Neonatal HSV

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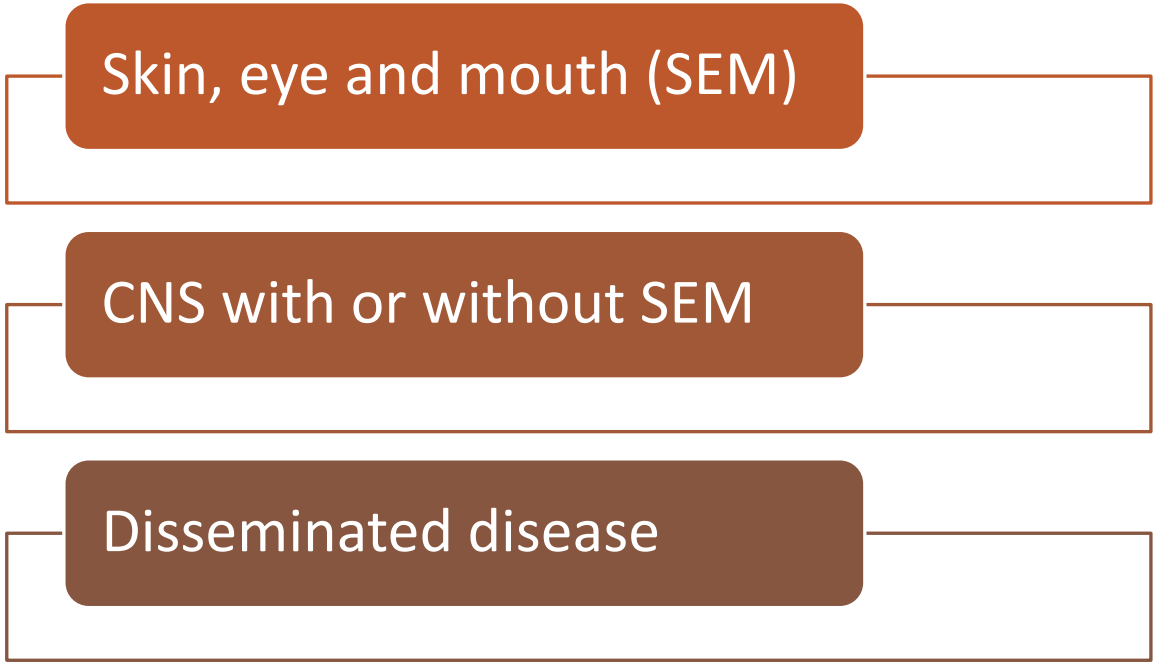
Vertical Transmission

Key Principles

- Most mothers of newborns with perinatally-acquired HSV infection lack a history of clinically evident genital herpes
- Highest risk factor for infection occurs in women with a **primary** genital HSV infection acquired near the time of delivery. The risk is slightly lower in women with a **non-primary first-episode** genital infection, and substantially reduced in women with **recurrent** HSV
- Viral shedding can occur in the absence of maternal symptoms and lesions
- The frequency of viral shedding is higher in HSV-2 versus HSV -1, yet clinical management of the pregnancy is not influenced by the type

Clinical Manifestations

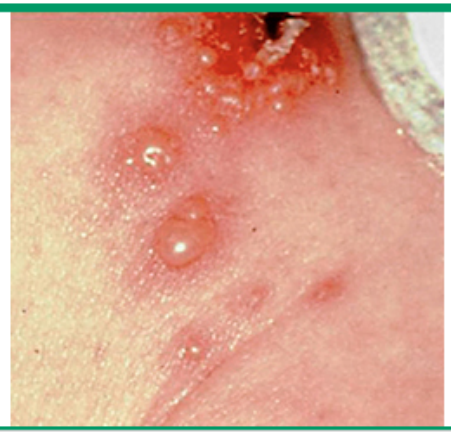
Can be categorized into three main categories for therapeutic and prognostic considerations:



Skin, Eye, and Mouth Disease

- Accounts for approximately 45% of neonatal HSV
- May appear benign at onset of illness, but is associated with a high risk of progression to CNS or disseminated disease if not treated
- Typically presents in the first **2 weeks** of life but may occur at any time during the first **6 weeks**
- Localized skin disease: coalescing or clustering vesicular lesions with an erythematous base that may begin or cluster at the presenting part of the body or at sites of trauma (such as a scalp monitor site)

Neck vesicles in neonate with herpes simplex virus infection



The early, untreated skin lesions associated with neonatal herpes simplex virus (HSV) infection are characteristically clear vesicles on an erythematous base, often touching or "kissing," or coalesced in groups of vesicles. Culture of the clear fluid aspirated or swabbed from the vesicles will readily grow HSV in 24 to 48 hours, and slides made from cells scraped from the base of the lesion will show HSV viral antigens by direct immunofluorescence assay (DFA).

Courtesy of Gail J Demmler-Harrison, MD, Texas Children's Hospital.

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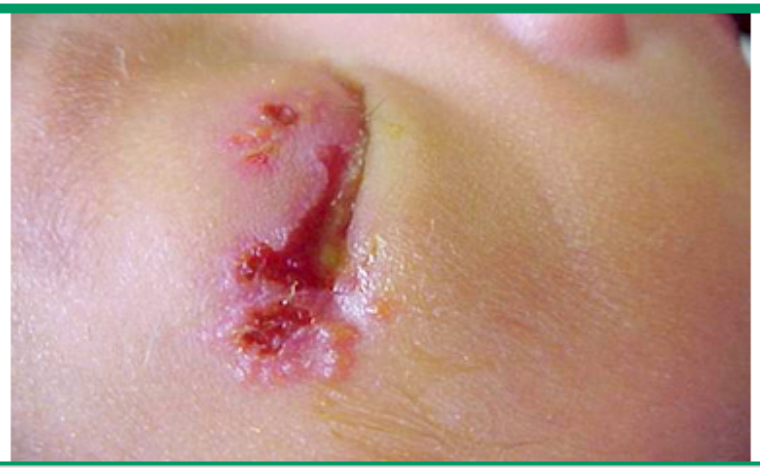
Skin, Eye, and Mouth Disease

- Infection of the eye may initially appear asymptomatic
- In the neonate, early signs include excessive watering of the eye, crying from apparent eye pain, and conjunctival erythema
- Periorbital vesicles may or may not be present at the time of presentation
- HSV keratoconjunctivitis may progress to cataracts and chorioretinitis and result in permanent vision impairment

Eye vesicles in neonate with herpes simplex virus infection



Neonate with herpes simplex virus (HSV) infection of the eye, showing characteristic coalescing vesicles on an erythematous base on eyelid and surrounding skin. Ophthalmologic evaluation of the eye should also be performed to determine if keratitis or keratoconjunctivitis is present.

Courtesy of Jenny Ravenscroft, MD, and Gail J Demmler-Harrison, MD, Department of Pediatrics, Texas Children's Hospital.

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Skin, Eye, and Mouth Disease

- HSV infection of the oropharynx may initially be asymptomatic, but also characterized by localized ulcerative lesions of the mouth, palate, and tongue
- Should be differentiated from other causes of oral lesions in the newborn, such as local trauma or other viral infections (enterovirus)
- Ultimately, any neonate with evidence of SEM disease should undergo a thorough evaluation for CNS and disseminated disease
- If SEM disease is treated early, before CNS or disseminated disease occurs, the outcome is favorable

CNS Disease – Presentation

- Approximately 1/3 of neonatal HSV involves the CNS
- Can occur as a result of localized retrograde spread (nasopharynx and olfactory nerves to the brain) or through hematogenous spread in neonates with disseminated disease
- Typically presents in the 2nd or 3rd week of life, but may occur any time during the first 6 weeks
- May occur with or without SEM involvement and with or without disseminated disease, but between 60-70% of neonates have skin vesicles at some point during the disease course
- Clinical manifestations: seizures (focal or generalized), lethargy, irritability, tremors, poor feeding, temperature instability, and full anterior fontanelle

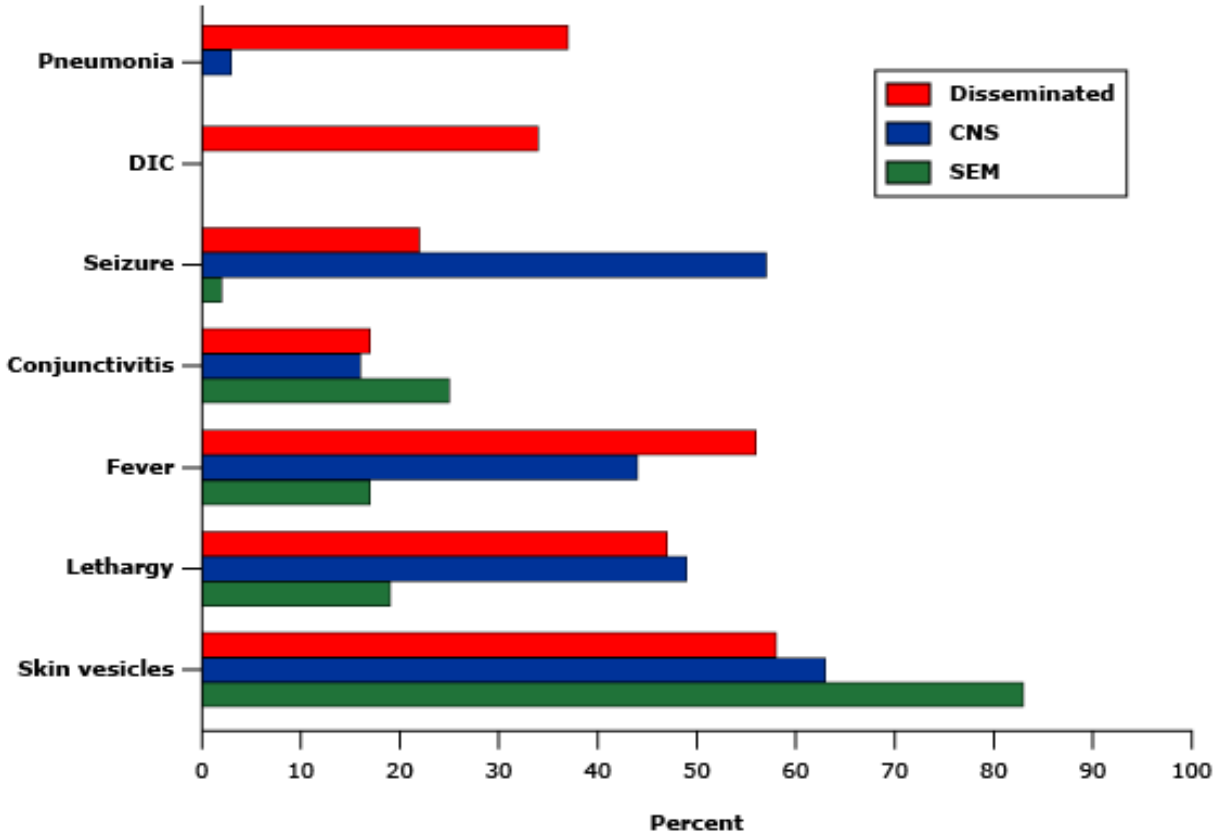
CNS Disease - Workup

- CSF analysis classically shows the following: mononuclear cell **pleocytosis**, normal/moderately low glucose concentration, mildly elevated protein
- Of note, CSF studies may be normal early in the course of the illness
- EEG often abnormal very early in the course of CNS disease and may show focal or multifocal periodic epileptiform discharges
- CT or MR imaging of the brain may be normal early in the course, but several days to a week into illness, may show parenchymal brain edema or attenuation, hemorrhage, or destructive lesions
- **Remember**: In the absence of vesicles, the initial presentation of HSV CNS disease may be indistinguishable from other causes of neonatal sepsis or meningitis!

Disseminated Disease

- **Liver**: including hepatitis, elevated liver transaminases, ascites, and direct hyperbilirubinemia
- **Lungs**: including PNA and hemorrhagic pneumonitis with or without effusion, that can progress to respiratory failure, requiring mechanical ventilation or extracorporeal life support
- **CNS**: Involved in 60-75% of cases, usually hematogenously acquired
- **Heart**: including myocarditis and myocardial dysfunction
- **Adrenal glands, Kidneys**
- **Bone marrow and coagulation system**: including DIC, thrombocytopenia and neutropenia
- **GI tract**: necrotizing enterocolitis
- **Skin and mucous membrane lesions**: however 20-40% of neonates with disseminated HSV do NOT have vesicles!

Signs and symptoms of neonatal herpes simplex virus infection



Signs and symptoms of neonatal herpes simplex virus infection at diagnosis and initiation of therapy.
SEM: skin, eyes, or mouth; CNS: central nervous system; DIC: disseminated intravascular coagulopathy.
Data from: Kimberlin DW, Lin C-Y, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 2001; 108:223.

Neonatal HSV – Evaluation & Diagnosis

- It is clinically **challenging** because early manifestations may be **subtle and nonspecific** and can mimic other viral illnesses (enterovirus) or bacterial diseases (meningitis, sepsis)
- Need to have a **high index of suspicion** in neonates and infants **up to 6 weeks of age**
- Consider the following:
  - Mucocutaneous vesicles
  - Sepsis-like illness → fever **OR** hypothermia, irritability, lethargy, respiratory distress, apnea, abdominal distension, hepatomegaly, or ascites
  - CSF pleocytosis
  - Seizures, focal neurological signs, abnormal imaging
  - Respiratory distress, apnea, or progressive pneumonitis
  - Elevated liver transaminases, viral hepatitis or acute liver failure
  - Conjunctivitis, excessive tearing or painful eye symptoms

Neonatal HSV - Detection

Specimens to collect:

- **Surface swabs**: such as from the conjunctivae, mouth, nasopharynx, rectum. Can process via HSV culture or HSV PCR
- **Swabs/Scrapings of skin lesions**: if skin or mucous membrane lesions are present
- **CSF**: All neonates with suspected HSV, even those that appear to have isolated SEM disease should undergo LP. In this case, PCR is test of choice.
- **Blood or plasma**: All neonates with suspected HSV of ANY classification should have blood/plasma samples tested for using PCR
- **Additional studies depending on specimen**: if available, tracheal aspirates in intubated infants for example, or peritoneal fluid in neonates undergoing peritoneal drainage or laparotomy

Neonatal HSV – Management

Acyclovir is the antiviral agent of choice for all categories of neonatal HSV.

- IV acyclovir should be administered at the time the diagnosis of neonatal HSV is **SUSPECTED** and continued while clinical observation, lab results and imaging are all completed.
- The dose for all forms of neonatal HSV is **60mg/kg per day IV divided q8hrs**
  - Adjusted for neonates with renal impairment
  - Lower dose used for infants who have reached 3 months of age
- Duration of therapy depends on the pattern of illness and response to therapy
  - SEM: 14 day minimum if disseminated and CNS disease have been excluded
  - Disseminated and CNS disease: 21 day minimum with a repeat LP near the end of therapy to ensure CSF is negative
  - If CSF persistently positive after 21 days of therapy, continue treatment and repeat LP weekly until negative
- Adverse Effects: kidney injury if not properly hydrated, dose-dependent reversible neutropenia

From CHOC FUO Care Guidelines

CHOC Children's Evidence Based Medicine Committee

Statement on Acyclovir Therapy in Neonates

Neonates < 4 weeks with fever:

Parenteral acyclovir (20 mg/kg IV q8hours) should be added empirically to antibiotics for neonates admitted with fever in the following situations;

1. Clinical signs of sepsis, toxic (including hypothermia, apneas, hypotension, other signs of shock)
2. Seizure
3. Maternal HSV
4. Physical exam findings consistent with Herpes simplex involvement (skin, eye, mucous membrane)
5. CSF pleocytosis with negative gram stain and consistent with aseptic meningitis.

Anytime acyclovir therapy is started on neonates one should perform a lumbar puncture and send the cerebrospinal fluid for HSV PCR.

In high risk situations where there is concern for disseminated HSV or SEM disease please send whole blood for HSV PCR, obtain swabs for HSV viral culture of at least 3 different mucous membrane (i.e. mouth, conjunctiva, nasopharynx, rectum), and any skin lesions and a panel 18. Obtain an Infectious Disease Consult.

https://www.choc.org/wp/wp-content/uploads/careguidelines/FeverInfantsLessThan90DaysCareGuideline.pdf

Sources

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- Riley, L., Wald, A., Hirsch, M., Lockwood, C., Mitty, J., and Barss, V. *Genital herpes simplex virus infection and pregnancy*. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 8, 2020.)
- Pamela Chayavichitsilp, Joseph V Buckwalter, Andrew C. Krakowski, Sheila F. Friedlander. *Herpes Simplex.* Pediatrics in Review Apr 2009, 30 (4) 119-130; **DOI:** 10.1542/pir.30-4-119