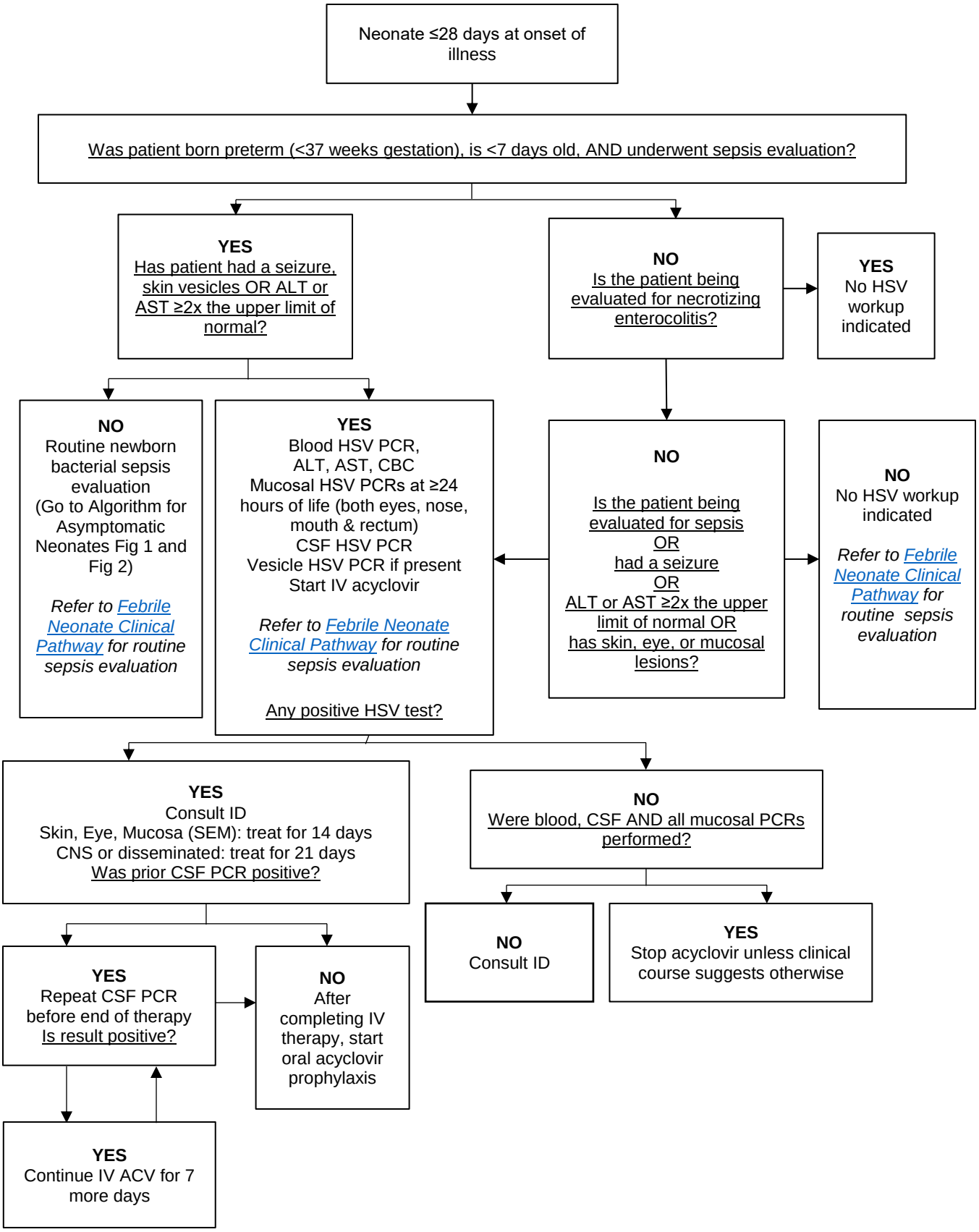
(Figure 2)



Johns Hopkins All Children's Hospital

HSV Evaluation of the Symptomatic Neonate

(Figure 3)



Background

Neonatal HSV (NHSV) infection affects approximately 1500 infants yearly (1, Kimberlin). Intrauterine infections account for less than 5% of cases with intrapartum acquisition accounting for >75% of cases. Of mothers who are seropositive for HSV-2, the majority are unaware of their infection. Studies have shown that 10-20% of women intermittently shed the virus. Caesarean section deliveries reduce the risk compared to vaginal deliveries but does not eliminate the risk for newborns (3, Upton) [Evidence level 5a, strongly recommended].

Infants born to mothers who have first time infection at the time of delivery are at greatest risk of NHSV infection with transmission rates up to 60%. HSV-neutralizing antibodies are produced by mothers and transmitted to the infant across the placenta after 32 weeks' gestation. First episode, non-primary infection maternal HSV infection results in vertical transmission of 30% of their infants. Infants born to mothers with recurrent infections have the lowest transmission risk at less than 2%, due to lower viral loads and the presence of passively acquired, type-specific HSV antibodies in the infant. (3, Upton)

Definitions

SEM infection: infection is localized to skin, eye, or mucosa (mouth or rectum) only
Disseminated disease: disease involving liver or lungs
CNS disease: manifests as seizures, CSF pleocytosis, or positive CSF HSV PCR
Symptomatic newborn: any neonate who present for evaluation of any symptom that warrants any testing for infection

<u>Definition of maternal infections:</u>
First episode primary infection- new infection with lesions, mother has no serum HSV antibodies
First episode nonprimary infection- new infection, mother has antibodies to other HSV type
Recurrent infection- mother has antibodies to the same HSV type as the cause of the current genital infection. (3, Upton)

Presentation

Infections typically present in the first 4 week of life but can present for the first time up to 6 weeks after birth. Classifications of infections are in 3 categories: skin, eye, mucous membrane infection (SEM); disseminated infection; and central nervous system infection. Presentation can be nonspecific in the absence of skin lesions. 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. (2, Long)

Which Neonates Should be Evaluated for HSV?

Symptomatic neonates up to 28 days of age should be evaluated for HSV if they present with a seizure, skin vesicles, elevated transaminases (2X the ULN), or for sepsis evaluation (including any bacterial cultures). [Evidence level 3a, strongly recommended]

Asymptomatic neonates up to 28 days of age should be evaluated for HSV according to the algorithm if the mother has genital herpes any time during the current pregnancy or delivery. [Evidence level 1a, strongly recommended]

Diagnostic Testing

Skin vesicles, conjunctiva or oral ulcers: swab for HSV culture and/or PCR. At JHACH, the PCR will generally provide faster results than HSV culture. [Evidence level 2a, strongly recommended]

Blood: HSV DNA PCR is the test of choice. A positive PCR is NOT evidence of disseminated disease, since some patients with clinical SEM disease may have a positive blood PCR. Order ALT and AST, and chest xray if indicated, for evidence of disseminated disease. [Evidence level 2a, strongly recommended]

CSF: HSV DNA PCR is the test of choice. HSV culture has very poor sensitivity and should not be ordered. [Evidence level 2a, strongly recommended]

Mucosal (surface) testing: The gold standard had been viral culture, but cultures can take up to 5 days to achieve a positive result, prolonging the duration of therapy for negative results. The yield on mucosal HSV cultures is higher if the specimens are collected at > 24 hours of age. (2, Long) [Evidence level 3a, strongly recommended]

HSV DNA PCR on mucosal specimens is more sensitive than HSV culture in adults, but such data is not available for neonates. (4, Wald) However, anecdotal information suggests that PCR is more sensitive than viral culture in neonates. In 2019, the AAP Committee on Infectious Diseases suggested for the first time in the Red Book that either HSV culture or PCR may be performed on mucosal swabs. Therefore, we recommend that PCR alone should be performed on mucosal swabs. [Evidence level 5, recommended] Five swabs should be obtained from left and right eyes, nose, mouth, and rectum and placed into a single viral transport tube and sent for HSV DNA PCR. 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.”

Management

Acyclovir Dose and Route
Because of poor oral bioavailability, neonatal herpes must be treated with intravenous (IV) acyclovir at a dose of 60 mg/kg/day divided every 8 hours. Doses should be adjusted for renal impairment.

If acyclovir is not available, use ganciclovir IV 6 mg/kg/dose every 12 hours.

Asymptomatic infant with Negative Studies
For asymptomatic infants whose HSV tests remain negative, 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 family prior to discharge. [Evidence level 1a, strongly recommended]

SEM Infection
For asymptomatic infants with any positive mucosal HSV studies and with negative CSF and blood PCR, IV acyclovir should be continued for a total of 10 days. [Evidence level 5a, strongly recommended]

SEM Disease
Infants with SEM disease and no evidence of CNS infection should be given IV acyclovir for 14 days, regardless of whether the blood PCR is positive or negative. [Evidence level 5a, strongly recommended]

Asymptomatic Newborns, Blood PCR positive
For asymptomatic infants with positive blood PCR and negative CSF PCR, IV acyclovir should be continued for a total of 14 days. [Evidence level 5a, strongly recommended]

Symptomatic Newborns
Symptomatic newborns with positive surface or blood PCR (and negative CSF PCR) should be treated with IV acyclovir for 14 days. [Evidence level 5a, strongly recommended]

Disseminated Disease
For disseminated disease, the duration of IV acyclovir therapy should be for 21 days. [Evidence level 5a, strongly recommended]

CNS Disease
In patients with seizures or positive CSF HSV PCR, IV acyclovir therapy should be continued for 21 days. For any infant whose initial CSF PCR is positive, a repeat lumbar puncture for CSF PCR should be repeated prior to the end of IV therapy (e.g. day 19-20) to confirm clearance of the virus. If the repeat CSF PCR is positive, IV acyclovir should be continued for 7 more days and the CSF PCR testing repeated weekly until CSF PCR is negative. When a repeat CSF PCR is negative, the IV acyclovir may be stopped. [Evidence level 5a, strongly recommended]

Incomplete Evaluation
If all indicated blood, CSF, or mucosal HSV studies were not performed during evaluation, we recommend consulting the Infectious Disease Service to determine the best duration of IV acyclovir. When an initial evaluation is performed at a referring hospital prior to transfer to JHACH, it is acceptable to recommend starting acyclovir before transfer because it will not affect the results of blood or CSF PCR collected at JHACH after transfer. If CSF is collected at another institution that cannot perform HSV PCR in house, please request that the remaining CSF be sent with the patient in order to be tested at JHACH. [Evidence level 5, recommended]

Suppressive therapy
Suppressive therapy with oral acyclovir until 6 months of age is recommended for all infants who received a 10-21 day course of IV acyclovir. The oral acyclovir dose is 300 mg/m2/dose TID. [Evidence level 5a, strongly recommended]

References

1. Kimberlin, D. et al. Guidance on Management of Asymptomatic Neonates Born to Women with Active Genital Herpes lesions. Pediatrics 2013;131(2):e635-646.

2. Long, SS. et al. Herpes Simplex Virus Infection in Young Infants During 2 decades of Empiric Acyclovir Therapy. The Pediatric Infectious Disease Journal 2011:30(7): 556-561.

3. Upton, A. Et al. Prevention and management of neonatal herpes simplex virus infections. Paediatr Child Health 2014;19(4):201-206.

4. Wald A, et al. Polymerase Chain Reaction for Detection of Herpes Simplex Virus (HSV) DNA on Mucosal Surfaces: Comparison with HSV Isolation in Cell Culture. Journal of Infectious Diseases 2003;188:1345-51.

Table of Evidence Levels (see note above)

Quality level	*Definition*
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5a or 5b	Other: General review, expert opinion, case report, consensus report, or guideline
5	Local Consensus

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

Strength	*Definition*
"Strongly recommended"	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient *(direct benefit)*
4. Burden to patient of adherence to recommendation *(cost, hassle, discomfort, pain, motivation, ability to adhere, time)*
5. Cost-effectiveness to healthcare system *(balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis)*
6. Directness *(the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome])*
7. Impact on morbidity/mortality or quality of life

Clinical Pathway Team

Neonatal HSV Clinical Pathway

Johns Hopkins All Children's Hospital

Owner(s): Juan Dumois, MD

Other Stakeholder Reviewers:

Hospitalist: John Morrison, MD, PhD

Emergency Medicine: Courtney Titus, PA-C

Clinical Pathway Management Team: Joseph Perno, MD; Courtney Titus, PA-C

Date Approved by JHACH Clinical Practice Council: June 25th, 2017

Date Available on Webpage: June 28th, 2017

Last Revised: January 15th, 2020

Disclaimer

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

The information and guidelines are provided "AS IS" without warranty, express or implied, and Johns Hopkins All Children's Hospital, Inc. hereby excludes all implied warranties of merchantability and fitness for a particular use or purpose with respect to the information. Johns Hopkins All Children's Hospital, Inc. shall not be liable for direct, indirect, special, incidental or consequential damages related to the user's decision to use the information contained herein.