

Herpes Simplex Virus, Meningitis and Encephalitis in Neonates

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KEY WORDS

■ HERPES SIMPLEX VIRUS ■ MENINGITIS ■ ENCEPHALITIS ■ NEONATES
■ CENTRAL NERVOUS SYSTEM ■ MANAGEMENT RECOMMENDATIONS

SUMMARY

The consequences of neonatal herpes simplex virus (HSV) infection can be severe. Disease can be localized to skin, eye and mouth (SEM disease), involve the central nervous system (CNS) or manifest as disseminated infection involving multiple organs. Most surviving infants in the latter two categories have neurological sequelae, and the mortality rate in the absence of therapy is very high (80%) for babies in the latter category. The *International Herpes Management Forum* (IHMF) has produced guidelines on the diagnosis, prevention and effective management of neonatal herpes. Neonatal herpes may occur in the absence of skin lesions, so if the infection is suspected, swabs of the oropharynx, conjunctiva, rectum, skin lesions, mucosal lesions and urine should be promptly taken and submitted for virus culture. Cerebrospinal fluid (CSF) should be submitted for polymerase chain reaction (PCR) detection of HSV DNA. Evidence for disseminated or CNS infection should be sought using liver function tests, complete blood cell count, CSF analysis and chest X-ray, if respiratory abnormalities are present. Neonates with suspected HSV infection should be treated with intravenous aciclovir (20 mg/kg) every 8 h for 21 days. If disease is localized to the SEM, treatment should be limited to 14 days. The neutrophil count for children receiving intravenous aciclovir should be monitored. If the absolute neutrophil count falls below 500/mm³, decreasing the aciclovir dose or administering granulocyte colony stimulating factor (G-CSF) should be considered. At the end of therapy in CNS and disseminated disease, PCR assessment of CSF should be used and treatment continued if the child remains PCR positive at this site.

Introduction

THE CONSEQUENCES OF neonatal herpes simplex virus (HSV) infection can be severe. Mortality following multiorgan disease in the absence of therapy is very high (80%), and most infants surviving central nervous system (CNS) or disseminated disease are neurologically impaired.^{1,2} This paper focuses on the transmission of HSV from the pregnant woman to the neonate, clinical manifestations of infection, risk factors for morbidity and mortality, and clinical trials of antiviral therapy in this population.

Epidemiology of Neonatal HSV Infection

The prevalence of neonatal herpes differs between countries. It is rarely seen in the UK (estimated incidence 1.65/100 000 live births),³ but has a higher incidence in the USA (an estimated 20–50 per 100 000 live births).⁴ This divergence between countries may partly reflect differences in the recognition and definition of the disease as well as true differences in the disease pattern.

Neonatal herpes can result from infection with either HSV-1 or -2, with the latter being associated with a poorer prognosis.^{5,6} HSV-2 is the most common cause of genital herpes in the majority of countries,⁷ where it is

responsible for approximately 85% of cases, and it is the HSV type involved in 70% of neonatal herpes.^{8,9} In Japan the epidemiology of HSV infection is different, as HSV-1 is more frequently associated with genital herpes than in other countries.¹⁰ In Tokyo, 40% of primary genital herpes results from HSV-1 infection, an observation which is in keeping with the relatively common occurrence of neonatal HSV-1 infection.^{11,12} Worldwide this balance does, however, appear to be changing.¹³ In the UK, a similar incidence of neonatal HSV-1 and HSV-2 infection is reported, which may be explained by the high prevalence of primary genital HSV-1 infection.^{14,15}

Transmission of HSV to the Neonate

ROUTE OF INFECTION

Neonatal infection with HSV most often occurs during delivery.¹⁶ Infection can also occur *in utero* (congenital) or following delivery (post-natal acquisition).

Intra-uterine infection: Intra-uterine infection represents approximately 5% of cases of neonatal herpes infection^{2,17} and may occur either as a result of an ascending infection from the cervix or vulva or as a consequence of transplacental transmission.¹⁸ During the first 20 weeks of gestation, HSV infection has been associated with spontaneous abortion, stillbirth and congenital malformations, particularly hydranencephaly and chorioretinitis, and scarring/lesions at birth.^{17–19}

Intra-partum infection: In 85% of cases, HSV infection is transmitted to the neonate during labour when the baby comes into direct contact with infected maternal secretions in the birth canal.¹⁶

Post-partum infection: Post-natal acquisition of HSV accounts for approximately 10% of all cases of neonatal herpes and occurs as a consequence of the baby coming into contact with an environmental source of HSV, such as a family member or caregiver with orolabial herpes, herpetic whitlow or lesions at other sites (e.g. breast).^{20–22}

FACTORS INFLUENCING TRANSMISSION OF HSV TO THE NEONATE

There are four factors which appear to influence the likelihood of transmission of HSV to the newborn:

- Type of maternal genital infection at the time of delivery (i.e. first episode, symptomatic reactivation or asymptomatic reactivation);
- Transmission of maternal transplacental antibodies (quantity and quality of maternal antibodies as a function of gestational age);
- Duration of ruptured membranes in the presence of active infection;
- Use of fetal scalp monitor at delivery.¹⁶

Type of maternal genital infection at delivery: Herpes simplex virus can be transmitted to the neonate when there are episodes of either symptomatic maternal recurrences or asymptomatic virus shedding. The latter

RECOMMENDATIONS AND STATEMENTS

- The neutrophil counts of children receiving intravenous aciclovir (60 mg/kg per day) should be monitored (category 1 recommendation)
- Neonatal herpes may occur in the absence of skin lesions. Thus, a high index of suspicion and prompt deployment of diagnostic methods are required. Whenever neonatal HSV infection is suspected, material from the skin or mucosal lesions, oropharyngeal swabs, conjunctival swabs, rectal swabs and urine should be submitted for virus culture. CSF should be submitted for PCR detection of HSV DNA (category 1 recommendation)
- Evidence of disseminated (visceral) or CNS infection must be sought by performing liver function tests, complete blood cell (CBC) count, CSF analysis and a chest X-ray if there are any respiratory abnormalities (category 1 recommendation)
- Polymerase chain reaction (PCR) analysis of cerebrospinal fluid (CSF) for HSV DNA should be used to diagnose CNS involvement in cases of suspected neonatal HSV infection (category 2 recommendation)
- PCR assessment of CSF should be strongly considered at the end of treatment for CNS and disseminated disease, and antiviral therapy continued if the patient remains PCR positive at this site (category 2 recommendation)
- Neonates with suspected or proven neonatal herpes should be treated with aciclovir 20 mg/kg every 8 h for 14–21 days. If the disease is limited to the skin, eye and mouth (SEM) (i.e. normal CSF, including negative CSF PCR), intravenous aciclovir treatment

(60 mg/kg per day) should be given for 14 days. For other forms of neonatal HSV infection (i.e. CNS or disseminated disease), administration of aciclovir for 21 days is advised. If a CSF analysis is not available, the longer treatment period should be used (category 2 recommendation)

- If absolute neutrophil counts (ANC) fall below 500/mm³, consideration should be given to decreasing the aciclovir dosage or administering granulocyte colony-stimulating factor (G-CSF) (category 2 recommendation)
- PCR detection of HSV DNA in dried blood spots on Guthrie cards may prove useful for retrospective diagnosis of HSV infection (research need recommendation)
- PCR detection of HSV DNA in peripheral blood mononuclear cells (PBMCs) and plasma may prove to be a useful tool for diagnosis of neonatal HSV infection (research need recommendation)

RECOMMENDATION AND STATEMENT CATEGORIES

Category 1

Consistent evidence from controlled clinical trials. For example, for an antiviral, this would include results from at least one well-designed, randomized, controlled clinical trial, and, in the case of laboratory studies, consistent evidence from comparative studies.

Category 2

Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than one centre), or from multiple time-series studies or dramatic results from uncontrolled experiments.

Category 3

Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Research Need

Area in which research is warranted.

can occur because of virus reactivation or due to acquisition of genital herpes during pregnancy.²³ The rate of asymptomatic virus shedding at labour (0.35–1.4%), as measured by virus culture, is similar to that at other times in pregnancy.²⁴ Of asymptomatic women who shed HSV in early labour, the risk of transmission to the neonate is much greater for women with first-episode primary infection (57%) or first-episode non-primary infection (25%), compared with those with recurrent infection (2%) (Figure 1).²⁵ The quantity and duration of virus shedding are higher and longer with primary infection than during recurrent

infection and, together with lack of completion of maternal seroconversion and transplacental passage of antibody, this is likely to be the reason for the greater risk with the former.^{24,26} The risk for acquisition of neonatal herpes is highest if HSV is acquired by the pregnant woman near the time of delivery.

Maternal antibody status: Several retrospective and prospective studies suggest that the risk of HSV transmission is high during vaginal delivery to neonates exposed to asymptomatic shedding or lesions (33% and 50%, respectively) in women with a first episode of

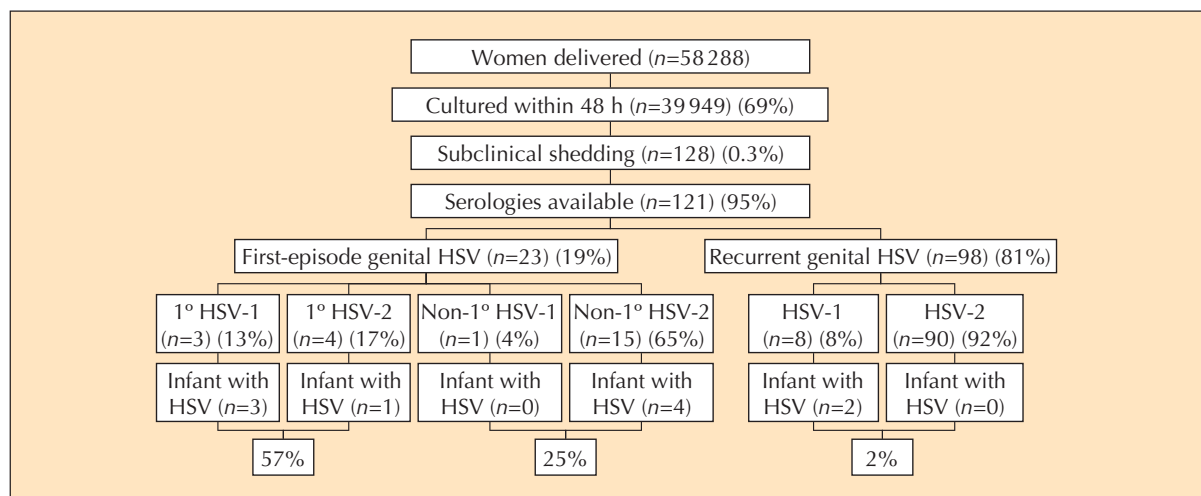


Figure 1: Frequency of neonatal herpes infection among women with first-episode and recurrent herpes simplex virus (HSV) infection.²⁵ Adapted with permission from: JAMA 2003;289:203–209. © 2003 American Medical Association. All rights reserved.

genital herpes.^{23,27,28} In contrast, the risk of transmission is low (<3%) in neonates exposed to women with an established history of genital herpes or who have type-specific antibodies directed against the virus isolated from culture.^{23,27,29,30} Transplacental maternal neutralizing and antibody-dependent cell-mediated cytotoxic (ADCC) antibodies have an ameliorative effect on the acquisition and severity of infection in babies exposed to HSV. The presence of maternal antibodies specific to HSV-2, but not HSV-1, also appears to reduce the neonatal transmission of HSV-2.^{23,27}

If HSV is acquired in late pregnancy, the risk of HSV transmission to the fetus is increased, as maternal antibodies do not develop rapidly, or are not significantly transferred across the placenta.^{28,31} The titre of antibody is also related to disease presentation as the highest transplacental antibody levels are associated with the mildest form of disease and the lowest levels with the most severe clinical manifestations.³²

Duration of ruptured membranes and invasive obstetrical procedures: Prolonged rupture of the membranes (i.e. longer than 6 h) appears to increase the risk of fetal infection, probably as a result of ascending infection from the cervix.³³ In addition, the application of fetal scalp monitors in the delivery suite increases the risk of transmission by providing a site of inoculation for the virus.^{34,35}

Clinical Manifestations of HSV Infection

HSV infection in neonates who become infected during or after birth can be divided into the following categories:

- Disease localized to the SEM;
- CNS disease (with or without SEM involvement);
- Disseminated infection (involving multiple organs such as the liver, lung, adrenal glands and/or brain).^{16,28,29}

The proportions of babies with the different types of HSV-related neonatal disease, mortality rates and incidence of neurological impairment in the absence of antiviral therapy are presented in Table 1.^{36,37}

SEM DISEASE

Skin, eye and mouth disease presents at approximately 10–11 days of age.³⁸ Disease localized to the SEM is often accompanied by discrete vesicles and keratoconjunctivitis. Even when cutaneous lesions are present, they may be difficult to detect without careful examination.

Infants with disease limited to the SEM do not die, although 30–40% later develop neurological impairment if they do not receive antiviral therapy. Significant findings include spastic quadriplegia, microcephaly and blindness. While the children may appear otherwise healthy after birth, the neurological impairment can become apparent in the following 6–12 months. Likely many, if not all, of these infants have subclinical infection of the CNS. Moreover, 75% of babies with SEM infection progress to either CNS or disseminated disease in the absence of antiviral therapy.³⁶ This is probably because a skin rash reflects

widespread viraemia that can lead to infection of organs such as the brain, liver or lungs. Consequently, all infants with SEM disease should be treated aggressively and followed carefully.

CNS DISEASE (ENCEPHALITIS)

Clinical manifestations of CNS disease (alone or in association with disseminated disease) include seizures, lethargy, irritability, tremors, poor feeding, temperature instability, bulging fontanelle and pyramidal tract signs.³⁹ When only the CNS is involved, there is initially unitemporal involvement that evolves to bitemporal disease and then panencephalitis as the disease progresses.

Virus can be cultured from the CSF in 25–40% of all cases when the brain of a newborn is involved.³⁸ Pleocytosis (50–100 white blood cells/mm³ that are predominantly mononuclear) and proteinosis are generally present, although some neonates with CNS infection have no CSF abnormalities.³⁹ Cutaneous vesicles are absent at presentation in about 40% of cases.^{38,40}

CNS disease alone occurs in 35% of HSV-infected infants and seizures are evident in nearly half of all presenting cases.³⁶ The mortality rate is 50% in untreated children and is usually related to brain-stem involvement. Although response to therapy is generally good, neurological sequelae are evident in nearly 70% of surviving neonates.³⁶

DISSEMINATED DISEASE

Infants with disseminated disease present between 9 and 11 days of age and have the worst prognosis of the three forms of disease.³⁸ Multiple organs are infected and signs include irritability, seizures, respiratory distress, jaundice, bleeding diatheses, shock and, often, vesicular exanthem.³⁹

Disseminated disease is seen in 22% of HSV-infected neonates, and mortality in the absence of treatment is high (approximately 85%).^{1,36,37} If treated, survival outcomes in neonates with disseminated disease are improved and nearly 70% survive.³⁸ Approximately 15% of these patients subsequently suffer from neurological sequelae.³⁸

Encephalitis is also common in disseminated disease, occurring in approximately 75% of infected neonates.³⁹ With disseminated disease, the brain is probably infected via a blood-borne route, whereas in CNS disease, infection is probably the result of neuronal spread.

Predictors of Morbidity and Mortality

Two prospective, multicentre analyses have reported predictors of morbidity and mortality from a group of neonates treated with either intravenous vidarabine or aciclovir. One of these analyses was a comparative trial of vidarabine and aciclovir and included 202 neonates aged <1 month with virologically confirmed HSV infection (85 had SEM involvement, 71 encephalitis and 46 disseminated disease).^{1,41} The second analysis examined risk factors in neonates that received either high-dose (60 mg/kg per day) or intermediate-dose (45 mg/kg per day) intravenous aciclovir (n.b. to

Table 1: Presentation and outcomes in neonatal herpes in the absence of antiviral therapy^{36,37}

Category of neonatal HSV infection	Proportion of neonates affected (%)	Mortality (%)	Neurological impairment (%)
SEM	18	0	38
Encephalitis	34	50	67
Disseminated	48	85	50

SEM, skin/eye/mouth.

ascertain predictors of morbidity and mortality, data for patients treated with standard-dose (30 mg/kg per day) aciclovir were taken from the comparative trial of vidarabine and aciclovir).^{6,38}

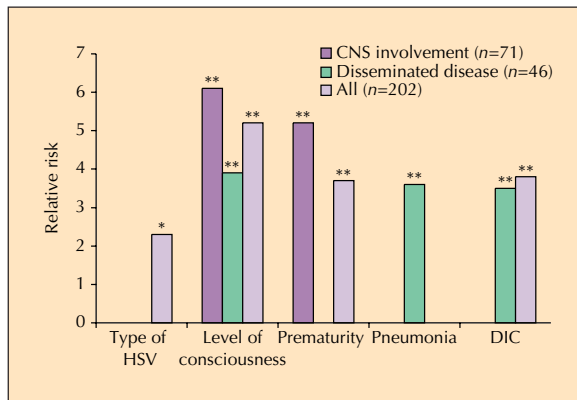


Figure 2: Factors significantly associated with mortality in neonates with virologically confirmed HSV infection.¹ * $P < 0.05$; ** $P < 0.01$. CNS, central nervous system; DIC, disseminated intravascular coagulopathy; HSV, herpes simplex virus. Reproduced with permission from Whitley R, Arvin A, Prober C et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. *N Engl J Med* 1991;**324**:450–454. © 1991 Massachusetts Medical Society. All rights reserved.

PREDICTORS OF MORTALITY

Mortality was significantly higher in neonates with disseminated infection than either CNS or SEM infection (57%, 15% and 0%). As patients with SEM disease do not die from their disease, the predictors of mortality are provided only for those with disseminated or CNS disease (Figure 2).¹

Disseminated infection: A multivariate analysis of the comparative trial found that the factors which were significant predictors ($P < 0.05$) of mortality in neonates with disseminated HSV infection were:

- Significantly reduced level of consciousness (semicomatose or comatose) at presentation;
- Disseminated intravascular coagulopathy;
- HSV pneumonia.¹

The analysis of the combined trials found that among patients treated with aciclovir (30 mg/kg per day), aspartate transaminase elevations ≥ 10 times the upper limit of normal at the initiation of therapy were associated with significantly increased mortality ($P = 0.0006$). Mortality was also significantly associated with the presence of lethargy at the start of therapy.

CNS disease: In the comparative trial, the following factors predicted mortality among neonates with CNS disease:

- Semicomatose or comatose at therapy initiation;
- Prematurity;
- Seizures.

The analysis of the combined trials confirmed that prematurity ($P = 0.0493$) and seizures at initiation of therapy ($P = 0.0637$) were associated with mortality, albeit at borderline levels of significance.³⁸

PREDICTORS OF MORBIDITY

The analysis of both the comparative and combined trials found that patients with CNS or disseminated disease were less likely to have developed normally at 12 months compared with patients with SEM disease.^{1,38}

Disseminated disease: In infants with disseminated disease, the comparative trial found that being semicomatose or comatose at therapy initiation was associated with a 4-fold increase in risk of morbidity. The analysis of the combined trials found that the association of seizures with morbidity was of borderline significance ($P = 0.076$).

CNS disease: The comparative trial found that seizures were associated with a 3.4-fold increase in the likelihood of morbidity. This was confirmed by the combined analysis, which documented a highly significant association between the two ($P = 0.0001$).

SEM disease: Infants with SEM disease experience cutaneous vesicle recurrences, the number of which correlates with neurological outcome.¹ In the comparative study, children who experienced three or more recurrences of SEM disease caused by HSV-2 in the first 6 months of life were 21 times more likely to develop neurological impairment than those children who had less than three recurrences.

DIFFERENCES IN PROGNOSIS BETWEEN HSV TYPES

The prognosis for neonatal HSV disease is considered to be better when infection is caused by HSV-1 than HSV-2, although there is insufficient evidence to confirm an association.³⁸ In the study comparing aciclovir with vidarabine, HSV-2 was associated with significantly higher morbidity than HSV-1 infection.¹ This finding is in keeping with other studies. In the combined analysis of two trials of intravenous aciclovir, involving 186 infants, there was no difference in the mortality rates for HSV-1 infection versus HSV-2 infection for any of the disease types. However, there was a trend to greater morbidity with HSV-2, which achieved borderline significance ($P = 0.10$).⁶ In another report, 50% of infants with HSV-2 encephalitis were microcephalic, 57% had seizures, 64% had ophthalmic defects, 64% had cerebral palsy and 57% had mental retardation.⁹ In comparison, infants with neonatal HSV-1 CNS disease treated with systemic antiviral chemotherapy had good neurological outcomes.

Diagnosis

- Neonatal herpes may occur in the absence of skin lesions. Thus, a high index of suspicion and prompt deployment of diagnostic methods are required. Whenever neonatal HSV infection is suspected, material from the skin or mucosal lesions, oropharyngeal swabs, conjunctival swabs, rectal swabs and urine should be submitted for virus culture. CSF should be submitted for PCR detection of HSV DNA (category 1 recommendation)
- Evidence of disseminated (visceral) or CNS infection must be sought by performing liver function tests, CBC count, CSF analysis and a chest X-ray if there are any respiratory abnormalities (category 1 recommendation)
- PCR analysis of CSF for HSV DNA should be used to diagnose CNS involvement in cases of suspected neonatal HSV infection (category 2 recommendation)

Early recognition and treatment of neonatal HSV infection are likely to be important in reducing mortality and the incidence of neurological sequelae in surviving infants.¹ The high risk of death or neurological damage requires that diagnosis be pursued promptly whenever neonatal HSV infection is suspected. Based upon the degree of clinical suspicion, empirical treatment with intravenous aciclovir should be initiated at the time the diagnostic studies are obtained. To achieve maximum benefit, aciclovir must be administered before widespread dissemination of HSV throughout the body or significant replication within the CNS.⁶

A paediatrician experienced at identifying the signs of neonatal herpes should examine the infant; however, as neonatal herpes can occur without skin lesions, diagnostic tests are required. Evidence of disseminated or CNS infection must be sought by performing liver function tests, CBC count, CSF analysis and a chest X-ray if there are any respiratory abnormalities. Biological specimens should be collected from all of the

following sites for virus culture detection (and with respect to CSF, for PCR analysis) of HSV:⁴²

- Skin
- Conjunctiva
- Mouth and throat
- Rectum
- Urine
- CSF.

DIAGNOSIS BY VIRUS CULTURE

The current standard for diagnosis of neonatal HSV infection is virus culture, although PCR is an alternative. A visible cytopathic effect is visible in 80% of cultures by 2 days and in 90% of cultures by 4 days.⁴³ Isolation of virus by culture from lesions, mucosal surfaces or CSF is commonly used, but can be problematic. For example, while culture from lesions is highly sensitive for HSV, skin lesions are often absent and fewer than 20% of newborns with HSV CNS disease have positive CSF cultures.⁴⁴ PCR assays for HSV DNA are more sensitive than culture for neurological infections.⁴⁵

DIAGNOSIS USING PCR

Polymerase chain reaction allows for the rapid diagnosis of neonatal herpes, particularly HSV infections in the CNS. Not only is it more sensitive than virus culture, it also avoids many of the problems associated with culture methods (e.g. inadequate quantity of specimen, bacterial contamination, inactivation of virus by suboptimal handling and transit delays). However, it is important that there is stringent quality control at the testing laboratory, and that the sensitivity and specificity of the assay is documented.

Several studies have investigated the predictive value of PCR in various fluids in infants with neonatal HSV disease (Table 2).^{45–47} Two of these studies have evaluated the use of PCR for monitoring during antiviral therapy, and subsequent morbidity and mortality outcomes, and these are also discussed in this section.^{45,48} They indicate that PCR should be used to diagnose neonatal herpes involvement of the CNS, but that the technique requires further investigation.

The use of PCR for diagnosis of neonatal HSV infection was validated by a retrospective analysis of stored CSF samples from 77 neonates with HSV disease. Virus was detected in 76%, 93% and 24% of babies with CNS disease, disseminated infection and SEM involvement, respectively.⁴⁵ As HSV DNA was detected in the CSF of infants with SEM, this suggests that HSV may infect the brain without overt symptoms; the management implications of this require further investigation.⁴⁵ Similarly, in another retrospective study, HSV DNA was found in serum and/or CSF specimens in 19 of 21 (90%) children with confirmed

HSV infections, 20 of whom had CNS disease.⁴⁶ HSV DNA was detected in the CSF and sera of 74% and 67% of patients, respectively. The relatively low rate of HSV DNA detection may be explained by the fact that the patients had been receiving therapy for at least 1 week when the CSF was first obtained.

Overall, the diagnostic sensitivity of PCR appears lower for patients with neonatal herpes encephalitis⁴⁵ than for adults.^{49,50} In neonatal encephalitis, the sensitivity of PCR for detecting HSV in CSF ranges from 71% to 100%.^{45,46,48,51} In comparison, for adults with biopsy-proven HSE, PCR of the CSF had a sensitivity of 98% and a specificity of 94%.⁵⁰ However, many of these specimens were only probed by PCR for HSV DNA well after a week into therapy – a time when viral DNA may no longer be detectable. This emphasizes the need for performance of PCR assessment of the CSF at the time of clinical presentation.

PCR monitoring during antiviral therapy:

- PCR assessment of CSF should be strongly considered at the end of treatment for CNS and disseminated disease, and antiviral therapy continued if the patient remains PCR positive at this site (category 2 recommendation)

Antiviral treatment lowers the HSV DNA concentration in the CSF. Therefore, it may be difficult to determine the sensitivity of PCR when patients are receiving treatment. A prospective analysis of seven neonates with HSV infection demonstrated that HSV DNA remained in the serum and/or CSF for 1–2 weeks after initiation of antiviral treatment (intravenous aciclovir 30 mg/kg per day for approximately 2 weeks or vidarabine).⁴⁸ This included one patient with negative cultures for HSV. One of the seven infants developed severe neurological impairment within 1 year of cessation of antiviral therapy, suggesting that detection of HSV DNA in the CSF of SEM patients has clinical relevance. HSV DNA was detected in the CSF of all four patients with CNS disease, but virus isolation was positive in only one case.⁴⁸ Overall, in a retrospective analysis, 95% of 19 infants with positive PCR results in CSF after the completion of 10 days' antiviral therapy (with either vidarabine or aciclovir) experienced significant morbidity or mortality.⁴⁵

Herpes simplex virus viral load in an individual is a most likely marker of therapeutic effect. In adults, the HSV titre in the CSF is prognostic; levels of >100 copies/ml correlate with a reduced level of consciousness and likelihood of future neurological impairment.⁵² The persistence of virus during antiviral therapy may reflect the inability of the host to control infection despite antiviral therapy.

Table 2: Studies that have investigated the predictive value of PCR in various fluids in patients with neonatal HSV disease^{45–47}

Study (design)	Patients (n)	HSV disease	Compartment	PCR positive (%)
Kimberlin <i>et al.</i> ⁴⁵ (ret)	77	CNS	CSF	76
		DIS	CSF	93
		SEM	CSF	24
Malm <i>et al.</i> ⁴⁶ (ret)	21	All	CSF	74
		All	Serum	67
Diamond <i>et al.</i> ⁴⁷ (con)	11	All	CSF	36
		All	Plasma	67
		All	PBMCs	60

CNS, central nervous system; DIS, disseminated; SEM, skin/eye/mouth; ret, retrospective; con, consecutive; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; PBMCs, peripheral blood mononuclear cells.

Potential PCR-based diagnostic methods:

- PCR detection of HSV DNA in dried blood spots on Guthrie cards may prove useful for retrospective diagnosis of HSV infection (research need recommendation)
- PCR detection of HSV DNA in PBMCs and plasma may prove to be a useful tool for diagnosis of neonatal HSV infection (research need recommendation)

Analysis of Guthrie cards: Preliminary results indicate that PCR to detect HSV DNA in dried blood spots on Guthrie cards can detect neonatal HSV infection.⁵³ Guthrie cards from four infants with suspected neonatal herpes and 73 controls were analysed by PCR. Three of the four suspected cases were positive for HSV-2 DNA and one was positive for HSV-1 DNA; of the controls, two were HSV-1 DNA positive while the remainder were HSV-1 and HSV-2 DNA negative. Thus, the sensitivity of this test was 100% and the specificity was 97%.⁵³ However, strict procedures are needed to monitor potential cross-contamination from adjacent Guthrie cards.

Analysis of peripheral blood mononuclear cells: PCR analysis of PBMCs and plasma may also be a useful diagnostic tool in neonatal herpes.⁴⁷ In a series of 11 consecutive cases of neonatal HSV infection, PCR was performed in specimens from at least one site. HSV DNA was detected in the PBMC of 60% (6 of 10) of infants tested, in the plasma of 67% (4 of 6 tested) and the CSF of 36% (4 of 11 tested). These data suggest that HSV viraemia is more frequent than previously thought and that PCR of plasma and PBMC could be used to diagnose HSV infection earlier.⁴⁷

Interventions to Prevent or Treat Neonatal HSV Disease

Below, we examine the use of aciclovir to treat or suppress neonatal HSV disease. In addition, we report the interventions used to prevent transmission of HSV to the neonate. Caesarean sections are used with the objective of preventing transmission to the newborn if a woman has lesions at delivery. Other strategies rely on antiviral therapy to prevent transmission of HSV.

ACICLOVIR THERAPY OF NEONATAL HERPES

- Neonates with suspected or proven neonatal herpes should be treated with aciclovir (20 mg/kg every 8 h for 14–21 days) If the disease is limited to the SEM (i.e. normal CSF, including negative CSF HSV PCR), intravenous aciclovir treatment (60 mg/kg per day) should be given for 14 days. For other forms of neonatal HSV infection (i.e. CNS or disseminated disease), administration of aciclovir for 21 days is advised. If a CSF analysis is not available, the longer treatment period should be used (category 2 recommendation)

Aciclovir and vidarabine have been shown to reduce the morbidity and mortality of HSV infection in the neonate.^{28,38,41,54} A study comparing aciclovir (10 mg/kg every 8 h for 12 days) with vidarabine (10 mg/kg every 8 h for 12 days) demonstrated that both drugs reduced overall mortality from SEM, disseminated disease or encephalitis to approximately 19%, and reduced morbidity.⁴¹ For both treatments, the outcome varied according to the extent of disease; no infants with SEM disease died, while the mortality rate was 14% in CNS disease and over 50% in disseminated disease (Figure 3).⁴¹

Vidarabine and aciclovir had similar effects on morbidity (Figure 3). Of the infants who survived, development was normal or mildly impaired in 95% of those with SEM involvement, 45% of those with CNS disease and in 65% of those with disseminated manifestations. In addition, the proportion of children

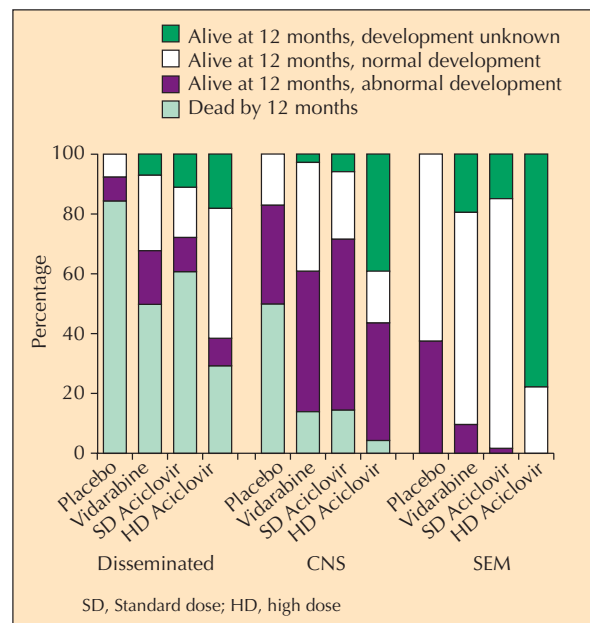


Figure 3: Morbidity and mortality in neonatal herpes following treatment with vidarabine or aciclovir (Note: mean duration of disease before initiation of therapy was 4 days).^{37,41} CNS, central nervous system; SEM, skin, eye and mouth. Kimberlin DW. *Advances in the treatment of neonatal herpes simplex infections*. Rev Med Virol 2001. © John Wiley & Sons Limited. Reproduced with permission.

returning to normal function was significantly greater than in earlier trials, possibly because the early antiviral therapy prevented disease progression. However, the mean duration of disease for all children before therapy was administered was 4 days and, thus, even earlier intervention may be possible.

In practice, aciclovir is used because of its safety profile and convenient dosing regimen.⁴¹ More recent studies have investigated treatment with higher doses of aciclovir and for longer periods,³⁸ as well as the potential of suppressive aciclovir therapy.⁵⁵ Efforts to improve both morbidity and mortality have resulted in the lengthening of treatment courses from 10 to 14–21 days, depending upon disease classification. A non-blinded clinical trial involving neonates with HSV infection has investigated the safety and therapeutic efficacy of high-dose intravenous aciclovir administered for this longer period.³⁸ Infants aged ≤ 1 month with confirmed HSV disease (either CNS, $n=28$; disseminated, $n=41$; SEM, $n=10$) received daily intravenous aciclovir 45 mg/kg or 60 mg/kg in three divided doses for 21 days. Infants were then followed up for the first 4 years of life.³⁸

Neonates with disseminated disease who received high-dose aciclovir (60 mg/kg per day) showed significantly improved rates of survival compared with those from a previous study treated with aciclovir 30 mg/kg per day (odds ratio [OR] 3.3; 95% confidence interval [CI] 1.4–7.9, Figures 4A and 4B).³⁸

Duration of therapy: The duration of intravenous aciclovir therapy depends on disease classification. If the disease is limited to the SEM (i.e. normal CSF both biochemically and by PCR), treatment should be for 14 days.⁵⁶ For disseminated and CNS neonatal HSV infections, administration for 21 days is advised. If a CSF analysis is not available, the longer treatment period should be used.

Suppressive therapy for neonatal HSV infection: The therapeutic use of suppressive aciclovir therapy in neonatal HSV infection is currently under investigation. Results from a Phase I/II trial indicating that suppressive therapy following completion of

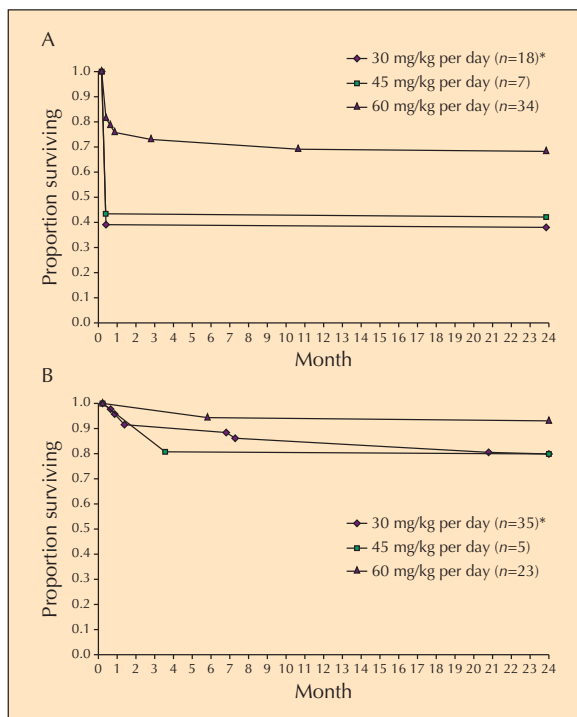


Figure 4: Mortality among infants with (A) disseminated or (B) CNS neonatal HSV disease receiving aciclovir.³⁸ *, historical cohort. Reproduced with permission from *Pediatrics* 2001;108:230–238, Figure 2, © 2001.

intravenous aciclovir treatment limits recurrences are presented in Table 3,⁵⁵ but a recommendation cannot be made on the basis of these preliminary data. As discussed below, neutropenia was reported in recent trials of aciclovir for the treatment and management of neonatal herpes. Furthermore, in considering the use of suppressive aciclovir, as the kidney eliminates aciclovir, it is important

to determine whether or not there is a risk of neonatal nephrotoxicity. Ongoing Phase III studies will ultimately ascertain if there is therapeutic benefit to suppressive therapy following treatment of acute disease, and if so whether the risk/benefit ratio favours routine utilization of this approach.

Effects of aciclovir on neonatal absolute neutrophil count:

- The neutrophil counts of children receiving intravenous aciclovir (60 mg/kg per day) should be monitored (category 1 recommendation)
- If ANC fall below 500/mm³, consideration should be given to decreasing the aciclovir dosage or administering GCSF (category 2 recommendation)

Neutropenia has been the most common side-effect seen in recent trials of aciclovir for the treatment and management of neonatal herpes. Decreased ANC counts were seen in 46% of neonates aged ≤1 month who received oral aciclovir suppressive therapy (300 mg/m² two or three times daily) for 6 months.⁵⁵ In the trial of high-dose intravenous aciclovir (60 mg/kg per day) for 21 days, transient neutropenia (ANC ≤1000/mm³) was observed in six of 29 (21%) recipients (Table 4); all had HSV disease localized in the SEM or CNS and thus the neutropenia could not be explained based upon widespread viral dissemination. Somewhat reassuringly, ANCs recovered during continuation of therapy (or after cessation of treatment) and no adverse sequelae were observed.³⁸ Specifically, no cases of systemic bacterial infection were noted, although the sample sizes were small.

In infants with disseminated disease, the development of neutropenia most likely reflects widespread virus replication that involves bone marrow hematopoietic cells. For those patients with SEM or CNS disease (i.e. localized disease), virus replication is unlikely to be the cause of neutrophil loss. The incidence of neutropenia with high-dose aciclovir suggests that it is prudent to monitor neutrophil counts. If ANC falls below 500/mm³ for a prolonged period, consideration should be given to decreasing the aciclovir dosage or administering GCSF.³⁸

Table 3: Cutaneous recurrences of HSV (primary end-point) during suppressive aciclovir therapy⁵⁵

Skin recurrences (n)	300 mg/m ² dose	
	3 × daily (n=16)	2 × daily (n=2)
0	13 (81%)	0
1	1 (6%)	1 (50%)
2	1 (6%)	1 (50%)
≥3	0	0
Unknown	1 (6%)	0

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Table 4: Effect of aciclovir therapy on ANC in patients with neonatal HSV disease^{38,45}

Study	Patients (n)	Dosage of aciclovir	ANC (per mm ³)	
			<500 (%)	500–1000 (%)
Kimberlin <i>et al.</i> ⁴⁵	5	Oral 300 mg/m ² twice daily	1 (20)	2 (40)
	21	Oral 300 mg/m ² three times daily	3 (14)	6 (29)
	26	Oral 300 mg/m ² (either twice daily or three times daily)	4 (15)	8 (31)
Kimberlin <i>et al.</i> ³⁸	4	Intravenous 45 mg/kg per day	0	1 (25)
	29	Intravenous 60 mg/kg per day	1 (3)	5 (29)
	33	Intravenous either 45 or 60 mg/kg per day	1 (3)	6 (18)

ANC, absolute neutrophil count.

Reducing the delay between onset of symptoms and treatment initiation: The average time between onset of neonatal herpes symptoms and hospital admission is 4 days,^{41,57} and a number of factors contribute to this delay. One is that although the delivering obstetrician may be aware of maternal genital herpes, the physician assessing the symptomatic infant often is not. Furthermore, parents may not understand the risks of vertical transmission and, therefore, may not seek medical advice when the child first becomes ill. The situation is complicated by the fact that the signs and symptoms of neonatal herpes can be non-specific and usually develop after the infant has been taken home.⁵⁷ Additionally, a history of genital HSV in the mother is usually not available, with 60–80% of infected infants being born to mothers with no history of genital HSV. Furthermore and as described below, such a history is not particularly helpful, since women with known history of genital HSV are actually at *lesser* risk of transmitting HSV to their babies compared with women who acquire HSV during pregnancy.

Educating parents with known genital herpes about risks to the child is one way to increase the possibility of earlier diagnosis. They should be familiarized with the signs and symptoms of neonatal herpes infection, and should receive explicit instructions as to when and how to seek medical attention for their newborn.

MANAGEMENT OF SUSPECTED OR PROVEN NEONATAL HSV INFECTION

The likelihood of neonatal herpes is influenced by the history and presentation of a woman with genital HSV infection at delivery. The risk of neonatal herpes is greatest if a woman has a clinically apparent first episode at delivery; the risk is lower if she has a recurrent episode and lowest if there is a history of genital HSV infection but no obvious lesions at delivery. The degree of risk influences the management strategies for both the mother and the infant.

Infant born vaginally or after prolonged rupture of membranes to a woman with clinically apparent first episode at delivery: In at least 10% of first clinical episodes of symptomatic genital herpes, there is serological evidence of HSV-2 indicative of past asymptomatic acquisition of HSV-2.⁵⁸ However, the majority of first clinical episodes of symptomatic genital herpes are true first episode illnesses. For this reason, surface specimens (but not a CSF sample) for virological assays should be obtained from the asymptomatic infant at 24 h of life because of the importance of early diagnosis. Prophylactic intravenous aciclovir (60 mg/kg per day in three divided doses) for 10 days is recommended (pre-emptive or expectant therapy). If disease develops, a work-up of the CNS is indicated, including CSF examination by PCR. If there is evidence of disseminated or CNS infection, the infant should be treated with intravenous aciclovir (60 mg/kg per day in three divided doses) for 21 days. At the completion of therapy, the child must be followed carefully for any evidence of infection.

Infant born vaginally or after prolonged rupture of membranes to a woman with clinically apparent recurrent genital herpes at delivery: Although the infant's parents should be educated about the signs of neonatal herpes, pre-emptive intravenous aciclovir is not appropriate because the risk of HSV transmission to the infant is low and the risk of developing the disease is small. Surface cultures (but not a CSF sample) should be obtained at 24 h of life, and treatment begun for 10 days if positive.

Infant born vaginally or after prolonged rupture of membranes to a woman with a history of genital HSV infection but no obvious lesions at delivery: As above, although parents should be educated about the signs of

neonatal herpes, pre-emptive intravenous aciclovir is not appropriate because the risk of HSV transmission to the infant is low and the risk of developing the disease is small.

Infant with a presentation compatible with neonatal HSV infection: Specimens for virological assay should be obtained from the infant at presentation because of the importance of rapid diagnosis. A work-up of the CSF, including PCR for HSV DNA, is advised. Intravenous aciclovir (60 mg/kg per day in three divided doses) for 14 days is recommended. If there is evidence of disseminated or CNS infection, the infant should be treated with intravenous aciclovir (60 mg/kg per day in three divided doses) for 21 days.

Management of HSE in Adults and Older Children Compared with Management of Neonatal CNS Disease

The anatomical distribution of HSE in adults generally displays a frontal-temporal pattern; in contrast, imaging studies of HSV-1 encephalitis in neonates and young children have shown a more diffuse bilateral disease.⁵⁹ Moreover, infants with HSV-2 encephalitis show periventricular white matter lesions and meningeal enhancement using magnetic resonance imaging (MRI).⁶⁰

Adults and older children are recommended to receive aciclovir 10 mg/kg every 8 h (with some experts recommending 15–20 mg/kg every 8 h) for 14–21 days for the treatment of HSE, based on clinical trial results that showed a clear benefit of therapy with aciclovir over vidarabine with respect to morbidity and mortality outcomes. However, both drugs showed similar efficacy in clinical trials involving the treatment of neonatal disease.^{28,38,41,54} Aciclovir is recommended as the drug of choice for the treatment of neonatal HSV disease because of its safety profile and ease of administration.

Strategies to Prevent Neonatal Acquisition of HSV Infection

DELIVERY BY CAESAREAN SECTION

Delivery by Caesarean section decreases the risk of neonatal acquisition of HSV when virus is present in the maternal genital tract.²⁵ However, the protection offered by Caesarean section is not complete; in large case series, 13–33% of newborns had HSV infection after delivery by this method.^{20,61,62}

SUPPRESSIVE THERAPY IN THE SEROPOSITIVE PARTNER OF A SERONEGATIVE GRAVID WOMAN
Two reasonably effective and clinically practical means of prevention, condoms and antiviral suppression, have recently been proven effective for preventing transmission of genital herpes among sexual partners. When condoms are used during more than 70% of sexual encounters between an HSV-2-positive man and an HSV-2-negative woman, HSV-2 transmission to the seronegative partner is reduced by more than 60%.⁶³ Additionally, valaciclovir suppressive therapy of genital herpes in the HSV-2 seropositive member of a serodiscordant couple can decrease the likelihood of HSV-2 transmission to the seronegative partner, with acquisition of symptomatic genital herpes disease being reduced by 77%, and with acquisition of genital HSV-2 infection (symptomatic or asymptomatic) being reduced by 50%.⁶⁴ Studies evaluating efficacy of these measures among couples with a seronegative pregnant woman and a seropositive man have not been undertaken.

SUPPRESSIVE THERAPY FOR MATERNAL GENITAL HSV INFECTION

Primary or first-episode genital herpes: For non-pregnant women, aciclovir shortens the duration and

lessens the severity of symptoms as well as decreasing the duration of virus shedding,⁶⁵ but there have been a limited number of studies evaluating the efficacy of aciclovir in pregnancy. Clinical trials evaluating the use of suppressive oral aciclovir in late pregnancy (from 36 weeks until delivery) are presented in Table 5.

In a placebo-controlled, double-blind, prospective study, aciclovir reduced the number of positive virus cultures and the need for Caesarean sections for women with first-episode genital herpes.⁶⁶ Oral aciclovir therapy (200 mg four times daily) given from 36 weeks gestation to delivery was compared with placebo in 46 pregnant women with first-episode genital herpes.⁶⁶ Caesarean delivery was performed if there was evidence of lesions at delivery. None of the 21 women treated with aciclovir had clinical evidence of recurrent genital herpes at delivery compared with nine of 25 women (36%) in the placebo group ($P=0.002$) (Table 6). This difference was reflected in the proportion of Caesarean deliveries ($P=0.002$). No women in either treatment group experienced asymptomatic virus shedding at delivery and no infant had neonatal herpes or experienced any adverse effects due to treatment.

The finding from the randomized trial described above – that aciclovir reduces the number of clinical

recurrences – is supported by an open-label study involving 96 women. Suppressive aciclovir (400 mg orally three times daily) from 36 weeks until delivery reduced clinical recurrences after a first episode of genital herpes during pregnancy.⁶⁷ From the intent-to-treat analysis, 4% of women had clinical recurrences, which is lower than the 18–37% reported for historical controls. Subclinical shedding, however, is not fully suppressed in patients studied to date,^{68,70} suggesting that neonatal transmission is likely still possible despite antiviral suppression in the mother.

Antiviral treatment of recurrent genital herpes in pregnancy: Suppressive aciclovir (200 mg four times daily) given during late pregnancy to 63 women with recurrent genital herpes significantly reduced the number of clinical recurrences in a placebo-controlled trial.⁷¹ However, the trial was too small to demonstrate conclusively a difference between aciclovir and placebo on the rate of Caesarean section, although there was a trend towards fewer Caesarean sections with treatment (Table 7).⁷¹

In a relatively large, randomized trial, pregnant women who had at least one episode of genital herpes during pregnancy were assigned to receive oral aciclovir from 36 weeks of gestation to term ($n=167$) or no

Table 5: Clinical trials that have evaluated the suppressive use of oral aciclovir in late pregnancy (36 weeks until delivery)^{66–69}

Study (design)	Patients (n)	Treatment (dosage)	Caesarean delivery (%)	HSV recurrence at delivery (%)	Asymptomatic shedding (%)
<i>In patients experiencing a first episode of genital herpes</i>					
Scott <i>et al.</i> ^{66,a}	21	Aciclovir 400 mg three times daily	0	0	0
	25	Placebo	36	36	0
Scott <i>et al.</i> ⁶⁷	96	Aciclovir 400 mg three times daily		1	1
<i>In patients with a history of genital herpes</i>					
Braig <i>et al.</i> ⁶⁸	167	Aciclovir 200 mg four times daily	8.4		0
	121	No treatment	16.5		5
	201	No treatment ^b	9.9		0.5
Watts <i>et al.</i> ⁶⁹	84	Aciclovir 400 mg three times daily	4	5	
	78	Placebo	10	14	

^aRandomized, placebo-controlled; ^bno active episodes at delivery; HSV, herpes simplex virus.

Table 6: Effect of aciclovir on clinical recurrences, number of Caesarean sections, cases of neonatal herpes and HSV shedding in pregnant women⁶⁶

	Aciclovir $n=21$ (%)	Placebo $n=25$ (%)	P -value
Clinical recurrences	0 (0)	9 (36)	0.002
Caesarean sections for HSV	0 (0)	9 (36)	0.002
Overall rate of Caesarean sections	4 (19)	10 (40)	
Neonatal herpes	0	0	

Table 7: Pregnancy outcome in a randomized, placebo-controlled trial of aciclovir⁷¹

	Aciclovir ($n=31$)	Placebo ($n=32$)	Odds ratio (95% confidence interval)
Clinical recurrence after trial entry	1	8	0.10 (0.00–0.86)
Clinical recurrence at time of labour	2	6	0.30 (0.03–1.9)
Caesarean section for HSV	4	8	0.44 (0.09–1.94)
Caesarean section for other reasons	3	2	1.61 (0.17–20.43)
Total Caesarean sections	7	10	0.64 (0.18–2.27)
Infants with neonatal herpes	0	0	

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Table 8: Recurrences and Caesarean section in a controlled trial of aciclovir in late pregnancy⁷⁰

Outcome	Aciclovir (n=46)	No treatment (n=46)
HSV recurrence/positive culture:		
<10 days before delivery	0	8 (17%)
During delivery	0	4 (9%)
Total	0	12 (26%)
Caesarean section for:		
Herpes	0	9 (20%)
Obstetric reasons	6 (13%)	6 (13%)
Total	6 (13%)	15 (33%)

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treatment (n=121). A control group comprised women not given prophylaxis who had a history of genital herpes, but no active episodes during pregnancy (n=201). The rate of Caesarean section was 8.4% in those receiving aciclovir, 16.5% in those given no treatment (75% of which were performed for genital herpes) and 9.9% in the control group (10% of which were performed for genital herpes).⁶⁸

In another randomized trial, pregnant women with recurrent HSV received aciclovir 400 mg three times daily (n=84) or placebo (n=78) from 36 weeks of gestation until delivery. Specimens for HSV culture and DNA PCR were self-collected. Lesions occurred at delivery in 5% of aciclovir-treated women compared with 14% of those receiving placebo. HSV culture and PCR positivity near delivery occurred in 0% and 2% of aciclovir-treated women and 7% and 34% of the placebo group, respectively. Caesarean delivery for HSV was performed in 4% of the aciclovir-treated group and 10% of the placebo group.⁶⁹

In a non-randomized, uncontrolled study, aciclovir reduced symptomatic recurrences and virus shedding in pregnant women with recurrent genital herpes (Table 8).⁷⁰ A total of 46 women received aciclovir (200 mg four times daily), generally within 1 week before expected term, and an unmatched cohort of 46 women were untreated. Aciclovir was given for an average of 10 days (range 3–27 days). No woman in the aciclovir group had a symptomatic recurrence during treatment, excreted virus during delivery or required Caesarean section because of herpes. In contrast, 12 (26%) untreated women had symptomatic recurrences within 10 days of delivery. Of these 12 women, nine had a Caesarean section because of HSV infection.⁷⁰

Overall, these trials in pregnant women suggest that aciclovir reduces the clinical recurrence rate and lowers the Caesarean section rate in women with first-episode and recurrent genital herpes. However, the sample sizes of these trials are too small for definitive conclusions to be drawn.

In summary, suppressive therapy with oral aciclovir reduced the need for Caesarean section for recurrent herpes both in women whose first clinical episode of genital HSV occurred during pregnancy⁶⁶ and in those with a previous history of genital herpes.⁶⁸ The impact on neonatal HSV disease cannot be assessed from these small trials, but the finding that subclinical shedding may still occur in women receiving oral aciclovir during the last weeks of pregnancy⁶⁸ suggests that neonatal transmission is possible despite antiviral suppression in the mother. Aciclovir concentrations in cord blood of babies whose mothers have received valaciclovir, approach levels that have appeared to cause significant neutropenia in infants receiving long-term oral aciclovir suppressive therapy following neonatal HSV disease.^{72,73} While neutropenia has yet to be observed among infants born to the small number of women in trials of aciclovir suppressive therapy, ongoing studies continue to investigate this possibility. The potential for fetal nephrotoxicity must also be assessed as aciclovir is eliminated mainly by the kidney.

Conclusions

Neonatal herpes can result from infection with HSV-1 or -2. The risk of transmission of HSV to the neonate is low in women with a history of genital herpes in the absence of identifiable lesions (3%) but is increased to approximately 50% in pregnant women developing a primary infection in the third trimester. Delivery by Caesarean section appears to decrease the risk of HSV transmission in the presence of an active lesion.

Approximately 30% of neonates with SEM disease who do not receive antiviral therapy will ultimately develop neurological impairment; however, 75% progress to either CNS or disseminated forms of the disease. CNS disease accounts for 35% of all cases of neonatal herpes, with seizures evident in half and mortality related to brain-stem involvement. Disseminated disease is the most severe form of neonatal herpes, with high rates of mortality. Fewer patients with HSV-1 appear to suffer subsequent neurological impairment.

Early recognition and treatment of neonatal HSV infection are important in decreasing both mortality and the incidence of neurological sequelae in surviving infants. Diagnosis is usually made using virus cultures from lesions or other surface sites, or by PCR of CSF. The diagnostic sensitivity of PCR analysis appears lower for neonatal than for adult herpes encephalitis. PCR of CSF or serum may prove beneficial for monitoring virus load during antiviral therapy, but further research is needed.

Aciclovir is indicated at a higher dose in neonates than for the treatment of HSE in older children and adults. It is recommended that neonates with disseminated disease or encephalitis be treated with aciclovir 20 mg/kg three times daily for 21 days. Currently available data do not support the routine use of oral suppressive aciclovir therapy following treatment of acute neonatal HSV disease. There is the potential for neutropenia and nephrotoxicity. Ongoing investigations will ultimately determine the risk/benefit ratio of such an approach.

Suppressive antiviral therapy for HSV-2-infected pregnant women in the final trimester appears to be effective in preventing recurrent episodes and shedding at delivery, thereby decreasing the necessity for Caesarean section. While neutropenia has yet to be observed among infants born to women receiving suppressive therapy, ongoing studies continue to investigate this possibility. The potential for fetal nephrotoxicity must also be assessed.

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