# Evaluation for HSV infection in infants with suspected sepsis (After hospital discharge and up to 6 weeks of age)

**PURPOSE:**
The purpose of this guideline is to standardize the workup/management for HSV of infants less than 6 weeks of age at SJCH. In cases where there is significant exam or laboratory evidence to suggest neonatal HSV disease, continue acyclovir and contact the infectious disease team. This guideline should be viewed as independent of decisions made about testing and empiric treatment for serious bacterial infections or other neonatal infections (e.g. adenovirus, TORCH infections).

**PATIENT POPULATION:**
This guideline includes all infants < 6 weeks of age (including late preterm) who were discharged to home after birth and required evaluation for rule-out sepsis.

**BACKGROUND:**
Neonates can acquire HSV infection during birth from an infected maternal genital tract or after birth from a caregiver who is shedding the HSV virus (cold sore or herpetic whitlow). Over 75% of neonates with HSV infection are born to mothers without symptoms or previous history of HSV infection[(1).] Neonatal HSV has high mortality and morbidity, even with the proper treatment.

**Timing:** Neonatal HSV infection can present anytime between birth and 6 weeks of age; although almost all infected infants develop clinical disease within the 1st month of life. Disseminated and SEM disease usually presents earlier in the first 2 weeks of life. CNS disease presents between 2-3 weeks of life.

Infants born to mothers treated with Valacyclovir during pregnancy may present with HSV at an older age

**Clinical Presentation:** HSV infection should be considered in neonates with fever (especially within the first 3 weeks of life), changes in behavior, seizures, vesicular rash, abnormal CSF findings, or focal neurologic findings.

Neonatal HSV infections are divided into 3 categories, with SEM disease being the most common:

- Disseminated disease (involving liver, lungs, and other organ systems, including CNS). More likely to present with “non-specific” symptoms such as fever, hypothermia, fussiness or lethargy ~ 25%
- Localized CNS disease (can also involve the skin). Typically present with “classic” HSV symptoms such as seizures and lesions. ~30%
- Disease only found in skin, eye, and/or mouth (SEM disease) ~ 45%.

More than 80% of neonates with SEM have skin vesicles; Approx. 2/3 of neonates with disseminated or CNS disease have skin lesions but these might not be present at the time of onset of symptoms.

**EVALUATION & MANAGEMENT:**

**Labs/Studies:** The following tests should be sent:

- Surface culture swabs from mouth, nasopharynx, conjunctivae, and anus for HSV culture (if available) or PCR
- Fluid from any vesicular lesions for HSV culture (if available) or HSV PCR
- CSF for HSV PCR
- Blood HSV PCR

- Liver alanine transaminase – ALT
- CXR

HSV PCRs may be obtained even if acyclovir has already been started. The purpose of the blood HSV PCR is to identify patients with viremia, which is thought to occur in **all** patients with disseminated disease. There is evidence that neonates with SEM and CNS disease may also have viremia at some point during their illness.

In cases where the clinician is unable to properly evaluate for pleocytosis (i.e. unable to obtain LP, uninterpretable due to many RBCs), we recommend testing for HSV and empiric treatment as outlined in flowchart. A repeat LP attempt is often necessary. An infectious diseases consult should be considered in these cases.

Other supportive treatments should be given as needed to manage fluid & electrolyte imbalances, hypoglycemia, seizure, respiratory distress or DIC

**REFERENCES:**

1. American Academy of Pediatrics. Herpes Simplex. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2018: 437-449.

2. Kimberlin, David W. et al. “Guidance on Management of Asymptomatic Neonates Born to Women With Active Genital Herpes Lesions.” *Pediatrics* 131.2 (2013): e635–e646. *PMC*. Web. 17 Feb. 2017.

3. D. W. Kimberlin, C. Y. Lin, R. F. Jacobs et al., “Natural history of neonatal herpes simplex virus infections in the acyclovir era,” Pediatrics,vol.108,no. 2, pp.223–229,2001.

4. Kestenbaum LA, Ebberson J, Zorc JJ, Hodinka RL, Shah SS. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. Pediatrics. 2010;125(2):2

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# Evaluation for HSV infection in infants with suspected sepsis

Is the patient critically ill? (hypotension, respiratory failure, poor perfusion, obtunded/comatose without immediate alternative explanation)

Yes

No

If **alternate diagnosis** is identified while evaluation in process→ **Consider discontinuing work up and Acyclovir therapy**

**Inclusion Criteria**: All infants (**up to 6 weeks of age**) who were discharged home after birth and require sepsis evaluation

**Exclusion Criteria**: NICU or nursery status after birth

Is the patient age

**3 weeks** or younger?
[2,3]

Yes

No

**HSV Work up: (Obtain all labs)**

- CSF Meningitis/Encephalitis Panel
- Blood HSV PCR
- HSV Culture from any skin, eye or mouth lesions concerning for HSV
- Surface swab Culture: if < 3 weeks old (same swab starting from conjunctiva, mouth, nasopharynx and anus)
- ALT [1]
- CXR if disseminated disease, liver disease or respiratory sym/signs
- IV Acyclovir 20 mg/kg/dose q 8 hrs

Complete High Risk Checklist →

**High Risk Checklist**

| Yes | No | |
|---|---|---|
| O | O | Close contact with active cold sores? |
| O | O | History of seizures or seizures during the evaluation? |
| O | O | Vesicles or crusted lesions on skin exam (Including scalp, eye or mouth) [3]? |
| O | O | Elevated transaminases? |
| O | O | Thrombocytopenia? |
| O | O | CSF pleocytosis? (WBC >19 in neonates 0-28 days, and WBC >9 in infants 29-56 days) [4] |

**If any "yes" proceed to High Risk recommendations**

Yes

High risk?

No

**Consider discontinuing Acyclovir if:**

- CSF PCR is positive for other virus (enterovirus or parechovirus)
- If there is no evidence of CNS, SEM or disseminated disease:
  - Negative Blood and CSF HSV PCR
  - Negative HSV culture from any lesion/Surface swab
  - No evidence of severe illness based on serial exams
- If alternate etiology is identified

**If testing positive:**

- Consult Pediatric ID for length of therapy and to ensure outpatient follow up.
- Consult ophthalmology
- Obtain neuroimaging, MRI preferred, CT and head US are alternatives

Do not initiate work up for HSV **and** do not give acyclovir
Consider other causes for fever

HSV Protocol

**Evaluation for HSV infection in infants with suspected sepsis**

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- Over 75% of neonates with HSV infection are born to mothers without symptoms or previous history of HSV infection.

- Neonatal HSV infection can present anytime between birth and 6 weeks of age; although almost all infected infants develop clinical disease within the 1st month of life. Disseminated and SEM disease usually presents earlier in the first 2 weeks of life. CNS disease presents between 2-3 weeks of life. Infants born to mothers treated with Valacyclovir during pregnancy may present with HSV at an older age.

- HSV infection should be considered in neonates with fever, changes in behavior, seizures, vesicular rash, abnormal CSF findings, or focal neurologic findings.

- More than 80% of neonates with SEM have skin vesicles; Approx. 2/3 of neonates with disseminated or CNS disease have skin lesions but these might not be present at the time of onset of symptoms.

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[1] Transaminase levels are usually elevated with disseminated disease. Although there are many causes of elevated transaminases in the newborn, elevations of ALT in an ill newborn should raise additional concern for disseminated HSV.

[2] The guideline's age cutoff is derived from published literature that suggests that neonates with HSV whose illness onset occurs > 14 days of age typically present with "classic" HSV symptoms such as seizures or skin, eye or mouth disease (SEM disease). Neonates whose illness onset begins ≤ 14 days of age are more likely to present with "non-specific" symptoms such as fever, hypothermia, fussiness or lethargy.

[3] The age cut-offs used in this guideline do not apply to neonates born prematurely. Infants born to mothers treated with valacyclovir during pregnancy may present with HSV at an older age.

[4] Skin vesicles or ulcers, mouth vesicles or ulcers, excessive tearing, or conjunctivitis (if not clearly related to *N. gonorrhea Chlamydia*, or other known cause).

[5] Monocytic pleocytosis is not always present in neonatal HSV. RBCs in the CSF are not significantly associated with HSV CNS disease, and are more likely to result from a traumatic tap.