Neonatal Herpes Simplex Virus Infection

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Epidemiology

Neonatal HSV is acquired during one of three distinct periods: intrauterine, peripartum, or postpartum. A majority of infants (~85%) acquire the infection perinatally or in the peripartum period [1]. Approximately 10% of infants with neonatal HSV disease are infected postnatally, while 5% acquire the infection during the intrauterine period [1].

The incidence of neonatal HSV infection is approximately 1 per 2000–5000 live births [1]. However, neonatal HSV can be challenging to diagnose, so this may be an underestimate. Risk factors that increase the likelihood of HSV transmission to the neonate from a mother who is shedding HSV genitally at the time of delivery include:

1. Type of maternal infection (primary versus recurrent) [2–6]
2. Maternal antibody status [6–9]
3. Duration of rupture of membranes [5]
4. Integrity of mucocutaneous barriers (using fetal scalp probe, incisions, etc.) [6, 10, 11]
5. Mode of delivery (cesarean section versus vaginal delivery) [6]

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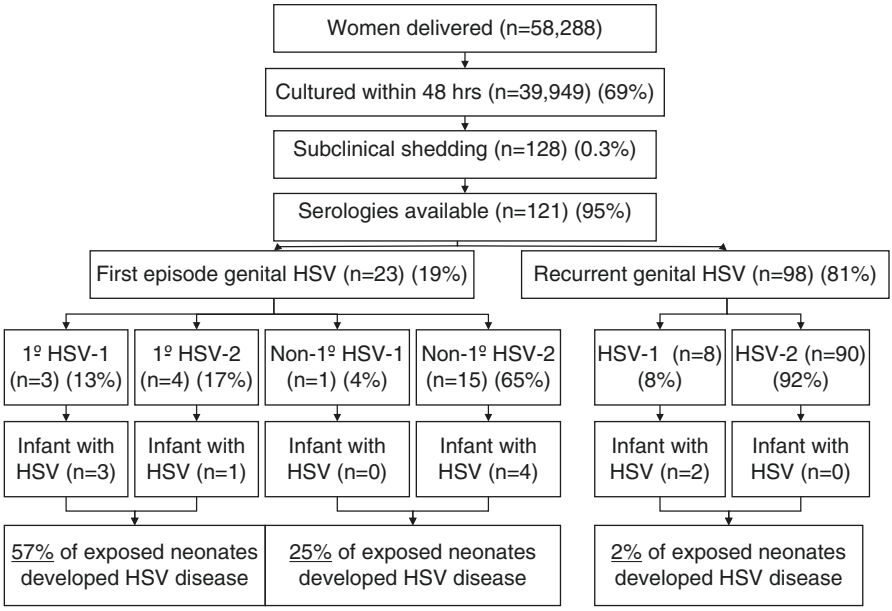

Fig. 1 Risk of neonatal herpes simplex virus (HSV) disease as a function of type of maternal infection. Adapted from [6]

Pathogenesis

Babies born to mothers with primary genital HSV infection near term (a first episode of genital HSV infection, with no preexisting antibody to either HSV type 1 [HSV-1] or HSV type 2 [HSV-2]) are at much greater risk of developing neonatal herpes than are babies who are born to mothers with recurrent genital HSV infection (i.e., who are shedding HSV-2 in the genital tract and who have preexisting HSV-2 antibody from infection earlier in life). This increased risk is due to two factors [2–6]. First, there is a lower concentration of transplacentally passaged HSV-specific antibodies present in babies born to women with primary infections [8]. In addition, these antibodies tend to be less reactive to the expressed peptides. Secondly, there is a larger load burden of the virus being shed vaginally, and for a longer period of time, in the maternal genital tract of women with primary infection compared with women with recurrent HSV infection [12]. This was demonstrated most effectively in a landmark study of approximately 60,000 women in labor who did not have any symptoms of genital HSV infection at the time of delivery. Of these women, approximately 40,000 had a vaginal swab obtained within 48 h of delivery for HSV detection (Fig. 1) [6]. Of these ~40,000 women, 121 had no visible evidence of genital HSV lesions but had HSV detected from their swab and also had sera available for HSV serologic testing, thereby allowing

for determination of first episode versus recurrent maternal infection classification. The trial found that 57% of babies born to moms with primary infection developed neonatal HSV, 25% of babies born to women with first episode non-primary infection developed neonatal HSV, and only 2% of babies born to women with recurrent HSV developed neonatal HSV. This same large study also confirmed that cesarean delivery effectively decreased transmission of HSV to the neonate when mothers are shedding in their genital tracts, affirming the results of a small study published in 1971 [5]. Despite this degree of protection, however, the risk of HSV transmission is not completely eliminated by cesarean delivery, and cases of neonatal HSV disease are well documented in babies delivered by cesarean delivery [13–15].

Clinical Findings

Neonatal HSV infection is classified based upon extent of involvement into one of three categories: (1) disseminated disease, (2) central nervous system infection, and (3) skin, eyes, and mouth infection. Disseminated disease involves multiple organs including but not limited to the lung, liver, adrenal glands, brain, and skin. Central nervous system (CNS) disease involves the brain and can have skin or mouth lesions as well. Skin, eyes, and mouth (SEM) disease is limited to only those areas. This classification is predictive of morbidity and mortality, with disseminated disease having the most significant mortality and CNS disease having the most significant morbidity [16–22].

Disseminated infection can manifest as severe hepatitis, disseminated intravascular coagulopathy, pneumonitis, and CNS involvement (seen in 60–75% of cases) [17, 21]. The mean age at presentation is around 11 days. Over 40% of disseminated HSV disease do not develop skin findings during the course of illness, which can delay diagnosis [14, 17, 22, 23].

Neonatal HSV CNS disease can present as seizures (focal or generalized), lethargy, poor feeding, irritability, or increased fussiness, tremors, temperature instability, and bulging fontanelle. The mean age of presentation is around 16 days [17]. Approximately 60–70% of babies with CNS disease will also have skin manifestations at some point in the disease course [17, 22]. Mortality is usually due to devastating brain destruction and atrophy, causing neurologic and autonomic dysfunction.

Skin, eyes, and mouth disease (SEM) has the best outcomes, with virtually no mortality and with morbidity associated solely with cutaneous recurrences but no neurologic sequelae (Table 1). Additionally, babies with SEM disease are most likely to have skin lesions (>80% of SEM patients), which facilitates diagnosis and allows prompt initiation of antiviral treatment before disease progresses. Presenting signs and symptoms of SEM disease include skin vesicles, fever, lethargy, and conjunctivitis [17]. Mean age of presentation is around 12 days. If SEM disease is not treated, it is likely to progress to CNS or disseminated disease [14].

Table 1 Mortality and morbidity outcomes among 295 infants with neonatal HSV infection, evaluated by the National Institutes of Allergy and Infectious Diseases' Collaborative Antiviral Study Group between 1974 and 1997

	Treatment			
Extent of disease	Placebo	Vidarabine	Acyclovir 30 mg/kg/day	Acyclovir 60 mg/kg/day
Disseminated disease	*n = 13*	*n = 28*	*n = 18*	*n = 34*
Dead	11 (85%)	14 (50%)	11 (61%)	10 (29%)
Alive	2 (15%)	14 (50%)	7 (39%)	24 (71%)
Normal	1 (50%)	7 (50%)	3 (43%)	15 (63%)
Abnormal	1 (50%)	5 (36%)	2 (29%)	3 (13%)
Unknown	0 (0%)	2 (14%)	2 (29%)	6 (25%)
Central nervous system infection	*n = 6*	*n = 36*	*n = 35*	*n = 23*
Dead	3 (50%)	5 (14%)	5 (14%)	1 (4%)
Alive	3 (50%)	31 (86%)	30 (86%)	22 (96%)
Normal	1 (33%)	13 (42%)	8 (27%)	4 (18%)
Abnormal	2 (67%)	17 (55%)	20 (67%)	9 (41%)
Unknown	0 (0%)	1 (3%)	2 (7%)	9 (41%)
Skin, eye, or mouth infection	*n = 8*	*n = 31*	*n = 54*	*n = 9*
Dead	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alive	8 (100%)	31 (100%)	54 (100%)	9 (100%)
Normal	5 (62%)	22 (71%)	45 (83%)	2 (22%)
Abnormal	3 (38%)	3 (10%)	1 (2%)	0 (0%)
Unknown	0 (0%)	6 (19%)	8 (15%)	7 (78%)

Diagnosis

HSV can be identified in clinical samples using either polymerase chain reaction (PCR) testing or viral culture. The diagnosis of neonatal HSV infections requires sampling of multiple sites:

1. Swabs of mouth, nasopharynx, conjunctivae, and rectum should be obtained for HSV surface cultures (if available) or PCR.
2. Specimens of skin vesicles should be obtained for culture (if available) or PCR.
3. CSF should be obtained for HSV PCR.
4. Whole blood should be obtained for HSV PCR.
5. Alanine aminotransferase (ALT) should be obtained as an indicator of hepatic involvement [25].

In past decades, the presence of red blood cells in CSF was suggestive of HSV CNS infection, likely due to relatively advanced disease due to diagnostic limitations; however, with development of more advanced imaging and diagnostic capabilities, hemorrhagic HSV encephalitis is less commonly seen now, and as such most HSV CNS CSF indices do not have significant numbers of red blood cells unless the procedure was traumatic. Performance of whole blood PCR adds to the other diagnostic

tools (surface and CSF cultures and PCR) but should not be used as the sole test for ruling in or ruling out neonatal HSV infection. Furthermore, viremia can occur in any of the three neonatal HSV disease classifications, so a positive whole blood PCR simply rules in neonatal HSV infection but does not assist in disease classification. HSV isolates grown in culture or HSV DNA detected by PCR can be typed to determine whether it is HSV-1 or HSV-2. Chest radiographs and liver function tests can aid in the diagnosis of disseminated infection. Of note, all infants with HSV disease, regardless of classification, need to have an ophthalmologic exam to look for ocular involvement. Infected neonates also should have neuroimaging studies (MRI preferably, but CT head or ultrasound are acceptable) performed [25].

Treatment

Before antiviral therapies were utilized, disseminated HSV disease caused death by 1 year of age in 85% of patients. In babies with CNS disease, mortality was 50% (Table 1) [20]. In a series of research studies conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) between 1974 and 1997, parenteral vidarabine, lower dose acyclovir (30 mg/kg/day), and higher dose acyclovir (60 mg/kg/day) were evaluated sequentially [18, 20, 24]. These series of studies determined that babies with neonatal HSV disease should be treated with parenteral acyclovir at a dose of 60 mg/kg/day divided in three daily doses (Figs. 2 and 3) [16]; the dosing interval may need to be increased in premature babies, based on their creatinine clearance [26]. The treatment duration is 21 days for babies with disseminated disease or CNS disease, while babies with SEM disease should be treated for 14 days [25]. All patients with CNS HSV disease should have a repeat lumbar puncture near the end of the 21-day course of acyclovir to document that the CSF PCR is negative; if the PCR remains positive, another week of parenteral acyclovir should be administered, and CSF

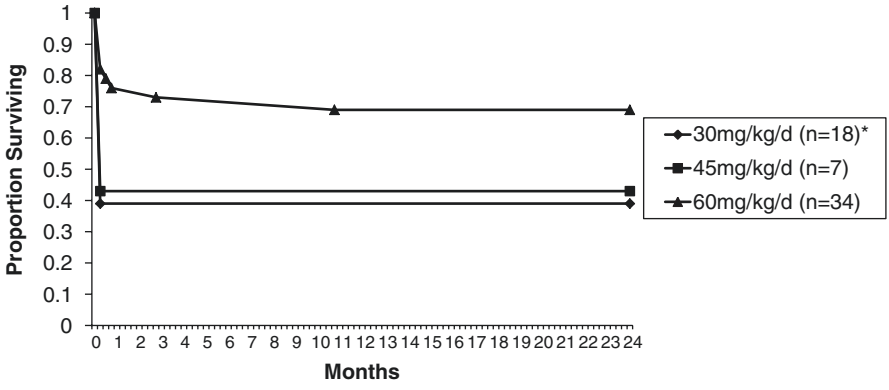

Fig. 2 Mortality in patients with disseminated neonatal herpes simplex virus disease. Adapted from [16]

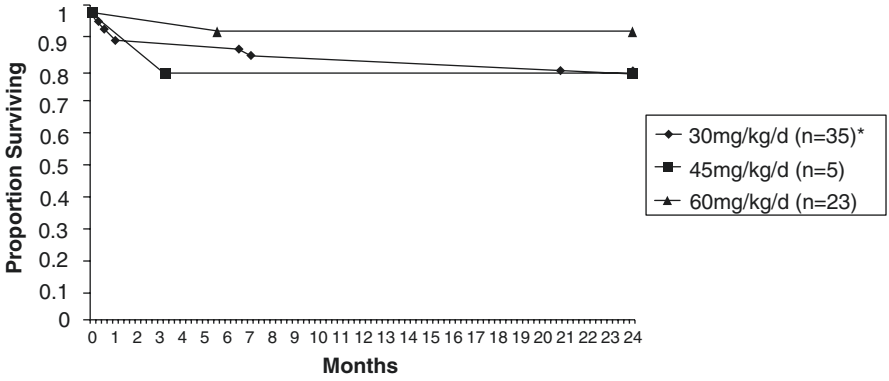

Fig. 3 Mortality in neonates with central nervous system HSV disease. Adapted from [16]

repeated in that manner until a negative CSF PCR is achieved [17, 27]. In contrast, the value of serial whole blood PCR determinations to gauge duration of therapy has not been established, and so blood PCR should not be performed following the initial testing to establish whether neonatal HSV infection exists.

The primary toxicity of higher dose parenteral acyclovir is neutropenia [16]. Absolute neutrophil counts (ANCs) should be monitored twice weekly throughout the course of parenteral therapy.

Oral acyclovir suppressive therapy for 6 months following acute parenteral treatment improves neurodevelopmental outcomes in babies with CNS disease [25]. HSV establishes latency in the sensory ganglia and occasionally reactivates and causes clinically apparent or occult recurrence of disease. A recent double-blind, placebo-controlled study conducted by the CASG involving infants with neonatal HSV with CNS involvement compared Bayley mental developmental scores at 1 year of babies receiving suppressive therapy with acyclovir for 6 months versus babies receiving placebo. The study found that the acyclovir group had a significantly higher mean Bayley score than the placebo group (88.2 vs. 68.1), indicating superior developmental outcomes at 1 year of age (Fig. 4) [29]. Suppressive acyclovir therapy has also been proven to prevent skin recurrences in any classification of HSV disease [28, 29]. Thus, infants should receive oral acyclovir at 300 mg/m^2/dose three times daily as suppressive therapy for 6 months following the initial parenteral treatment course. This dose should be adjusted for growth monthly, and ANCs should be monitored at 2 and 4 weeks after starting therapy and then monthly thereafter while oral acyclovir is administered [25].

Prevention

During pregnancy, all women should be asked about previous or current signs of genital infection. However, if they have not had signs, this does not rule out infection since most adults with genital HSV infection have never had clinically

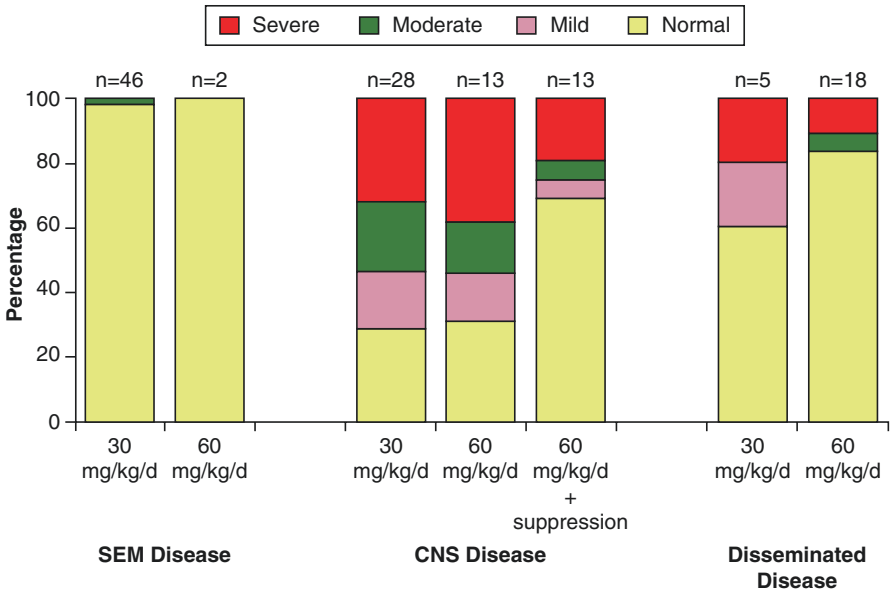

Fig. 4 Morbidity among patients with either skin, eye, and mouth (SEM), central nervous system (CNS), or disseminated neonatal herpes simplex virus disease with known outcomes after 12 months of life as a function of initial acyclovir treatment and suppressive therapy. Adapted from [16, 29]

identifiable symptomatic disease. Any pregnant woman with active genital infection should be given suppressive antiviral therapy at or beyond 36 weeks gestation, per the American College of Obstetricians and Gynecologists [25]. Any person coming in contact with a neonate should always have proper hand hygiene with good handwashing. Finally, any family members with known herpetic lesions on their mouths (cold sores or fever blisters) or hands (herpetic whitlow) should avoid contact with neonate, including nuzzling or kissing the neonate [25].

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