Intrauterine and perinatal transmission of herpes simplex virus (HSV) to the fetus or the newborn is a possible cause of neonatal sepsis. The main clinical manifestations of congenital HSV infection are skin scars, chorioretinitis and microcephaly. The three main forms of neonatal HSV infection are skin, eye and mouth disease diagnosed in 45% of the cases, central nervous system disease diagnosed in 30% of the cases and disseminated disease recognized in 25% of the cases.

Overview of HSV Infections

Congenital HSV infection is a debatable entity and has been reported only few times in medical literature. In this article, we will mainly discuss the three types of neonatal herpes simplex virus infections which are named after the extent of the disease and the major organs involved.

The acquisition of HSV type 1 or type 2 without prior exposure to the virus in the
mother is known as primary infection. Non-primary infection refers to the acquisition of an HSV type in a subject with previous exposure to another HSV type. In this case, the subject will have pre-formed antibodies against that other HSV type at the time of exposure to the new HSV type.

**Reactivation of HSV occurs when the same type is identified in skin lesions** in a patient with documented antibodies against that type, also known as previous exposure. Symptomatic shedding of HSV is defined as the presence of genital herpes with the detection of HSV-1 or HSV-2 from the lesions by culture or polymerase chain reaction testing.

**Transmission of Neonatal HSV infection**

Neonatal HSV infection can be acquired in 3 distinct periods:

1. Rarely intrauterine, accounting for 1 in 250,000 deliveries.
2. The vast majority are acquired perinatally in 85% of Neonatal HSV infection, especially in maternal HSV infection, longer duration of ruptured membranes and using fetal scalp monitors.
3. HSV can also be acquired postnatally in 10% of cases, especially when the infant comes in contact with a caretaker with herpes labialis infection.

**Epidemiology of Neonatal HSV Infections**

To study the epidemiology of HSV infections in neonates, it is helpful to study the epidemiology of genital HSV infections during pregnancy and the perinatal period.

Up to 20% of pregnant women in the United States are found to be seropositive for HSV-2. Most genital herpes infections are asymptomatic and go unnoticed by the patient. Up to two thirds of pregnant women who acquire HSV-1 or HSV-2 during pregnancy do not develop any symptoms.

Women with documented history of HSV acquisition before pregnancy have a 70% chance of developing a recurrence during pregnancy. Another 14% of those women are expected to develop prodromal symptoms suggestive of HSV reactivation at time of delivery.

Neonatal HSV infection is reported in up to 60% of the newborns of mothers who developed a primary HSV infection around the time of delivery. On the other hand, only 3% of the newborns of women who develop a recurrent HSV infection around the time of delivery develop neonatal HSV infection.

The estimated incidence of neonatal HSV infections is around 1 in 3200 deliveries. In the United States, up to 1500 new cases of neonatal HSV infection are diagnosed each year.

**Risk Factors**

Neonatal HSV infections happen only if the mother is shedding the virus at the time of delivery. Being symptomatic is not related to the risk of neonatal HSV infection, as shedding is the more important factor here. Approximately 1.4% of women with prior history of recurrent genital herpes are found to be shedding the virus at the time of delivery.
Another important risk factor for neonatal transmission is whether the maternal infection was a primary infection or a recurrent one. **Primary maternal HSV infections near the time of delivery are associated with a significantly higher risk of virus shedding at time of delivery** and potentially neonatal HSV infection.

The other **risk factors** for neonatal HSV infection are **vaginal delivery** in a mother who is shedding the virus, the **use of fetal scalp electrodes and other instrumentation during pregnancy**, and the **type of HSV**. Maternal HSV-1 genital infection is associated with a higher risk of neonatal HSV acquisition compared to HSV-2. To **lower the risk** of transmission to the neonate, **caesarean delivery** is recommended. It should be noted, however, that caesarean delivery in the case of prolonged rupture of membranes in a mother who is shedding the virus might not lower the risk of virus transmission to the neonate.

**Clinical Presentation of Neonatal HSV Infections**

**Neonatal HSV infections can be classified into:**

1. Sisseminated disease
2. Central nervous system disease
3. Skin, eye or mouth (SEM) disease

The manifestations, sites of involvement, development, treatment and mortality are not the same and are based on the type of the disease.

**Intrauterine HSV Infection**

Before we discuss neonatal HSV infections in detail, let us talk about the **least common type** of HSV infections in the pediatric population, **intrauterine HSV infections**. The estimated incidence of intrauterine HSV infection is 1 in 300,000 live births. The main manifestations of intrauterine HSV infection are:

- Skin scarring
- Rash
- Aplasia cutis
- Hyperpigmentation
- Hypopigmentation
- Microphthalmia
- Chorioretinitis
- Optic atrophy
- Intracranial calcifications
- Microcephaly
- Encephalomalacia

Because of the severe manifestations, the **diagnosis is rarely missed** at time of birth.

**Disseminated Neonatal HSV Infection**

The disseminated form of neonatal HSV infection is reported in **one-quarter of the cases. The disease involves the:**

- Central nervous system
- Liver
- Lungs
Adrenal glands
- Skin
- Eyes
- Mucus membranes

**Patients might present with:**
- Encephalitis
- Hepatic failure
- Respiratory failure
- A skin rash
- Disseminated intravascular coagulation

**Despite the severity of the presentation, up to 83 % of the survivals are expected to recover and develop normally.** Mortality rate is highest in this form of disease, around 29 %.

**Central Nervous System (CNS) Neonatal HSV Infection**

One third of the cases of neonatal HSV infection mainly present with CNS disease. Unfortunately, CNS neonatal HSV disease has a grim prognosis with only one third of the survivals achieving normal development 1 year after adequate antiviral treatment. Mortality from CNS disease is estimated to be around 4 %.

**The main presentations of CNS neonatal HSV disease are:**
- Seizures
- Poor feeding
- Temperature instability
- Lethargy
- Skin rash

**SEM Neonatal HSV Infection**

Fortunately, this is the most common form of neonatal HSV infections. Up to 45 % of the cases are found to belong to the SEM disease type. Involvement is limited to the skin, eyes and the mucus membranes. Patients typically present with a vesicular rash. All neonates with SEM disease are expected to completely recover and normally develop after one year of adequate antiviral therapy.

**Diagnostic Workup for Neonatal HSV Infections**

**Initial Diagnosis**

The definitive method to diagnose neonatal HSV infection is isolation of HSV by culture. HSV can be cultured from the conjunctivae, nasopharynx, mouth or anus of the neonate. In severe cases, culture of the cerebrospinal fluid or blood might be prepared. It should be noted, however, that the diagnostic yield of skin and eye cultures is excellent and superior to any other site.

Neonates with central nervous system HSV infections should undergo a polymerase chain reaction (PCR) test to confirm the diagnosis. PCR is superior to HSV cultures in that it can provide results much faster. The sensitivity and specificity of PCR for CNS HSV infections is around 100 %.
Negative PCR, HSV cultures, and other rapid tests don’t exclude neonatal HSV. **Serologic testing** for diagnosing neonatal HSV infections is **not recommended**.

**Workup to detect complications**

1. Brain imaging by CT & MRI is recommended to detect the severity and extent of brain involvement. *HSV infection usually affect the tempero-parietal region (High Yield USMLE question).*
2. Chest radiograph may detect bilateral diffuse pneumonitis in patients with disseminated disease.
3. Abdominal U/S may detect enlarged liver or evidence of ascitis in infants with acute liver failure.

**Management of Neonatal HSV Infections**

Once the diagnosis of neonatal HSV infection is confirmed, **antiviral therapy** should be started. Intravenous acyclovir at the dose of 20 mg/kg three times a day is the treatment of choice for neonatal HSV infections regardless of the form of the disease.

The duration of the acute stage of treatment is dependent on the form of the disease.

1. **SEM** disease is typically treated with **14 days of intravenous acyclovir**.
2. **Disseminated disease** is treated for **21 days**.
3. **CNS disease** is treated for **21 days**, then a repeat cerebrospinal fluid PCR is indicated. If the PCR is still positive, then intravenous acyclovir should be continued until PCR negativity is observed.

After this initial treatment, the infant should be put on **maintenance antiviral suppressive therapy**. Oral acyclovir at the dose of 300 mg/m2/dose three times a day for 6 months is recommended in all forms of the disease. Acyclovir might cause neutropenia; therefore, absolute neutrophil count should be monitored while the infant is receiving treatment.

**References**


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