Neonatal herpes simplex virus infection: Management and prevention

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Literature review current through: Mar 2022. | **This topic last updated:** Sep 11, 2018.

INTRODUCTION

Neonatal infection with herpes simplex virus (HSV) occurs in 1 out of every 3200 to 10,000 live births, causes serious morbidity and mortality, and leaves many survivors with permanent sequelae [1-4]. Despite this seemingly low prevalence, neonatal HSV accounts for 0.2 percent of neonatal hospitalizations and 0.6 percent of in-hospital neonatal deaths in the United States, and is associated with substantial health care resource utilization [5-8].

The management and prevention of neonatal HSV infection will be reviewed here. The clinical features and diagnosis of neonatal HSV infection and non-neonatal herpes simplex virus infection are discussed separately:

- (See "Neonatal herpes simplex virus infection: Clinical features and diagnosis".)
- (See "Genital herpes simplex virus infection and pregnancy".)
- (See "Herpetic gingivostomatitis in young children".)
- (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection".)

OVERVIEW

The treatment of neonatal herpes simplex virus (HSV) infection involves supportive measures and antiviral therapy.

Supportive measures — Supportive measures for the critically ill neonate with disseminated or central nervous system (CNS) disease include:

- Fluid and electrolyte maintenance and avoidance of hypoglycemia. (See "Fluid and electrolyte therapy in newborns" and "Management and outcome of neonatal hypoglycemia".)
- Management of shock and systemic inflammatory response. (See "Septic shock in children: Rapid recognition and initial resuscitation (first hour)" and "Septic shock in children: Ongoing management after resuscitation".)
- Provision of oxygen and mechanical ventilator support. (See "Respiratory support, oxygen delivery, and oxygen monitoring in the newborn" and "Overview of mechanical ventilation in neonates".)
- Nutritional support. (See "Overview of enteral nutrition in infants and children" and "Parenteral nutrition in infants and children".)
- Control of seizures. (See "Treatment of neonatal seizures".)
- Management of disseminated intravascular coagulation, including fresh frozen plasma and/or platelet transfusions in patients with significant bleeding. (See "Disseminated intravascular coagulation in infants and children", section on 'Management'.)
- Antimicrobial treatment for secondary bacterial infections, especially for gram-negative organisms in neonates with ascites and liver necrosis. (See "Management and outcome of sepsis in term and late preterm infants", section on 'Antibiotic therapy'.)
- Intravenous immune globulin, especially if myocardial dysfunction/myocarditis or systemic inflammatory response is present [9]. (See "Treatment and prognosis of myocarditis in children", section on 'Intravenous immune globulin'.)
- Other interventions, such as glucocorticoids, exchange transfusion, and liver transplantation have been reported in case reports [9-12].

ACYCLOVIR THERAPY

We recommend acyclovir as the antiviral agent of choice for the treatment of all categories of neonatal herpes simplex virus (HSV) infections, including skin, eye, and mouth (SEM), central

nervous system (CNS), and disseminated disease (table 1) [13-16]. (See "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Neonatal HSV'.)

Treatment of neonatal HSV disease with antiviral therapy improves survival and outcome, especially if treatment is begun early in the course of illness [14,15,17]. Before antiviral therapy was available, the one-year mortality rates for neonates with disseminated and CNS HSV disease were 85 and 50 percent, respectively [18]. With the advent of antiviral therapy, mortality rates declined to 29 and 4 percent, respectively [14,15,19].

Antiviral therapy also has increased the proportion of survivors of disseminated disease who have normal neurologic development (from 50 to approximately 80 percent) [14,18,19]. Antiviral therapy does not appear to have affected the proportion of survivors of CNS disease with normal neurologic development (approximately 30 percent both before and after antiviral therapy became available) [14,18,19].

Early antiviral treatment of infants with SEM disease prevents progression to CNS or disseminated disease [20]. Between 50 and 60 percent of infants with SEM who do not receive antiviral therapy progress to CNS or disseminated disease.

In a randomized controlled trial, the morbidity and mortality were similar among infants treated with acyclovir and vidarabine [15]. However, vidarabine has systemic toxicity and a dosing schedule that requires 12-hour infusions.

The mechanism of action, pharmacokinetics, and toxicity of acyclovir are discussed separately. (See "Acyclovir: An overview".)

Indications — Indications for acyclovir therapy include [13,21-23]:

- Virologically proven HSV disease (see "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Detection of HSV')
- Clinically suspected HSV disease (figure 1), pending viral studies (see "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Clinical manifestations')
- Asymptomatic but at risk due to exposure (maternal active genital lesions) (algorithm 1) (see 'Management of the asymptomatic exposed infant' below)

The indications for initiation of empiric acyclovir are not standardized. Most experts agree that empiric acyclovir is indicated for neonates with clinical features suggestive of HSV infection, which include mucocutaneous vesicles (picture 1A-C), seizures, lethargy, respiratory distress,

thrombocytopenia, coagulopathy, blood oozing from intravascular catheter sites, hypothermia, sepsis-like illness, hepatomegaly, ascites, or markedly elevated transaminases (figure 1) [13,21-23]. Many experts recommend empiric treatment for ill-appearing neonates with fever or aseptic meningitis until results of HSV workup are known. However, expert opinions differ regarding the relative benefits, risks, and cost-effectiveness of empiric acyclovir before virologic confirmation in other clinical situations (eg, cerebrospinal fluid [CSF] pleocytosis with a predominance of mononuclear cells in an otherwise well-appearing infant, persistent or recurrent erythema or purulence/crusting at the site of a scalp electrode, fever without localizing signs in an infant ≤21 days of age, etc) [21-24]. (See "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Clinical manifestations'.)

The full course of acyclovir therapy should be administered for infants with positive HSV cultures or DNA polymerase chain reaction (PCR), and infants with negative virologic studies in whom neonatal HSV is strongly suspected. (See 'Duration of therapy' below.)

Timing — Intravenous (IV) acyclovir should be administered at the time the diagnosis of neonatal HSV is **suspected**. Prompt administration improves outcome [5,14,15,17,25]. Acyclovir therapy should be continued while clinical observation and results of laboratory and imaging evaluations are completed.

Pretreatment evaluation — A comprehensive laboratory evaluation for HSV should be performed before initiation of acyclovir therapy. The evaluation should include (if the infant is clinically stable enough to undergo it) [13,19]:

- Testing to detect HSV, including **all** of the following (see "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Specimens to collect'):
  - Surface HSV cultures or HSV PCR from the conjunctivae, mouth, nasopharynx, and rectum
  - HSV culture or HSV PCR of swabs/scrapings of skin and mucous membrane lesions, if present; direct immunofluorescence assay (DFA) may be used in addition to culture to permit rapid detection
  - CSF HSV PCR
  - Whole blood or plasma HSV PCR
  - Viral culture or HSV PCR of other specimens that are readily available (eg, tracheal aspirates in intubated patients)

- Testing to determine the degree of organ involvement and studies to exclude other diseases that may cause similar symptoms (see "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Additional studies'):
  - Complete blood count (CBC), including differential and platelet count
  - Liver transaminases, total and direct bilirubin, ammonia (ammonia should be performed to exclude liver failure and metabolic disease in neonates with elevated liver enzymes and fulminant sepsis, but is not necessary for all neonates with suspected HSV)
  - Blood urea nitrogen (BUN), creatinine, and urinalysis (to assess renal function and hydration status)
  - CSF cell count and differential, glucose, protein
  - Ophthalmologic examination
  - Neuroimaging (see "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Brain imaging')
  - Electroencephalogram (EEG) in neonates suspected to have CNS disease (see "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Electroencephalogram')
  - Chest radiograph, for neonates with respiratory distress
  - Blood and CSF cultures to evaluate for bacterial sepsis

Initial treatment

Dose — The dose of acyclovir for all forms of neonatal HSV is 60 mg/kg per day intravenously divided every eight hours [14]. The dose of acyclovir must be adjusted for neonates with renal impairment. A lower dose is also used for infants who have reached three months of age.

The benefits of this dose compared with standard-dose acyclovir 30 mg/kg per day were established in an open-label study in which 72 neonates with CNS or disseminated HSV were treated with acyclovir 60 mg/kg per day for 21 days [14]. Their outcomes were compared with those of infants in an earlier trial who were treated with acyclovir 30 mg/kg per day for 10 days [15]. The higher dose was associated with increased survival at 24 months (odds ratio [OR] 3.3, 95% CI 1.5-7.3).

Duration of therapy — The duration of acyclovir therapy for neonatal HSV infection depends upon the pattern of illness and response to therapy [5,13,14,16]:

- **Skin, eye, and mouth disease** – Localized skin, eye, and mouth (SEM) disease should be treated for a minimum of 14 days if disseminated and CNS disease have been excluded (table 1).

- **Disseminated and CNS disease** – Disseminated and CNS disease should be treated for a **minimum** of 21 days. Because the persistence of HSV DNA in the CSF is associated with poor outcome, lumbar puncture should be repeated near the end of therapy to ensure that CSF HSV PCR is negative [5,13,19,26-29].

  For infants with persistently positive CSF HSV PCR despite 21 days of acyclovir therapy, antiviral treatment is continued and CSF HSV PCR testing is repeated weekly until negative [13,19]. Consultation with a pediatric infectious disease specialist is warranted in cases of persistently positive CSF or blood HSV PCR. The clinical significance of persistently positive blood PCR is uncertain. Data from a small cohort of infants (n = 6) with disseminated HSV disease who were monitored with serial plasma HSV PCR levels during treatment suggest that acyclovir therapy has a uniform and predictable effect on plasma HSV level regardless of the baseline viral level and that this monitoring can be used to help guide duration of therapy [30]. In our practice, we repeat the blood HSV PCR at the end of the 21-day treatment course to assess for viremia clearance. If the blood HSV PCR is persistently positive, additional IV acyclovir therapy and/or evaluation for primary immune disorder (eg, T cell or NK cell disorders) is undertaken.

Adverse effects — Systemic acyclovir therapy is well tolerated by most neonates and side effects are unusual. Potential adverse effects include:

- Kidney injury caused by crystallization in the renal tubules, which is more likely to occur if the neonate is dehydrated
- Dose-dependent reversible neutropenia [5,14,19]
- Ulceration at the site of peripheral extravasation
- Seizures, especially if the dose is not adjusted in patients with renal impairment

Monitoring — Routine monitoring for neonates receiving IV acyclovir includes the following:

- **Renal function** – BUN and creatinine are monitored once or twice weekly, depending on the clinical status of the patient. For patients with acute kidney injury and/or severe disseminated HSV disease, BUN and creatinine should be monitored daily. In addition, the infant's hydration status should be monitored by assessing intake and output and

measuring urine specific gravity. In our practice, we aim to keep urine specific gravity <1.010 during acyclovir therapy to reduce renal toxicity. The acyclovir dose should be adjusted if creatinine clearance is lower than expected for age of patient.

- **Absolute neutrophil count** – Absolute neutrophil count (ANC) should be followed approximately twice per week during the course of therapy [14,19]. The acyclovir dose should be reduced or granulocyte colony-stimulating factor should be administered if the ANC remains <500/microL for an extended period of time without an alternative explanation for the neutropenia.

- **Infusion site** – Monitoring of the local infusion site is important because local infiltration can cause superficial or deep ulcerative lesions. If possible, administration through central access or a peripherally-inserted central catheter (PICC) is preferred.

Intravenous acyclovir not available — If intravenous (IV) acyclovir is not available, in agreement with the American Academy of Pediatrics (AAP) Committee on Infectious Diseases, we suggest IV ganciclovir as a first-line alternative [31-33]; the dose is 6 mg/kg every 12 hours IV for infants ≤90 days of age and 5 mg/kg every 12 hours IV for infants >90 days. We suggest IV foscarnet as a second-line alternative; the dose is 60 mg/kg every 12 hours IV.

Oral suppressive therapy — Following parenteral treatment for all forms of neonatal HSV disease (SEM, CNS, and disseminated disease) (table 1), we suggest suppressive therapy with oral acyclovir 300 mg/m^2 per dose three times per day for six months; the dose should be adjusted each month to account for growth [13,29,34]. This recommendation is based on a randomized clinical trial in which suppressive therapy reduced cutaneous recurrences and was associated with improved neurologic outcomes in infants with CNS disease [34]. If HSV eye disease is present, many experts suggest oral suppression for up to one year. (See 'Treatment of eye disease' below.)

Acyclovir is preferred to valacyclovir because the safety and efficacy of valacyclovir have not been established in infants younger than two years of age. Furthermore, since only tablet form is available, an extemporaneously compounded valacyclovir oral suspension (25 to 50 mg/mL) must be specially prepared for infants [35]. Based on limited data on the pharmacokinetics and safety of valacyclovir in pediatric patients, doses of 10 to 20 mg/kg of extemporaneously compounded valacyclovir oral suspension, administered twice daily, produce favorable acyclovir blood concentrations and appear well tolerated in most children [36,37].

The effectiveness of long-term suppression with oral acyclovir in reducing the risk of CNS recurrence after neonatal HSV disease is unknown. CNS recurrence in neonates receiving long-term oral suppression has been documented [38]. Nonetheless, oral acyclovir suppression

appears to be associated with improved neurodevelopmental outcome. In a multicenter trial, 74 infants (45 with CNS HSV disease, 29 with SEM HSV disease) were randomly assigned to oral acyclovir 300 mg/m^2 per dose three times per day or placebo immediately following parenteral acyclovir treatment [34]. In children with CNS involvement, acyclovir suppression was associated with higher mean infant development scores at 12 months of age (88 versus 68 on the Bayley Scales of Infant Development, 2nd edition in which scores range from 50 to 150). The incidence and degree of neutropenia were similar in the treatment and placebo groups.

Adverse effects of oral acyclovir suppression may include dose-dependent reversible neutropenia (in one-half to two-thirds of infants in previous studies) and emergence of HSV mutants that are acyclovir resistant [5,19,38,39]. We monitor the ANC monthly in neonates receiving oral suppressive therapy. (See 'Monitoring' above.)

Treatment of recurrences — The optimal management of cutaneous recurrence is not established. However, treatment doses of oral acyclovir (10 to 20 mg/kg per dose three times per day for young infants, or 10 to 15 mg/kg per dose four to five times per day for older infants and children) may be administered early at the time of each cutaneous recurrence to reduce the discomfort and shedding associated with the lesions, or preemptively, for a brief period of one to two weeks, when a cutaneous recurrence is anticipated, such as times of high stress or exposure to sunlight.

In patients with frequent cutaneous recurrences that are painful or disruptive to daily life, long-term oral suppression may be of benefit. There is a broad range of acceptable doses. The author of this topic review generally prefers acyclovir 20 mg/kg per dose twice per day, but in some patients, 10 mg/kg per dose twice per day is effective. Suppression may be discontinued, and the patient observed, if no cutaneous recurrences are documented after a 12-month period.

An increase of the dosing frequency to three or four times daily for a brief period of time may be of benefit if a recurrence "breaks through" twice-daily oral suppression. HSV lesions that occur while the patient is receiving acyclovir three to four times per day should be cultured and the HSV isolate tested for acyclovir resistance.

Treatment of eye disease — Neonates with ocular HSV involvement, such as keratitis, should receive a topical ophthalmic solution (eg, 1% trifluridine, 0.1% idoxuridine [iododeoxyuridine], or 0.15% ganciclovir) in addition to systemic acyclovir therapy [13]. They should also be referred to an ophthalmologist for consultation.

We suggest long-term suppressive therapy (up to one year) with oral acyclovir (300 mg/m^2 per dose three times per day or 10 to 20 mg/kg per dose three times per day) for patients with HSV

involvement of the eye if there is a risk of impaired vision with reactivation [5,19,29]. (See 'Oral suppressive therapy' above.)

OUTCOME

The outcome of neonatal herpes simplex virus (HSV) disease depends upon the clinical pattern. HSV infection is lifelong, even with appropriate therapy. Recurrence of mucocutaneous lesions, eye disease, and/or central nervous system (CNS) disease may occur.

Disseminated disease — The one-year mortality rate for disseminated disease is 29 percent [14]. The risk of mortality is increased in infants with lethargy, severe hepatitis, acute liver failure, coma or near-coma at the time of presentation, disseminated intravascular coagulopathy, prematurity, and pneumonitis [19,40,41].

Approximately 80 percent of survivors of disseminated neonatal HSV disease may have normal neurologic development [14,18,19]. The risk of neurodevelopmental abnormalities (eg, developmental delay, hemiparesis, persistent seizures, microcephaly, blindness) is increased among infants with seizures at or before the initiation of antiviral therapy [19].

Severe hepatitis, caused by either HSV-1 or -2, may cause potentially fatal, acute liver failure in neonates with disseminated disease. Liver transplantation has been carried out successfully in a few reported neonates with fulminant hepatic failure associated with disseminated neonatal HSV disease [10,42,43].

Central nervous system disease — The one-year mortality rate for CNS disease is 4 percent [14]. Prematurity, seizures, and coma or near-coma at the time of presentation are associated with increased risk of mortality in CNS disease [19,40,41].

Approximately 30 percent of survivors of neonatal CNS HSV have normal neurologic development [14,18,19]. The risk of neurodevelopmental abnormalities is increased among infants with seizures at or before the initiation of antiviral therapy [19].

Skin, eye, and mouth disease — Mortality is rare in neonatal HSV disease that is localized to the skin, eye, and mouth (SEM; in whom disseminated and CNS disease have been appropriately excluded). Less than 2 percent of acyclovir recipients have developmental delay after recovery from neonatal SEM HSV disease [14,15,19]. The risk of neurodevelopmental abnormalities is increased in infants with ≥3 recurrences of skin lesions before six months of age [41]. Patients with ocular involvement are at risk for long-term complications, including vision loss, and require close follow-up. If HSV eye disease is present, many experts suggest oral

suppression for up to one year. (See 'Long-term follow-up' below and 'Treatment of eye disease' above.)

Cutaneous recurrence — Even after successful parenteral treatment, recurrence of HSV can occur and may be a lifelong problem for the patient and family. Fortunately, recurrence of CNS disease is rare [38,39]. However, recurrent vesicles at sites in the skin, eyes, and mouth (SEM) are common and occur in 50 to 80 percent of neonates, with 1 to 12 episodes in the first year of life [13]. Infants with ≥3 cutaneous recurrences during the first six months of life are at increased risk of neurodevelopmental abnormalities at follow-up [41]. Recurrence of skin lesions may affect child care arrangements and is disruptive to the lives of patients and their families [19].

Because the risk of recurrence in survivors of neonatal HSV disease is high, long-term suppressive therapy with oral acyclovir is recommended to reduce skin or eye recurrences during infancy [5]. (See 'Oral suppressive therapy' above.)

LONG-TERM FOLLOW-UP

Survivors of neonatal herpes simplex virus (HSV) infection, especially infants with involvement of the central nervous system (CNS), should be followed closely for achievement of developmental milestones [19]. They should undergo formal neurodevelopmental assessments as indicated. Referral to early intervention programs (eg, physical therapy, occupational therapy, speech therapy) should be made at the earliest sign of potential impairment. (See "Developmental-behavioral surveillance and screening in primary care", section on 'Follow-up'.)

Audiologic assessments are usually recommended as well. However, evidence suggests that the incidence of hearing loss after neonatal HSV disease is low [44]. (See "Hearing loss in children: Screening and evaluation".)

Patients with eye disease require careful follow-up with an ophthalmologist. To reduce the risk of recurrent eye disease, many experts suggest oral suppression with acyclovir for up to one year in this setting. Late onset recurrences have been reported [45,46]. The family should be counseled to seek medical care promptly if symptoms of eye disease recur.

PREVENTION

General measures — Strategies for prevention of intrauterine and perinatally acquired herpes simplex virus (HSV) infection, including identification of high-risk pregnant women, cesarean

delivery, maternal antiviral therapy, and anticipatory guidance for pregnant women and partners, are discussed separately. (See "Genital herpes simplex virus infection and pregnancy", section on 'Screening pregnant women with no HSV history'.)

Postnatal transmission of HSV can be prevented by counseling family members with active HSV lesions (cold sores, herpetic whitlow, herpetic gingivostomatitis) or a history of cold sores or HSV lesions in the recent past to avoid close contact with and avoid kissing the newborn infant. Women with herpetic breast lesions should not breastfeed from the affected breast until the lesions have resolved because direct contact with the lesions may transmit the HSV to the infant [47]. Mothers should use careful hand hygiene and cover any lesions with which the infant might come into contact.

Infants born to women with **active HSV lesions** should be managed with contact precautions during hospitalization, with a private room, or while rooming with the mother [13]. Some experts suggest that contact precautions are not necessary for such infants who are born by cesarean delivery <4 hours after rupture of membranes. Contact precautions are not necessary for infants born to women with a history of **recurrent** genital HSV who have no genital lesions at the time of delivery.

Contact precautions also should be used for infants who are hospitalized with HSV infection if they have mucocutaneous lesions [13]. The median duration of viral shedding from skin vesicles and mucosal lesions in infants receiving acyclovir therapy is five to eight days [14]. However, contact precautions may be continued for a longer period of time if the patient is hospitalized. (See "Infection prevention: Precautions for preventing transmission of infection", section on 'Contact precautions'.)

Infants and children with cutaneous recurrence of neonatal HSV should be counseled to cover the lesions to prevent potential transmission through direct contact [48].

Vaccine — There is no licensed, effective vaccine against HSV-1 or HSV-2 infection. However, a candidate HSV-2 gD subunit vaccine is in phase III clinical trials [5,49].

MANAGEMENT OF THE ASYMPTOMATIC EXPOSED INFANT

Overview — The optimal management of asymptomatic infants who are exposed to maternal herpes simplex virus (HSV) at delivery (as documented by maternal virologic testing or active genital lesions [16]) has not been evaluated in controlled trials [29]. However, experts and expert groups provide some guidelines regarding the need for cultures and prophylactic or anticipatory antiviral therapy based upon the risk of transmission under various circumstances (

algorithm 1) [13,16,50-54]. Consultation with a pediatric infectious diseases specialist is suggested for guidance in difficult clinical situations.

The risk of transmission to the infant depends upon a number of factors, including (see "Genital herpes simplex virus infection and pregnancy", section on 'Vertical transmission') [13,54]:

- Whether the maternal infection is primary or recurrent (the risk is highest with primary infection)
- Maternal HSV antibody status
- Duration of rupture of membranes
- The integrity of mucocutaneous barriers (eg, the use of fetal scalp electrodes)
- Cesarean versus vaginal delivery

The risk of transmission is greatest (25 to 60 percent) among infants delivered vaginally or ≥4 hours after rupture of membranes to mothers with active genital lesions and no history of HSV infection [1,13,29,54]. The risk of transmission is lower (<2 percent) for infants delivered vaginally or ≥4 hours after rupture of membranes to mothers with recurrent HSV infection and active genital lesions. The risk of transmission is lowest among infants born by cesarean delivery within four hours of rupture of membranes [13,29]. However, given that cesarean delivery does not completely eliminate the risk of HSV, asymptomatic infants who are delivered by cesarean section in women with active genital HSV lesions are managed in the same manner as those who are delivered vaginally [54].

Availability of type-specific polymerase chain reaction (PCR) or culture testing of maternal genital lesions and type-specific maternal HSV serology permits more accurate characterization of the type of maternal infection (table 2) and, therefore, estimation of the risk of transmission [1,54].

The 2013 American Academy of Pediatrics (AAP) clinical report on the management of asymptomatic infants born to women with active genital herpes lesions provides guidance on the evaluation and management of asymptomatic neonates in settings where type-specific HSV testing with rapid turn-around time is available [54]. The recommendations in the 2018 AAP report of the Committee on Infectious Disease (Red Book) are consistent with the 2013 guidelines [13]. The approach that is described in the sections that follow is consistent with the AAP guidelines, but also provides recommendations for settings where type-specific HSV serologic testing with rapid turn-around time is not available.

Monitoring — All neonates who are born to women with active genital HSV lesions or a history of genital HSV but no active lesions at the time of delivery should be monitored for clinical evidence of HSV infection (eg, skin or scalp rashes, conjunctival lesions, irritability, sepsis, etc) (

figure 1) during the first six weeks of life [13]. The infant's parents and caregivers should be educated about the signs of neonatal HSV infection.

Infants who develop clinical evidence of HSV infection should undergo full clinical and virologic evaluation (including HSV blood PCR; surface cultures; cerebrospinal fluid [CSF] HSV PCR, cell count, and chemistries; and serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST]; CBC with differential and platelet count) and acyclovir 60 mg/kg per day intravenously (IV) divided every eight hours should be administered while results of virologic evaluation are pending. (See 'Acyclovir therapy' above and "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Laboratory evaluation'.)

Maternal history of HSV, no active lesions — The risk of transmission of HSV to infants born to women with a history of genital HSV but no active genital lesions at the time of delivery is low. Such infants who are asymptomatic should be monitored for neonatal HSV infection. However, we do not suggest that they be evaluated for neonatal HSV or receive prophylactic acyclovir [13]. (See 'Monitoring' above.)

Maternal history of HSV, active lesions — The risk of transmission of HSV to infants born to women with a history of genital HSV and active genital lesions at the time of delivery is relatively low (<2 percent) [1,13,29,54].

We suggest that the evaluation of asymptomatic infants born to women with a history of genital HSV and active genital lesions at the time of delivery include the following studies obtained at approximately 24 hours of age (whether they were delivered vaginally or by cesarean section) (algorithm 1) [13,29,54]:

- Surface cultures (ie, swabs of the mouth, nasopharynx, conjunctivae, rectum, scalp electrode site [if present], and possibly urine for viral culture)
- HSV blood PCR

Surface cultures obtained before 12 to 24 hours may reflect contamination during delivery, rather than infection. The sensitivity of viral cultures for detecting neonatal HSV infection in infants whose mothers were treated with antiviral medication during pregnancy is not known [13].

If the surface cultures or blood HSV PCR are positive, the asymptomatic neonate should undergo full virologic evaluation (CSF for HSV PCR, cell count, chemistries; serum ALT; CBC with differential and platelet count) and be treated with acyclovir (60 mg/kg per day IV divided every eight hours). (See 'Acyclovir therapy' above.)

We do not suggest routine prophylactic acyclovir for asymptomatic neonates who are born to women with a history of genital HSV and active genital lesions at the time of delivery [13,54].

However, prophylactic acyclovir (60 mg/kg per day IV divided every eight hours) may be warranted (after full HSV evaluation, including HSV blood PCR; surface cultures; CSF HSV PCR, cell count, and chemistries; serum ALT; CBC with differential and platelet count) for asymptomatic neonates born to women with recurrent HSV infection and additional risk factors for transmission (eg, rupture of membranes >4 to 6 hours, gestation <37 weeks, scalp electrode, skin lacerations) [1,54]. If acyclovir is initiated for such patients, it may be discontinued after three to five days if the infant remains asymptomatic and HSV PCR and viral cultures are negative.

No maternal history of HSV, active lesions — The risk of transmission of HSV to infants born to women with no history of genital HSV and active genital lesions at the time of delivery is between 25 and 60 percent [5,13,29].

We suggest that the evaluation of asymptomatic infants born to women with no history of genital HSV and active genital lesions include the following studies obtained at approximately 24 hours of age (whether they were delivered vaginally or by cesarean section) (algorithm 1) [13,54]:

- Surface cultures (ie, swabs of the mouth, nasopharynx, conjunctivae, rectum, scalp electrode site [if present] and possibly urine for viral culture)
- HSV blood PCR
- CSF HSV PCR, cell count, chemistries
- Serum ALT and AST
- CBC with differential and platelet count

We also suggest sending maternal blood for type-specific HSV serology as soon as possible after delivery (if available) to more accurately characterize maternal infection (table 2) [13,54].

Surface cultures obtained before 12 to 24 hours may reflect contamination during delivery, rather than infection. The sensitivity of viral cultures for detecting neonatal HSV infection in infants whose mothers were treated with antiviral medication during pregnancy is not known [13].

We suggest that asymptomatic neonates born to women with no history of genital HSV and active genital lesions at the time of delivery be treated with acyclovir 60 mg/kg per day IV divided every eight hours after evaluation for HSV [13,54].

The duration of acyclovir is determined by the neonate's clinical status, results of the neonate's evaluation for HSV disease, and maternal HSV infection classification (algorithm 1) [13,54]:

- For neonates born to women with active genital HSV lesions and no history of genital HSV infection in whom **type-specific HSV serologic testing is not available** who remain asymptomatic and whose HSV evaluation is negative, we suggest that prophylactic acyclovir be continued for 10 days.

- For neonates born to women with active genital HSV lesions and no history of genital HSV infection but **recurrent HSV infection** (**by serologic testing** (table 2)) who remain asymptomatic, we suggest that acyclovir be discontinued at 48 to 72 hours if HSV PCR and viral studies are negative.

- For neonates born to women with **primary genital HSV** infection or nonprimary **first episode genital HSV** infection (based on serologic testing (table 2)) or assumed primary or nonprimary first episode infection (based on strong clinical suspicion and discordant or unavailable genital and serologic test results) who remain asymptomatic and whose HSV evaluation is negative, we suggest that acyclovir be continued for 10 days.

In all cases, if the infant becomes symptomatic or the HSV evaluation is abnormal (including positive PCR, culture, abnormal CSF, or serum ALT >2 times the upper limit of normal), we recommend that acyclovir be continued for at least 14 days (for SEM infection) or at least 21 days (for CNS or disseminated disease) and that the infant undergo additional evaluation (including eye examination and neuroimaging). (See 'Pretreatment evaluation' above and 'Acyclovir therapy' above.)

INVESTIGATIVE THERAPIES

Investigative therapies for neonatal herpes simplex virus (HSV) disease include human and humanized monoclonal antibodies directed against HSV gB and gD glycoproteins. These therapies have been beneficial in animal models of HSV disease. Studies in humans have shown that high titers of neutralizing antibodies protect neonates following perinatal HSV exposure [5]. At present, antibody therapy for treatment or prevention of neonatal HSV is limited by the lack of an HSV hyperimmune globulin preparation and the variable amount of anti-HSV antibodies in intravenous immune globulin preparations.

SUMMARY AND RECOMMENDATIONS

Treatment

- We recommend acyclovir as the antiviral agent of choice for the treatment of all categories of neonatal herpes simplex virus (HSV) infections, including skin, eye, and mouth (SEM); central nervous system (CNS); and disseminated disease (table 1) (**Grade 1A**). The dose is 60 mg/kg per day intravenously (IV) divided every eight hours for all forms of neonatal HSV. (See 'Acyclovir therapy' above and 'Dose' above.)

- Acyclovir should be administered at the time neonatal HSV is suspected and continued pending results of clinical, laboratory, and imaging evaluations. Clinical features suggestive of HSV infection include mucocutaneous vesicles, seizures, aseptic meningitis, lethargy, respiratory distress, pneumonitis, thrombocytopenia, coagulopathy, hypothermia, hepatitis, sepsis-like illness, and elevated transaminases (figure 1). Many experts recommend empiric treatment for ill-appearing neonates with fever or aseptic meningitis until results of HSV work-up is known. (See 'Indications' above and 'Timing' above and "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Clinical manifestations'.)

- A comprehensive laboratory evaluation for HSV should be performed before initiation of acyclovir therapy. (See 'Pretreatment evaluation' above and "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Evaluation and diagnosis'.)

- The duration of IV acyclovir therapy for neonatal HSV infection depends upon the pattern of illness and response to therapy. SEM disease is treated for a **minimum** of 14 days; CNS and disseminated disease are treated for a **minimum** of 21 days. (See 'Duration of therapy' above.)

- Neonates with ocular HSV involvement should receive a topical ophthalmic solution (eg, 1% trifluridine, 0.1% idoxuridine [iododeoxyuridine], or 0.15% ganciclovir) in addition to systemic acyclovir therapy and consultation with an ophthalmologist. (See 'Treatment of eye disease' above.)

- We suggest oral acyclovir suppressive therapy for six months immediately following parenteral acyclovir for all categories of neonatal HSV disease, including SEM, CNS, and disseminated disease (table 1) (**Grade 2B**). We suggest a longer duration of oral suppressive therapy (up to one year) for infants with HSV eye disease that, if reactivated, has potential to threaten vision (**Grade 2C**). (See 'Oral suppressive therapy' above.)

Prevention

- Strategies for prevention of intrauterine and perinatally acquired HSV infection are discussed separately. (See "Genital herpes simplex virus infection and pregnancy", section on 'Pregnancy management'.)

- The risk of postnatal transmission of HSV can be minimized by counseling family members with active or recent history of HSV lesions (cold sores, herpetic whitlow, herpetic gingivostomatitis) to avoid close contact with and kissing the newborn infant. (See 'General measures' above.)

- Neonates with perinatal exposure to HSV should be monitored for clinical evidence of HSV infection. Neonates who develop clinical evidence of HSV infection should undergo full virologic evaluation and be started on IV acyclovir. (See 'Acyclovir therapy' above and "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Laboratory evaluation'.)

- The evaluation and management of asymptomatic neonates who are exposed to HSV during delivery depends upon the mother's history of genital HSV, maternal serologies for type-specific HSV (if available), and the presence or absence of HSV genital lesions at the time of delivery (algorithm 1). All such infants should be monitored for evidence of HSV infection (eg, skin or scalp rashes, conjunctival lesions, irritability, sepsis, etc (figure 1)) during the first six weeks of life. (See 'Management of the asymptomatic exposed infant' above.)

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Topic 6040 Version 36.0

GRAPHICS

Summary of clinical, laboratory, radiographic findings, and treatment of neonatal herpes simplex virus (HSV) infection

	Proportion of cases	Clinical manifestations	Diagnostic testing for HSV*			
			Viral culture of surface specimens¶	Viral culture of skin lesion scrapings$^{\Delta}$	Blood or plasma HSV PCR	
SEM disease	45%	▪ Characteristic vesicular lesions ▪ Conjunctivitis, excessive tearing ▪ Ulcerative lesions of the mouth, palate, and tongue	Positive in >90%	Positive in >90%	Positive in approximately 75%	N
CNS disease	30%	▪ Seizures ▪ Lethargy ▪ Irritability ▪ Tremors ▪ Poor feeding ▪ Skin lesions are present in 60 to 70%	Positive in >90%	Positive in >90% if lesions are present; however, skin lesions are often not present	Positive in approximately 65%	P ir 1(

				at the onset of disease		
Disseminated disease	25%	▪ Sepsis syndrome ▪ Fever or hypothermia ▪ Hepatitis ▪ Respiratory distress ▪ DIC ▪ Skin lesions are present in 60 to 80% ▪ CNS involvement occurs in 60 to 75%	Positive in >90%	Positive in >90% if lesions are present; however, skin lesions are often not present at the onset of disease	Positive in 100%	P ir

HSV: herpes simplex virus; PCR: polymerase chain reaction; CSF: cerebrospinal fluid; SEM: skin, eyes, mouth; CNS: central nervous system; EEG: electroencephalogram; DIC: disseminated intravascular coagulopathy; DFA: direct immunofluorescence assay; BSA: body surface area.

* All of these diagnostic tests should be performed in any neonate with suspected HSV infection.

¶ Surface cultures are performed on swab specimens collected from the conjunctivae, mouth, nasopharynx, and rectum. Some experts suggest these be obtained with a single swab, starting with eyes and ending with the rectum, and placed in one viral transport media tube. Alternatively, they may be collected with multiple swabs, which are then placed in a single viral transport media tube.

Δ DFA permits rapid detection of HSV antigens in skin lesion scrapings; however, DFA is not as sensitive as culture and therefore viral culture should also be performed.

◇ The dose of acyclovir must be adjusted for neonates with renal impairment and/or weight <1kg. Refer to Lexicomp for additional dosing information. If IV acyclovir is not available, ganciclovir as an alternative. Refer to the UpToDate topic on management of neonatal HSV infection for additional information. Oral acyclovir dosing is based on BSA, which is calculated as follows: square root (Height [cm] * Weight [kg] / 3600). The oral suppressive acyclovir dose should be adjusted each month to account for growth.

§ Idoxuridine (iododeoxyuridine) is not available in the United States.

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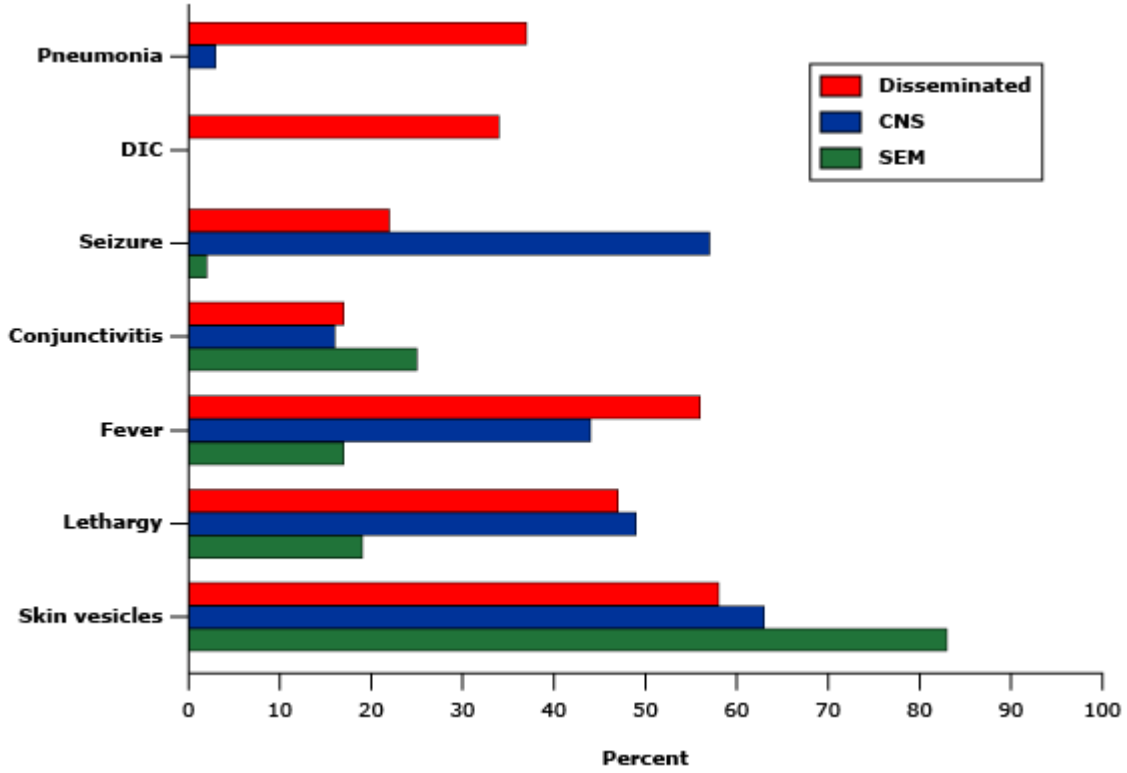
Graphic 106132 Version 2.0

Signs and symptoms of neonatal herpes simplex virus infection



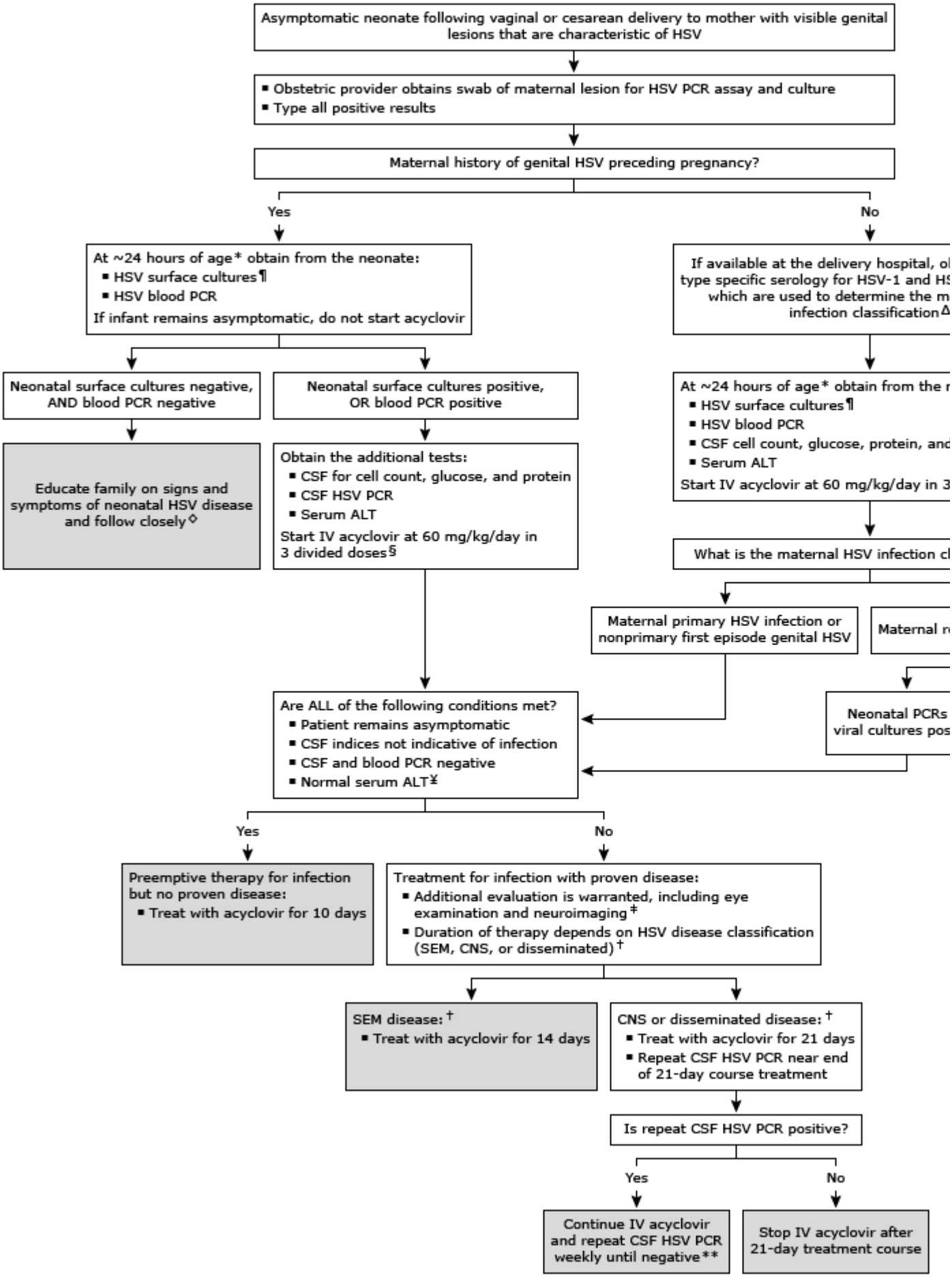
Signs and symptoms of neonatal herpes simplex virus infection at diagnosis and initiation of therapy.

CNS: central nervous system; SEM: skin, eyes, or mouth; 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.

Graphic 67814 Version 3.0

Algorithm for the evaluation and management of asymptomatic neonates afte delivery to women with active genital herpes lesions


Asymptomatic neonate following vaginal or cesarean delivery to mother with visible genital lesions that are characteristic of HSV
Obstetric provider obtains swab of maternal lesion for HSV PCR assay and culture
Type all positive results
Maternal history of genital HSV preceding pregnancy?
Yes
No
At ~24 hours of age* obtain from the neonate:
HSV surface cultures¶
HSV blood PCR
If infant remains asymptomatic, do not start acyclovir
If available at the delivery hospital, ob
type specific serology for HSV-1 and HS
which are used to determine the m
infection classification△
Neonatal surface cultures negative, AND blood PCR negative
Neonatal surface cultures positive, OR blood PCR positive
At ~24 hours of age* obtain from the n
HSV surface cultures¶
HSV blood PCR
CSF cell count, glucose, protein, and
Serum ALT
Start IV acyclovir at 60 mg/kg/day in 3
Educate family on signs and symptoms of neonatal HSV disease and follow closely◇
Obtain the additional tests:
CSF for cell count, glucose, and protein
CSF HSV PCR
Serum ALT
Start IV acyclovir at 60 mg/kg/day in 3 divided doses§
What is the maternal HSV infection cl
Maternal primary HSV infection or nonprimary first episode genital HSV
Maternal n
Neonatal PCRs
viral cultures pos
Are ALL of the following conditions met?
Patient remains asymptomatic
CSF indices not indicative of infection
CSF and blood PCR negative
Normal serum ALT¥
Yes
No
Preemptive therapy for infection but no proven disease:
Treat with acyclovir for 10 days
Treatment for infection with proven disease:
Additional evaluation is warranted, including eye examination and neuroimaging‡
Duration of therapy depends on HSV disease classification (SEM, CNS, or disseminated)†
SEM disease:†
Treat with acyclovir for 14 days
CNS or disseminated disease:†
Treat with acyclovir for 21 days
Repeat CSF HSV PCR near end of 21-day course treatment
Is repeat CSF HSV PCR positive?
Yes
No
Continue IV acyclovir and repeat CSF HSV PCR weekly until negative**
Stop IV acyclovir after 21-day treatment course

This algorithm should be applied only in facilities where access to PCR and type-specific serologic testing is r time for test results is appropriately short. In situations where this is not possible, the approach detailed in t and perhaps no, applicability.

HSV: herpes simplex virus; PCR: polymerase chain reaction; CSF: cerebrospinal fluid; ALT: alanine aminotran skin, eye, and mouth; CNS: central nervous system.

* Evaluation and treatment is indicated prior to 24 hours of age if the infant develops signs and symptoms c mucocutaneous vesicles, seizures, lethargy, respiratory distress, thrombocytopenia, coagulopathy, hypothe hepatomegaly, ascites, or markedly elevated transaminases). In addition, immediate evaluation and treatme prolonged rupture of membranes (>4 to 6 hours) or if the infant is preterm (≤37 weeks gestation).

¶ Surface cultures should be obtained from ALL of the following sites: conjunctivae, mouth, nasopharynx, a neonate had a scalp electrode placed, its site should be cultured.

Δ For details regarding determining maternal HSV infection classification, refer to UpToDate's content on ge pregnancy.

◇ Discharge after 48 hours of negative HSV cultures (and negative PCRs) is acceptable if other discharge cri ready access to medical care, and a person who is able to comply fully with instructions for home observatio these conditions are not met, the infant should be observed in the hospital until HSV cultures are finalized a 96 hours after being set up in cell culture, whichever is shorter.

§ The dose of acyclovir must be adjusted for neonates with renal impairment and/or weight <1 kg. Refer to I information. If IV acyclovir is not available, ganciclovir is an alternative. Refer to UpToDate's content on man infection for additional information.

¥ Serum ALT values in neonates may be elevated due to noninfectious causes (eg, delivery-related perfusior >2 times the upper limit of normal may be considered suggestive of neonatal disseminated HSV disease for

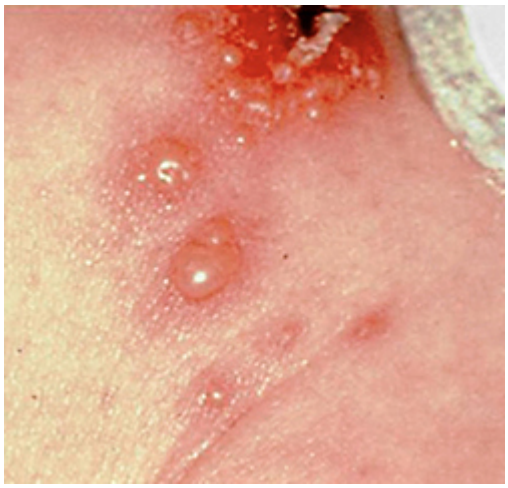
‡ Refer to UpToDate's content on clinical features and diagnosis of neonatal HSV infection for more details.

† Refer to UpToDate's content on diagnosis of neonatal HSV infection for details of distinguishing between t (SEM, CNS, and disseminated disease).

** Consultation with a pediatric infectious disease specialist is warranted in cases of persistently positive CS

Graphic 106124 Version 10.0

Neck vesicles in neonate with herpes simplex virus infection



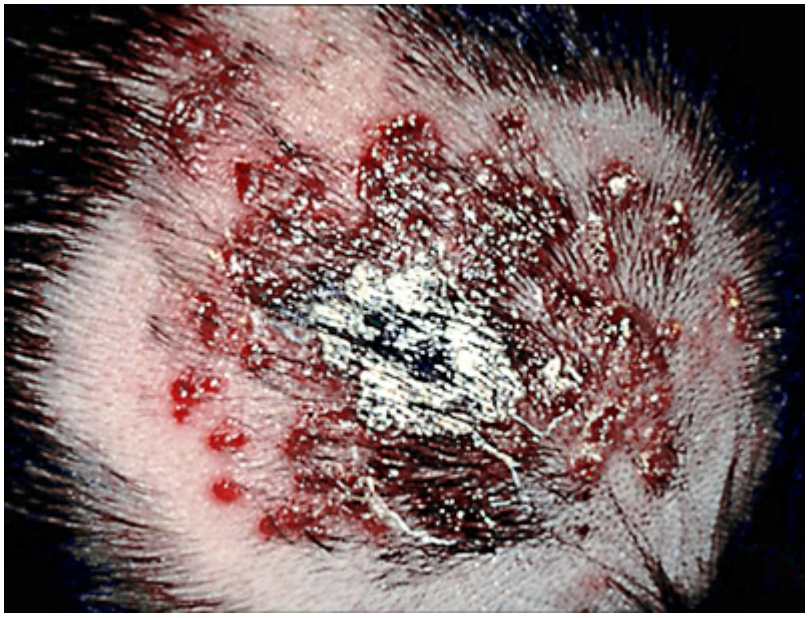
The early untreated skin lesions associated with neonatal HSV infection are characteristically clear vesicles on an erythematous base, often touching or "kissing," or coalesced in groups of vesicles. Culture of the clear fluid aspirated or swabbed from the vesicles will readily grow HSV in 24 to 48 hours,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

HSV: herpes simplex virus; DFA: direct immunofluorescence assay.

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

Graphic 75059 Version 4.0

Neonatal herpes simplex virus scalp vesicles



Scalp lesions of neonate with skin, eye, and mouth neonatal HSV infection associated with fetal scalp monitor. Gram-stained smear and bacterial cultures were negative, and the lesions did not respond to topical and systemic antibiotics. Viral cultures grew HSV type 2, and the lesions responded to intravenous acyclovir.

HSV: herpes simplex virus

Courtesy of Jane Troendle-Atkins, MD, and Gail J Demmler-Harrison, MD, Texas Children's Hospital.

Graphic 56041 Version 3.0

Eye vesicles in neonate with herpes simplex virus infection

Neonate with 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.

HSV: herpes simplex virus.

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

Graphic 78598 Version 4.0

Clinical designation of genital herpes simplex virus infection (HSV)

Direct viral test result*	Type-specific serologic status¶		Classification of genital HSV infection
	HSV-1 antibodies	HSV-2 antibodies	
HSV-1 detected	–	–	Primary HSV-1 infection
	–	+	Nonprimary first episode HSV-1 infection[Δ]
	+	– or +	Recurrent HSV-1 infection
HSV-2 detected	–	–	Primary HSV-2 infection
	+	–	Nonprimary first episode HSV-2 infection
	– or +	+	Recurrent HSV-2 infection

* Testing of the ulcerative lesion with culture, polymerase chain reaction, or direct fluorescent antibody.

¶ Performed at the time of initial presentation with the ulcerative lesion.

Δ Nonprimary first episode genital HSV-1 infection is rare.

Graphic 80693 Version 4.0

Contributor Disclosures

Gail J Demmler-Harrison, MD Grant/Research/Clinical Trial Support: Merck [Cytomegalovirus]; Microgen [Cytomegalovirus]. Consultant/Advisory Boards: Moderna [Cytomegalovirus]. Other Financial Interest: Elsevier textbook royalties. All of the relevant financial relationships listed have been mitigated. **Sheldon L Kaplan, MD** Grant/Research/Clinical Trial Support: Pfizer [Streptococcus pneumoniae]; Merck [Staphylococcus aureus]; MeMed Diagnostics [Bacterial and viral infections]; Allergan [Staphylococcus aureus]. Consultant/Advisory Boards: MeMed Advisory Board [Diagnostics bacterial and viral infections]. Other Financial Interest: Pfizer [PCV13, linezolid]; Elsevier [Pediatric infectious diseases]. All of the relevant financial relationships listed have been mitigated. **Leonard E Weisman, MD** Equity Ownership/Stock Options: Vax-Immune [Ureaplasma diagnosis, vaccines, antibodies, other medical diagnostics and pre-analytical devices]. Patent Holder: Baylor College of Medicine [Ureaplasma diagnosis, vaccines, antibodies, process for preparing biological samples]. All of the relevant financial relationships listed have been mitigated. **Carrie Armsby, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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