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[Intervention Review]

Antiviral agents for treatment of herpes simplex virus infection in neonates

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ABSTRACT

Background

Herpes simplex virus (HSV) is a rare but serious neonatal pathogen. Prior to the availability of antiviral drugs the mortality associated with all but localised neonatal infection was high, with 85% of infants with disseminated HSV infection and 50% of infants with encephalitis dying by one year of age. The morbidity in the survivors of multiorgan infection was also high, with up to 50% experiencing long-term neurological sequelae.

Objectives

To determine the effect of antiviral agents in the treatment of neonatal HSV infections on mortality, progression of disease and neurodevelopmental sequelae at approximately one year. The secondary objective was to assess the effect of antiviral agents on major complications associated with the use of these agents including nephrotoxicity and bone marrow suppression.

Search methods

Trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2008), MEDLINE (1996 - Nov 2008), EMBASE (1982 - Nov 2008) and reference lists of published trials.

Selection criteria

Randomised and quasi-randomised controlled trials of antiviral therapy in infants less than one month of age with virologically proven HSV infection were included.

Data collection and analysis

Data were extracted and the analyses performed independently by two review authors. Studies were analysed for methodological quality using the criteria of the Cochrane Neonatal Review Group. All data were analysed using RevMan 5.1. When possible, meta-analysis was performed to calculate typical relative risk, typical risk difference, along with their 95% confidence intervals (CI).

Main results

Two eligible studies of a total of 273 infants were included. Both studies were randomized controlled trials. One study treated 63 infants with vidarabine or placebo (Whitley 1980) and the other study treated 210 infants with aciclovir or vidarabine (Whitley 1991).

In the study comparing vidarabine with placebo (Whitley 1980), infants with all forms of neonatal HSV disease were included [disseminated disease, central nervous system (CNS) disease alone, and skin, eye and mouth (SEM) disease]. There was no significant reduction in the

risk of mortality when analyzed as an entire group; however, mortality was significantly reduced when data from infants with CNS disease or disseminated disease were combined. There was no difference in the rate of neurological abnormalities in survivors at one year when analyzed as an entire group or by disease category.

There was no difference between aciclovir and vidarabine (Whitley 1991) in preventing mortality from neonatal HSV disease, in preventing disease progression, in reducing the incidence of neurological abnormality at one year, or in the incidence of drug-induced renal or bone marrow toxicity. In infants with SEM disease, there was no significant difference in neurological outcome with aciclovir compared vidarabine treatment. Both drugs were well tolerated in the newborn period.

Authors' conclusions

There is insufficient trial evidence to evaluate the effects of antiviral agents with controls or with each other. The rarity of the condition makes effectively powered clinical trials difficult to perform. The efficacy of newer antiviral agents with better bioavailability (e.g. valaciclovir, valganciclovir) for the treatment of neonatal disease needs to be evaluated in randomised trials. The efficacy of oral formulations need to be evaluated as they may be useful for infants with skin, eye or mouth HSV disease or in the treatment of infants with recurrences after the neonatal period.

PLAIN LANGUAGE SUMMARY

Antiviral agents for treatment of herpes simplex virus infection in neonates

The virus herpes simplex (herpes) causes a rare but devastating disease in the newborn that can range from skin and eye infection to shock, organ failure, brain infection, and death. Newborn herpes infection is an uncommon complication of active genital herpes in the mother around the time of delivery or after direct contact with a herpes blister ("fever blister", "cold sore") of an infected caregiver. We reviewed five studies conducted to assess the effects of antiviral agents (medications that reduce the spread of virus in the body) on mortality and long-term complications of herpes disease in the newborn. Antiviral agents were shown to reduce mortality from the condition, but the reduction was not statistically significant due to the small number of infants in the study. There was insufficient trial data to guide caregivers regarding the duration of antiviral therapy or dose.

BACKGROUND

Description of the condition

Herpes simplex virus (HSV) is a rare but serious neonatal pathogen. The incidence of HSV infection ranges from 1:3,500 to 1:5,000 live births in the USA (Sullivan-Bolyai 1983; Gutierrez 1999), to 1:10-50,000 live births in the United Kingdom (Tookey 1996) and Australia (Jones 2006). Both type 1 and type 2 HSV can cause neonatal disease with the predominant type varying around the world (Garland 2001). The majority of infected infants acquire the infection after passage through an infected birth canal, while 5 - 10% are infected postnatally by a caregiver and about 5% are infected *in utero* (Whitley 1993). Neonatal infection may result in disease localised to the skin, eye or mouth, encephalitis, pneumonitis or disseminated infection (Whitley 1993).

The highest attack rate for neonatal HSV disease is in offspring of women experiencing their first genital HSV infection who have not seroconverted to HSV prior to the onset of labour (Brown 1997). The use of fetal scalp electrodes is an additional risk factor for neonatal HSV infection (Whitley 1993). The diagnosis of neonatal HSV disease is made difficult by the fact that over 70% of women with genital HSV infection are unaware of their condition (Brown 1991). Therefore, there is often a significant delay between the onset of symptoms in the infant and the initiation of antiviral therapy.

Description of the intervention

The first drugs that demonstrated efficacy *in vivo* against HSV were idoxuridine, vidarabine, and trifluridine (Naesens 2001). Due to toxicity with systemic administration, these drugs were replaced by the nucleoside analogues; first aciclovir and, more recently, ganciclovir, penciclovir, and their respective pro-drugs (inactive precursor of the drugs that are metabolised in the body into the active form) (Naesens 2001). These agents are converted to monophosphate metabolites by the HSV enzyme thymidine kinase and then to di- and triphosphate products by cellular enzymes that inhibit viral DNA synthesis by a variety of mechanisms (Naesens 2001). Of these drugs, only aciclovir and vidarabine have been evaluated in the context of neonatal HSV disease. Prior to the availability of these drugs, the mortality associated with all but localised neonatal infections was very high; 85% of infants with disseminated HSV infection and 50% of infants with encephalitis died by one year of age (Whitley 1980a). The morbidity in the survivors of multi-organ infection was also high, with up to 50% experiencing long-term sequelae such as seizures, developmental delay, cerebral palsy, visual or hearing impairment and learning difficulties (Whitley 1980). In the 1980's, the mortality rate from neonatal HSV disease improved with the availability of the intravenous antiviral agents vidarabine and aciclovir, although there was a less dramatic improvement in the morbidity rate (Whitley 1983; Whitley 1991). Aciclovir has become the favoured agent over vidarabine as it is more easily administered (Kimberlin 2001). In general, these agents are well tolerated in the newborn period aside from reversible neutropenia observed with high doses of aciclovir and the putative risks of nephrotoxicity from both agents (Kimberlin 2001a).

More recent changes to the therapy of neonatal HSV disease have come about in the form of increased dosing regimens and increased duration of therapy (Kimberlin 2001a) in an attempt to further

reduce the death rate and the rate of recurrence. In addition, the availability of the highly sensitive polymerase chain reaction (PCR) to identify HSV DNA in the cerebrospinal fluid (CSF) or blood has redefined the natural history of neonatal HSV disease (Malm 1999; Diamond 1999). This technique may have an impact on the classification of neonatal HSV disease in two ways: first, some infants classified clinically as having skin, eye or mouth disease may now have HSV DNA detected in the CSF and be redefined as having central nervous system disease and second, infants with suspected HSV encephalitis without a skin focus from which to culture the virus may now have their condition proven by PCR. The increased use of molecular techniques to diagnose neonatal HSV disease has not been shown to reduce the time to institution of treatment (Kimberlin 2001a) as treatment is usually initiated on an empirical basis because of the high mortality.

Why it is important to do this review

A previous review of antiviral therapy for neonatal HSV infection using systematic methodology published by Baley and Fanaroff 1992 (Baley 1992) did not evaluate trials of different dosing regimens of aciclovir. In light of the recent changes in clinical practice stated above, we have systematically evaluated the efficacy of antiviral agents used to treat neonatal HSV disease.

OBJECTIVES

The principle objective was to assess the effect of antiviral agents on mortality, progression of disease and prevention of neurodevelopmental sequelae in neonates with virologically confirmed HSV infection. The secondary objective was to assess the incidence of the major complications associated with the use of antiviral agents for the treatment of neonatal HSV infection.

The following comparisons were planned:

1. Vidarabine vs. placebo or no treatment
2. Aciclovir vs. placebo or no treatment
3. Aciclovir vs. vidarabine
4. Different dosing regimens of vidarabine (15 vs. 30 mg/kg/day) given intravenously as a 12 hour infusion
5. Different dosing regimens of aciclovir (30 mg/kg/day vs. 45 mg/kg/day vs. 60 mg/kg/day) given for the same duration (intravenous infusion for 21 days)
6. Different durations of treatment, (10 vs. 14 vs. 21 days) using the one dosing regimen of aciclovir (30 mg/kg/day intravenously, divided into three doses)
7. Different durations of treatment, (10 vs. 14 vs. 21 days) using the one dosing regimen of vidarabine (15 mg/kg/day or 30 mg/kg/day, intravenously over 12 hours)

Prespecified subgroup analysis included:

1. Category of neonatal herpes simplex virus disease at study entry: 1) HSV disease of the skin, eye, or mouth 2) HSV central nervous system disease, or 3) disseminated HSV infection
2. HSV serotype: type 1 or type 2
3. Gestational age: preterm (< 37 weeks gestation) or term

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised controlled trials were included.

Types of participants

Hospitalised newborn infants less than one month of age with virologically confirmed HSV infection.

Virologically confirmed HSV infection was defined by the study investigators. This was usually defined as isolation of HSV by viral culture from herpetic vesicles, cerebrospinal fluid (CSF), conjunctivae, urine, stool or brain biopsy specimens. Alternative methods were by the detection of HSV DNA by polymerase chain reaction in the infants CSF or blood.

Types of interventions

Interventions included parenteral antiviral drug treatments (such as aciclovir, vidarabine, and foscarnet).

Comparisons were made between a given parenteral antiviral agent vs. control/placebo, parenteral aciclovir vs. vidarabine and between different lengths of treatment of one dosing regimen of aciclovir and between different doses of aciclovir for a stated duration.

Types of outcome measures

Primary outcome measures:

1. Mortality within the first year of life
2. Progression of disease and the development of neurodevelopmental sequelae at approximately one year of age
3. Progression of disease was defined as the development of new lesions after the initiation of therapy in the time frame defined by the study authors or by a change in the classification of neonatal HSV disease from skin, eye, mouth (SEM) disease to central nervous system (CNS) disease or disseminated HSV infection (involvement of multiple viscera including liver, lungs, adrenal glands and/or disseminated intravascular coagulation with or without CNS or SEM disease, using age-related normal values as defined by the study authors) and from CNS disease to disseminated HSV infection.
4. Neurodevelopmental sequelae was defined using the definition of abnormality and the standardised infant developmental assessment tool(s) as described by the study authors. A *post hoc* analysis was added of death or neurodevelopmental abnormality at one year to evaluate combined adverse outcomes.

Secondary outcomes measures:

1. Harms from intervention (nephrotoxicity or marrow suppression) were defined using the units and range of normal values stated by the study authors
2. Adverse clinical reactions to the antiviral agent, namely unexpected side effects not commonly associated with the drug, as defined by the study authors
3. Virologically proven recurrences within the first year of life defined by the study investigators. This is usually defined

as isolation of HSV by viral culture from herpetic vesicles, cerebrospinal fluid (CSF), conjunctivae, urine, stool or brain biopsy specimens. Alternative methods are detection of HSV DNA by polymerase chain reaction in the infants CSF or blood.

4. CSF examination for cell count, protein, and glucose using units and age-defined range of normal values as defined by the study authors
5. CSF for the presence of HSV DNA detected by PCR using the method and lower limit of detection as defined by the study authors

Search methods for identification of studies

See: Collaborative Review Group search strategy

A systematic and comprehensive literature search was carried out to identify eligible RCTs using the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 4, 2008), MEDLINE (1966 - 2008), EMBASE (1982 - 2008) using the following search terms as Medical Subject Heading (MeSH) and text words: antiviral agents and/or acyclovir and/or ganciclovir and/or valaciclovir and/or and/or valganciclovir and/or famciclovir and/or penciclovir and/or foscarnet and/or newborn and/or neonate and/or infant and/or herpes simplex virus and/or all possible suffixes and derivatives. We searched for human studies in newborn infants with English language reports and reports in foreign languages with an English language abstract. We searched for additional studies through article reference lists and through contact with local and international experts.

Data collection and analysis

The standard methods of the Cochrane Collaboration and its Neonatal Review Group were used. Two review authors worked independently to search for and assess trials for inclusion and methodological quality. Eligible studies were assessed using the following key criteria: allocation concealment (blinding of randomisation), blinding of intervention, completeness of follow-up and blinding of outcome measurement. The review authors extracted data independently. The data were checked and entered into the Cochrane Review Manager (RevMan) computer software by one review author.

Statistical analyses were performed using the RevMan software. Dichotomous outcomes were expressed as relative risk (RR) with 95% confidence intervals, risk difference (RD). Continuous outcomes were to have been stated as mean differences for individual trials and weighted mean differences for meta-analyses.

Assessment of heterogeneity

Heterogeneity of treatment effect was examined using the I squared statistic. Subgroup analyses were performed where data were available.

RESULTS

Description of studies

We identified five potentially eligible trials assessing the efficacy of antiviral therapy for neonatal HSV disease. Two of these studies met the inclusion criteria: [Whitley 1980](#), and [Whitley 1991](#). Both these studies were published as complete articles. A report by Corey and colleagues ([Corey 1988](#)) described a subset of infants

enrolled in the randomised control trial that was later reported by [Whitley 1991](#). This paper reported the outcome of neonatal HSV encephalitis according to HSV serotype and was included in the subgroup analyses of the [Whitley 1991](#) study. A report by Sullender ([Sullender 1987](#)) was also on a subset of infants enrolled in the trial reported by [Whitley 1991](#). However, this report did not provide additional data for this analysis because it was a descriptive report of neonatal immunity and not a randomized controlled trial.

There were three excluded studies. The study of Skoldenberg ([Skoldenberg 1984](#)) was excluded even though it was a randomised controlled trial of antiviral therapy for HSV encephalitis because all patients in the study population were beyond the neonatal period (i.e. greater than four weeks of age). The youngest infants in this study were four months of age. The study of [Whitley 1983](#) described an open label trial of 39 infants less than one month of age with virologically proven HSV that were treated with one of two different doses of vidarabine: 15 mg/kg/day (16 infants) or 30 mg/kg/day (23 infants) both given as a 12 hour infusion for a duration that ranged from one to > 10 days ([Whitley 1983](#)). The study was excluded because it was not randomized or quasi-randomized based on current criteria but instead used two consecutive enrolment periods to allocate infants in an open fashion to two different doses. Allocation to different dosing regimens was on an *ad hoc* basis. Outcome data was combined with infants reported in the trial of [Whitley 1980](#), which had compared vidarabine 15 mg/kg/day for 10 days vs. placebo ([Whitley 1980](#)). There were no randomised controlled trials that compared different doses of aciclovir or different durations of one dose of aciclovir in infants with neonatal HSV disease. Kimberlin described the use of different doses and durations of aciclovir for the treatment of neonatal HSV disease ([Kimberlin 2001a](#)). However, this study was excluded from this review because the study compared two escalated doses of acyclovir (45 mg/kg/day and 60 mg/kg/day) with historical controls from the previously reported trial which used a dose of 30mg/kg/day of acyclovir ([Whitley 1991](#)).

The table "Characteristics of Included Studies" contains the details of the included studies. Both studies compared the efficacy of antiviral agents in preventing mortality and morbidity of neonatal HSV disease. The study by [Whitley 1980](#) was a multicentre trial run by the National Institute of Allergy and Infectious Diseases Collaborative Group (NIAID) in the United States. The study began in 1974 with unstated duration and compared vidarabine with a placebo. The later study by [Whitley 1991](#) was also run through NIAID. This study was conducted from 1981 to 1988 and compared the two antiviral agents, aciclovir with vidarabine. The inclusion criteria and primary and secondary outcome measures were the same for both studies. Newborn infants less than one month of age with virologically confirmed HSV infection were eligible for enrolment in both studies irrespective of gestational age or co-morbidities. Neonates with signs of HSV disease at birth (i.e. congenital HSV disease) were excluded only in the study by [Whitley 1991](#). Both studies analysed the mortality and neurological morbidity up to one year of age and analysed these outcomes according to category of neonatal HSV disease : i.e. skin, eye, mouth (SEM), central nervous system disease (CNS) or disseminated infection with or without encephalitis. The two studies had the same definitions for the category of HSV disease. Infants were classified as having disseminated infection if they had multiorgan involvement as shown by elevated hepatic transaminases, pneumonitis, or disseminated

intravascular coagulation. Infants were classified as having CNS disease if they had an abnormal neurological examination or CSF abnormalities such as pleocytosis or elevated CSF protein, with or without skin or eye involvement. Infants were classified as having disease localised to the skin, eye or mouth if they had no evidence of other organ involvement. Hematological, liver and renal abnormalities and adverse clinical events were recorded in both trials, but the laboratory definitions of abnormality were not stated for the laboratory parameters in the trial by [Whitley 1980](#).

The study by [Whitley 1980](#) enrolled 63 neonates with virologically confirmed HSV disease whose disease was diagnosed in the first month of life. No exclusion criteria were specifically listed but it was stated that all infants were enrolled regardless of gestational age, birth weight, and concurrent medical conditions. There were no demographic or clinical differences between the groups. Thirty one infants were randomised to receive intravenous vidarabine at a dose of 15 mg/kg/day over 12 hours at maximum concentration of 0.7 mg/ml for ten days. At entry, four infants in the vidarabine treatment group had SEM disease, ten had CNS disease alone, and 14 had disseminated infection. Thirty two infants were randomised to receive intravenous placebo. In the placebo group, nine infants had SEM disease at study entry, six had CNS disease alone, and 13 had disseminated infection. After enrolment, infants were monitored daily until death or discharge for at least 30 days for evidence of progressive disease (the presence of new lesions, CNS, respiratory, hepatic, or other complications of viral disease) or other concomitant medical conditions or infections. Seven infants were excluded from the efficacy analysis after randomisation. Four infants in the placebo group were given vidarabine because of progressive disease, two infants in the treatment group received a higher dose than stated in the protocol, and one infant in the treatment group received a second course of vidarabine. Outcomes were reported on the remaining 56 infants who were equally divided between the two groups; therefore, analysis was not performed on an intention-to-treat basis.

The study by [Whitley 1991](#) enrolled 210 infants with virologically proven neonatal HSV infection. Eight had disease at birth suggestive of intrauterine HSV infection and were excluded from efficacy analysis. Ninety-five infants received vidarabine at 30 mg/kg per day over 12 hours by continuous infusion. One hundred and seven infants received intravenous aciclovir, 30 mg/kg/day divided into three equal doses given eight hours apart. In the aciclovir treated group, there were 54 infants with SEM disease, 35 infants with CNS disease and 18 infants with disseminated infection. In the vidarabine group, there were 31 infants with SEM disease, 36 with CNS disease and 28 with disseminated infection. There were no demographic differences between the groups and the proportion of premature infants was similar in both groups. However, the treatment groups were dissimilar with respect to the category of HSV disease and, therefore, disease severity. Twenty nine percent and 33 percent of infants who received vidarabine had disseminated HSV disease or skin eye mouth disease respectively compared to 17% and 50% of aciclovir-treated infants. Infants were monitored for progression of disease on treatment, mortality, neurodevelopmental morbidity at approximately one year, virologically proven skin recurrences at one and six months after completion of therapy, nephrotoxicity and other adverse reactions. Follow-up was until death or approximately 12 months of age and was complete for mortality but not for neurological

sequelae at approximately one year of age (data only reported for 146/167 surviving infants).

Risk of bias in included studies

See: Table "Characteristics of Included Studies"

The two trials included in the study were performed fifteen to twenty years ago. They have a number of methodological flaws as judged by current criteria of study quality that are detailed below.

Whitley 1980

The method of randomisation was not stated in this study. Also not stated was the number of infants who were eligible for the study. There were no demographic or clinical differences between the groups. Seven infants were excluded post-randomisation, four infants who received the placebo were given vidarabine due to progressive disease, two required a higher dose of vidarabine and one required a second course of vidarabine. Analysis was not performed by intention-to-treat. There was complete follow-up of all enrolled patients.

Whitley 1991

Assignment of study medication was determined by a randomization schedule stratified according to centre by closed envelope technique. Block randomisation was used. The intervention was not blinded. Follow-up of enrolled infants was not complete for neurodevelopmental morbidity at approximately one year of age.

Effects of interventions

Both studies in the review report on the efficacy of antiviral treatment for neonatal HSV infection. One study of 63 infants (Whitley 1980) compared vidarabine and placebo. Another study of 210 infants (Whitley 1991) compared vidarabine with aciclovir.

VIDARABINE VS. PLACEBO OR NO TREATMENT (COMPARISON 1)

Primary Outcomes

Mortality within the first year of life overall, by disease category or by gestational age (Outcomes 1.1 - 1.3):

In the study by Whitley 1980, mortality in the first year of life was reported for 56 out of 63 infants randomized to receive either vidarabine or placebo. The mortality for infants was less in infants treated with vidarabine compared with a placebo when all infants were analyzed, with a reduction from 32% to 53% (RR 0.60, 95% CI 0.32, 1.14) but the difference did not reach statistical significance. The reduction in mortality from vidarabine treatment was greater for infants with disseminated neonatal HSV disease (RR 0.68, 95% CI 0.41, 1.12) and for infants with CNS disease alone (RR 0.20, 95% CI 0.03, 1.51) compared to infants with skin, eye and mouth (SEM) disease (RR 0.67, 95% CI 0.03, 13.60) but the confidence intervals were wide and so the differences were not significant when analysed separately. However, the reduction in mortality was significant when data from the infants with disseminated disease or CNS disease was combined (RR 0.51, 95% CI 0.28, 0.91). Only one infant with SEM disease died in this study and that infant was from the placebo group. In the vidarabine treated group, 14 infants were born at term (greater than or equal to 37 weeks gestation) and 14 were preterm (< 37 weeks gestation), whereas in the placebo group, 15 infants were born at term and 13 were born prematurely. No differences were observed in the effect of vidarabine in reducing

mortality from neonatal HSV disease when the study population was analysed according to gestational age (term RR 0.60, 95% CI 0.26, 1.35; preterm RR 0.62, 95% CI 0.22, 1.71).

Progression of Disease while on treatment (Outcome 1.4):

Information regarding progression of disease was available for this systematic review in 56/63 infants in the study by Whitley 1980. Eight infants in this study were reported to have progression of disease while on treatment, four from the placebo group and four from the vidarabine group. These infants were not included in the final efficacy analyses. Presence or absence of progression of disease on treatment for the remaining 56 enrolled infants was not clearly stated.

Abnormal neurodevelopment at about one year in total and by disease category at presentation in all enrolled infants (Outcomes 1.5, 1.6):

No difference was observed in the number of infants with neurological abnormalities at one year between the 28 vidarabine-treated infants and 28 placebo-treated infants when compared using all enrolled infants as the denominator (RR 1.50, 95% CI 0.62, 3.65). Of the 28 infants enrolled in the vidarabine treatment group, 4 had SEM disease at diagnosis, 10 had CNS disease and 14 had disseminated disease. Of the 28 infants enrolled in the placebo group, nine had SEM disease at diagnosis, six had CNS disease and 13 had disseminated disease. No difference in the number of survivors at one year with neurological abnormalities was observed between treatment groups when analyzed by disease category at presentation (Whitley 1980).

Abnormal neurodevelopment or death in total and by disease category (post-hoc analysis) (Outcomes 1.7, 1.8):

We also analysed combined data for either death or neurological abnormality at one year to take into account differences in the number of infants available to be evaluated at one year of age due to differences in mortality rate. There was still no statistically significant difference between the treatment or controls groups when analysed in this manner (RR 0.86, 95% CI 0.60, 1.22) (Outcome 1.7) or by disease category (Outcome 1.8) (Whitley 1980).

CNS abnormalities (Microcephaly, Eye abnormalities, Seizures, Cerebral palsy, Developmental delay) up to three years by HSV serotype:

CNS outcomes other than neurodevelopment were not analysed by HSV serotype in the study by Whitley 1980.

Secondary Outcomes

Harms from Intervention: Leucopenia, thrombocytopenia, aspartate transaminase elevation and total bilirubin elevation (Outcomes 1.09 - 1.11):

Adverse effects on renal function, bone marrow and liver were monitored in all subjects in the trial reported by Whitley 1980. No infants in the treatment or placebo group had demonstrated renal toxicity. Non-significantly fewer infants in the vidarabine-treated group developed leucopenia (RR 0.65 95% CI 0.41, 1.03) or thrombocytopenia (RR 0.61, 95% CI 0.36, 1.05) compared to the placebo group. No differences between the two groups were observed in the presence or absence of liver function test abnormalities as shown by AST elevation (RR 3.0, 95% CI 0.33, 27.12). No difference in total bilirubin was reported, but specific data was not provided.

Adverse clinical reaction:

The trial reported by [Whitley 1980](#) recorded no adverse clinical reactions in either treatment group.

Virologically proven recurrences:

The presence of HSV recurrences after the completion of therapy was not reported in the study by [Whitley 1980](#).

CSF examination at end of treatment:

The study by [Whitley 1980](#) did not compare CSF examination (including the presence of HSV DNA by PCR) at the end of therapy according to intervention.

ACICLOVIR VS. PLACEBO OR NO TREATMENT

No eligible studies were found.

ACICLOVIR VS. VIDARABINE (COMPARISON 2)

Primary Outcomes

Mortality within the first year of life in total, by disease category or by gestational age (Outcomes 2.1 - 2.2):

Comparison of the two antiviral agents aciclovir and vidarabine in the study by [Whitley 1991](#) revealed no evidence of a difference in preventing mortality in neonates with HSV disease when all categories of disease were included (RR 0.75, 95% CI 0.41, 1.37). There were no differences between the two drugs noted when mortality was analysed by category of disease. No infants with SEM disease died in this study. No details were provided about mortality according to gestational age in this study.

Progression of Disease while on treatment (Outcome 2.3):

In the study reported by [Whitley 1991](#), HSV disease progressed on treatment in 12 infants. There was no difference between treatment groups in the development of progression of neonatal HSV disease after initiation of therapy (RR 0.89, 95% CI 0.30, 2.66).

Abnormal neurodevelopment at about one year in total and by disease category (Outcome 2.4 - 2.6):

In the study by [Whitley 1991](#), the effect of vidarabine and aciclovir on the neurodevelopmental outcome at approximately one year of age was reported for 79 of 98 (81%) surviving aciclovir-treated infants and 67 of 81 (83%) surviving vidarabine-treated infants. Neurological sequelae was less in surviving infants who had been treated with aciclovir (25%) compared to surviving infants treated with vidarabine (34%) but the difference did not reach statistical significance when using all enrolled infants as the denominator for each treatment group as a whole (RR 0.82, 95% CI 0.50, 1.34), when analyzed by disease category or when data from infants with disseminated or CNS disease were combined. Although a trend to a more favourable neurodevelopmental outcome at one year was present in the aciclovir-treated infants with SEM disease compared to those with the same disease category treated with vidarabine, the difference was not statistically significant (RR 0.19 95% CI 0.02, 1.76).

Abnormal neurodevelopment or death in total and by disease category (post-hoc analysis) (Outcome 2.7):

We also analysed combined data for death or neurological abnormality at one year to take account for differences in the number of infants who may be evaluated at one year of age due to differences in mortality rate. No difference was noted when the presence of neurological abnormality at one year or death was compared between the two antiviral agents when the group was

analysed as a whole (RR 0.79 95% CI 0.57, 1.10) or by disease category ([Whitley 1991](#)).

CNS abnormalities (Microcephaly, Eye abnormalities, Seizures, Cerebral palsy, Developmental delay) up to three years by HSV serotype (Outcomes 2.8 - 2.12):

The presence or absence of markers of neurological abnormality were analysed by HSV serotype for a subset of 23 infants from the 202 total infants enrolled in the multicentre study reported by [Whitley 1991](#). The 23 infants were reported by [Corey 1988](#) and had been consecutively enrolled at one site; 10 into the aciclovir treatment group, and 13 into the vidarabine treatment group. The infants were analysed for the presence of microcephaly, eye abnormalities, seizures, cerebral palsy, or developmental delay according to HSV serotype at 3 years of age. While the presence of microcephaly, eye abnormalities, seizures, or developmental delay was more common in infants who had neonatal HSV encephalitis caused by HSV-2 compared to HSV-1, no differences were observed according to the type of antiviral agent.

Secondary Outcomes

Adverse effects on renal function, liver function and bone marrow (Outcomes 2.13 - 2.16):

Adverse effects were monitored in all subjects in the trial reported by [Whitley 1991](#). There were no clinically significant differences in the adverse effects between the two antiviral agents, although fewer infants treated with aciclovir developed leucopenia or thrombocytopenia compared to infants treated with vidarabine (leucopenia RR 0.08, 95% CI 0.00, 1.44; thrombocytopenia RR 0.22, 95% CI 0.08, 0.64) ([Whitley 1991](#)). Very few infants developed AST or total bilirubin elevation in either treatment group and the differences were not significant.

Adverse clinical reaction (Outcome 2.17):

In [Whitley 1991](#), seven infants were reported to have adverse clinical reactions but the frequency of events was not different between the two treatment groups. The events reported included a rash (one in each of the vidarabine and acyclovir group), tremulousness (two in the vidarabine and one in the acyclovir group), diarrhoea (one in the vidarabine group) and vomiting (one in the acyclovir group).

Virologically proven recurrences (Outcome 2.18):

The presence of HSV recurrences after the completion of therapy was reported in the study by [Whitley 1991](#). Information was only available on a subset of these infants (49 aciclovir treated infants and 42 vidarabine treated infants). In this series, 17 virologically confirmed skin recurrences were reported in 49 aciclovir treated infants within one month after the completion of therapy compared to eight events in 42 vidarabine treated infants. The differences were not statistically significant (RR 1.82, 95% CI 0.88, 3.79).

CSF examination at end of treatment:

The study by [Whitley 1991](#) did not compare CSF examination (including the presence of HSV DNA by PCR) at the end of therapy according to intervention.

DIFFERENT DOSING REGIMENS OF VIDARABINE

No eligible studies were found.

DIFFERENT DOSING REGIMENS OF ACICLOVIR

No eligible studies were found.

DIFFERENT DURATIONS OF ACICLOVIR TREATMENT

No eligible studies were found

DIFFERENT DURATIONS OF VIDARABINE TREATMENT

No eligible studies were found.

DISCUSSION

Neonatal HSV disease is an uncommon but life-threatening condition with significant morbidity in many of the infants who survive. This systematic review is a summary of the two original trials of antiviral agents to treat neonatal HSV disease that were performed 15 to 20 years ago, as there have been no randomised controlled trials evaluating interventions to treat this disease since that time. The original trial reported by [Whitley 1980](#) of vidarabine vs. placebo for neonatal HSV disease reported a statistically significant reduction in mortality in vidarabine-treated infants with CNS or disseminated disease when the groups were combined compared to those treated with placebo. In this systematic review, the same observation was made, however, when the entire group was analyzed or when these disease categories were analysed individually, the reduction in mortality due to vidarabine did not achieve statistical significance. However, the results of this systematic review need to be interpreted with caution given the small numbers involved and problems in study design of these two trials such as failure to perform intention-to-treat analysis in both studies, and lack of blinding in the trial by [Whitley 1980](#). Historically, the use of antiviral agents against systemic HSV disease has been temporally associated with improved mortality from this condition, although in the same time period there were also improvements in the intensive care support of the sick neonate and in diagnostic techniques. Confirmation of the clinical efficacy of antiviral agents for neonatal HSV disease is now difficult as it is no longer possible to include a placebo group. A control group was not included in the subsequent trial comparing aciclovir with vidarabine for ethical reasons. Therefore, the protective efficacy of vidarabine displayed in the subsequent trial could not be reconfirmed except by extrapolation to the previous controls from the earlier study.

This review found no evidence of a difference between aciclovir and vidarabine with respect to the prevention of mortality and morbidity from neonatal HSV disease. There were no statistically significant differences between these therapies for either the aforementioned outcomes or for progression of disease when analysed by gestational age, HSV serotype or disease classification. However, these findings should be interpreted with caution due to small numbers in the subgroup analyses.

The original dose and duration of aciclovir in the study for the treatment of neonatal HSV disease reported by [Whitley 1991](#) was 30 mg/kg/day of aciclovir given intravenously for 10 days. Early CNS recurrence after the cessation of aciclovir and the finding of long-term neurological deficit in infants originally classified with the non-lethal SEM form of the disease raised concern about persistence of HSV in the CNS at the end of therapy and occult CNS recurrences, respectively. This led to the clinical practice of increased aciclovir dose for this condition (initially 45 mg/kg/day, then 60 mg/kg/day) and for a longer duration of therapy (up to the current practice of 14 days for SEM disease and 21 days for CNS and disseminated infections). It is important to note that these dose escalations are not based on clinical trial results. [Kimberlin](#)

[2001](#) reported a study evaluating the effects of the increased doses and durations of aciclovir; however, this trial could not be included in this review because the subjects reported were not all enrolled in a blinded randomised trial and the investigators used historical controls. In this study, which ran from 1989 to 1997, an earlier calendar year of birth was not associated with increased mortality suggesting but not proving that the improved mortality was more likely due to increased aciclovir dose rather than technological advances in intensive care. The rarity of this condition makes evaluation of small changes in therapy difficult to conduct even by large, multicentre collaborative groups.

This systematic review reflects the fact that research into the treatment of neonatal HSV disease has advanced little over the last two decades. Advances have been made in efforts to reduce vertical transmission of HSV. In a recent systematic review, antiviral prophylaxis given in pregnancy to women with genital herpes have been shown to reduce the incidence of viral shedding at delivery and the rate of Caesarean Section for genital herpes; however, studies were insufficiently powered to determine the effect of this intervention on neonatal HSV infection ([Hollier 2008](#)). The use of oral aciclovir prophylaxis in infants that survive neonatal HSV infection to reduce CNS sequelae has also been recently evaluated in a Phase I/II trial. However, there was a high rate of neutropenia in treated infants. There have also been case reports of late CNS recurrences despite the use of oral aciclovir prophylaxis that have raised concerns regarding the efficacy of this therapy ([Kimberlin 1996](#); [Fonseca-Aten 2005](#)).

AUTHORS' CONCLUSIONS

Implications for practice

The use of systemic antiviral agents to reduce the high morbidity and mortality from neonatal herpes simplex virus disease is an established clinical practice based on the original clinical trial results of [Whitley 1980](#) that suggested improved mortality in neonates with HSV disease of the CNS or disseminated infection. There is insufficient trial evidence to support a preference for the use of aciclovir or vidarabine or the use of increased dose and duration of aciclovir therapy for this condition.

Implications for research

The efficacy of newer antiviral agents with better bioavailability (e.g. valaciclovir, valganciclovir) for the treatment of neonatal herpes simplex virus disease needs to be evaluated in randomised trials. However, the rarity of the condition makes effectively powered clinical trials difficult to perform. These agents are available as oral formulations and may be useful for infants with skin, eye and mouth HSV disease, or in the treatment of infants with recurrences after the neonatal period.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Whitley 1980

Methods	Randomised controlled trial. Method of randomisation not stated. Blinding of intervention and outcome assessment was not stated. Analysis was not performed by intention to treat (see notes). Follow-up incomplete (see notes).
Participants	Multicentre trial conducted in the USA from 1974 for unstated duration. Enrolled: 63 subjects aged < 1month with virologically confirmed HSV infection. Number eligible for enrolment not stated. Exclusions were not stated. Characteristics of participants were similar in relation to sex, gestational age, duration of disease prior to diagnosis, and category of HSV disease in treatment and placebo groups. (Vidarabine: 4 SEM, 10 CNS, 14 disseminated; Placebo: 9 SEM, 6 CNS, 13 disseminated).
Interventions	Treatment group: intravenous vidarabine 15mg/kg/day over 12hrs for 10 days (n=31 enrolled, 28 analysed). Control group: intravenous placebo (n= 32 enrolled, 28 analysed).
Outcomes	All outcomes were dichotomous variables. Primary outcomes: mortality within the first year of life, progression of HSV disease while on treatment, neurodevelopmental sequelae at about 1 year. Secondary outcomes: presence or absence of nephrotoxicity, bone marrow suppression, nausea, vomiting, diarrhoea, acute neurologic toxicity, hepatic dysfunction. Mortality and neurodevelopmental morbidity were analysed according to the category of HSV disease. Mortality at one year was also analysed by gestational age (preterm < 37 weeks vs. term).
Notes	Seven infants were excluded post randomisation, 4 from the placebo were given vidarabine because of progressive herpetic disease, 2 from the vidarabine group received a higher than specified dose and one from the vidarabine group required a second course of therapy. Study run through NIAID, USA. Drug and placebo supplied by Warner-Lambert/ Parke-Davis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Whitley 1991

Methods	Randomised controlled trial. Assignment of study medication determined by a randomization schedule stratified according to centre by the closed envelope technique. Block randomisation was used. Allocation blinded. Intervention: not blinded. Blinding of outcome assessment unknown. Analysis not by intention to treat (see notes). Follow-up incomplete (see notes).
Participants	Multicentre trial conducted in the USA from 1981-1988. Enrolled: 210 infants < 1 month of age with virologically proved neonatal HSV infection. Number eligible not stated. Excluded: 8 infants with evidence of disease at birth (i.e. chorioretinitis, skin lesions, scarring or hydrocephalus). No demographic or clinical differences between the two treatment groups, except for category of HSV disease. (Aciclovir: N=107, 54 SEM, 35 CNS, 18 disseminated; Vidarabine n = 95, 31 SEM, 36 CNS, 28 disseminated).
Interventions	Treatment group: Vidarabine 30 mg/kg/day concentration not exceeding 0.7mg/ml in standard intravenous fluid (n= 95). Control group: Acyclovir 30 mg/kg/day divided into three doses, given every eight hours in 50mls standard IV fluid over 1 hour for ten days. (n=107).
Outcomes	All outcomes were dichotomous variables. Primary outcomes: mortality within the first year, neurodevelopmental morbidity at after one year of life, and progression of disease while on therapy. All were analysed by disease category. Secondary outcomes were: the presence of absence of skin recurrences, adverse clinical outcomes, bone marrow suppression, nephrotoxicity, or liver function test abnormalities. Leukopaenia and thrombocytopenia. Progression of disease. Recurrence Skin recurrence Minor adverse reactions: rash, diarrhoea, tremulousness and vomiting. Neurodevelopmental sequelae at 1 year. Virus shedding during treatment.
Notes	Mortality data provided for 202/210 enrolled infants (107 aciclovir, 95 vidarabine). Eight infants were excluded post randomisation as they had signs of HSV disease at birth (number in each group not stated). Follow-up at one year was provided for 146/167 survivors at one year (Aciclovir: 79/91, vidarabine 67/76). Reasons for loss to follow up not stated. Study run through NIAID, USA. Drug and placebo supplied by Warner-Lambert/ Parke-Davis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Kimberlin 2001a	Outcomes for escalated doses of acyclovir were compared to historical controls.
Skoldenberg 1984	Participants were all older than one month of age.
Whitley 1983	An open study of two doses of vidarabine compared to historical controls of treated infants from the cited study of Whitley 1980

DATA AND ANALYSES

Comparison 1. Vidarabine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality up to one year	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.32, 1.14]
2 Mortality up to one year by disease category	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Skin/eye/mouth	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.03, 13.60]
2.2 Central nervous system	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.51]
2.3 Disseminated HSV disease	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.41, 1.12]
2.4 Central nervous system and/or disseminated HSV disease	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.28, 0.91]
3 Mortality up to one year by gestational age	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Term infants (greater than or equal to 37 weeks)	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.26, 1.35]
3.2 Preterm infants (less than 37 weeks gestation)	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.22, 1.71]
4 Progression of disease while on therapy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Abnormal neurodevelopment at one year	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.62, 3.65]
6 Abnormal neurodevelopment at approximately 1 year of age by disease category	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Skin/eye/mouth	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.11, 5.18]
6.2 Central nervous system	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.31, 4.69]
6.3 Disseminated HSV disease	1	27	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [0.47, 29.06]
7 Abnormal neurodevelopment or death at approximately one year of age	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.60, 1.22]
8 Abnormal neurodevelopmental or death at approximately one year of age by disease category	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Skin/eye/mouth	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.09, 3.57]
8.2 Central nervous system	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.29, 1.23]
8.3 Disseminated HSV disease	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.71, 1.21]
9 Leucopenia	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.41, 1.03]
10 Thrombocytopenia	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.36, 1.05]
11 Aspartate transaminase elevation	1	56	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.33, 27.12]

Analysis 1.1. Comparison 1 Vidarabine vs placebo, Outcome 1 Mortality up to one year.

Analysis 1.2. Comparison 1 Vidarabine vs placebo, Outcome 2 Mortality up to one year by disease category.

Analysis 1.3. Comparison 1 Vidarabine vs placebo, Outcome 3 Mortality up to one year by gestational age.

Analysis 1.4. Comparison 1 Vidarabine vs placebo, Outcome 4 Progression of disease while on therapy.

Analysis 1.5. Comparison 1 Vidarabine vs placebo, Outcome 5 Abnormal neurodevelopment at one year.

Analysis 1.6. Comparison 1 Vidarabine vs placebo, Outcome 6 Abnormal neurodevelopment at approximately 1 year of age by disease category.

Analysis 1.7. Comparison 1 Vidarabine vs placebo, Outcome 7 Abnormal neurodevelopment or death at approximately one year of age.

Analysis 1.8. Comparison 1 Vidarabine vs placebo, Outcome 8 Abnormal neurodevelopmental or death at approximately one year of age by disease category.

Analysis 1.9. Comparison 1 Vidarabine vs placebo, Outcome 9 Leucopenia.

Analysis 1.10. Comparison 1 Vidarabine vs placebo, Outcome 10 Thrombocytopenia.

Analysis 1.11. Comparison 1 Vidarabine vs placebo, Outcome 11 Aspartate transaminase elevation.

Comparison 2. Aciclovir vs vidarabine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality up to one year	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.41, 1.37]
2 Mortality up to one year by disease category	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Skin/eye/mouth	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Central nervous system	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.33, 3.25]
2.3 Disseminated HSV disease	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.72, 2.06]
2.4 Central nervous system disease or disseminated disease	1	117	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.58, 1.77]
3 Progression of disease while on therapy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Abnormal neurodevelopment at approximately one year of age	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.50, 1.34]
5 Abnormal neurodevelopment at approximately one year by disease category	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Skin/eye/mouth	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.76]
5.2 Central nervous system	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.77, 1.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Disseminated HSV disease	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.13, 2.87]
6 Abnormal neurodevelopment at approximately one year of age or death	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.10]
7 Abnormal neurodevelopment at approximately one year of age or death by disease category	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Skin/eye/mouth	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.76]
7.2 Central nervous system	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.84, 1.63]
7.3 Disseminated HSV disease	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.70, 1.46]
8 Microcephaly in CNS HSV neonatal infection up to three years by HSV serotype	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 HSV-1	1	9	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 HSV-2	1	14	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.35, 2.88]
9 Eye abnormalities in CNS HSV neonatal infection up to three years by HSV serotype	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 HSV-1	1	9	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.13, 48.85]
9.2 HSV-2	1	14	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.49, 2.33]
10 Seizures in CNS HSV neonatal infection up to three years by HSV serotype	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 HSV-1	1	9	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 HSV-2	1	14	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.55, 3.26]
11 Cerebral palsy in CNS HSV neonatal infection up to three years by HSV serotype	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 HSV-1	1	9	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 HSV-2	1	14	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.49, 2.33]
12 Developmental delay in CNS HSV neonatal infection up to three years by HSV serotype	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 HSV-1	1	9	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 HSV-2	1	14	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.31, 2.10]
13 Leucopenia	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.44]
14 Thrombocytopenia	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.08, 0.64]
15 Aspartate transaminase elevation	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.10, 3.47]
16 Total bilirubin elevation	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.04, 4.82]
17 Adverse clinical events	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.15, 2.90]
18 Virologically proven recurrences	1	91	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.88, 3.79]

Analysis 2.1. Comparison 2 Aciclovir vs vidarabine, Outcome 1 Mortality up to one year.

Analysis 2.2. Comparison 2 Aciclovir vs vidarabine, Outcome 2 Mortality up to one year by disease category.

Analysis 2.3. Comparison 2 Aciclovir vs vidarabine, Outcome 3 Progression of disease while on therapy.

Analysis 2.4. Comparison 2 Aciclovir vs vidarabine, Outcome 4 Abnormal neurodevelopment at approximately one year of age.

Analysis 2.5. Comparison 2 Aciclovir vs vidarabine, Outcome 5 Abnormal neurodevelopment at approximately one year by disease category.

**Analysis 2.6. Comparison 2 Aciclovir vs vidarabine, Outcome 6
Abnormal neurodevelopment at approximately one year of age or death.**

**Analysis 2.7. Comparison 2 Aciclovir vs vidarabine, Outcome 7 Abnormal
neurodevelopment at approximately one year of age or death by disease category.**

Analysis 2.8. Comparison 2 Aciclovir vs vidarabine, Outcome 8 Microcephaly in CNS HSV neonatal infection up to three years by HSV serotype.

Analysis 2.9. Comparison 2 Aciclovir vs vidarabine, Outcome 9 Eye abnormalities in CNS HSV neonatal infection up to three years by HSV serotype.

Study or subgroup	Aciclovir n/N	Vidarabine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable Test for overall effect: Z=0.16(P=0.87)					
Favours aciclovir 0.02 0.1 1 10 50 Favours vidarabine					

**Analysis 2.10. Comparison 2 Aciclovir vs vidarabine, Outcome 10
Seizures in CNS HSV neonatal infection up to three years by HSV serotype.**

Study or subgroup	Aciclovir n/N	Vidarabine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.10.1 HSV-1					
Whitley 1991	0/5	0/4			Not estimable
Subtotal (95% CI)	5	4			Not estimable
Total events: 0 (Aciclovir), 0 (Vidarabine) Heterogeneity: Not applicable Test for overall effect: Not applicable					
2.10.2 HSV-2					
Whitley 1991	4/6	4/8		100%	1.33[0.55,3.26]
Subtotal (95% CI)	6	8		100%	1.33[0.55,3.26]
Total events: 4 (Aciclovir), 4 (Vidarabine) Heterogeneity: Not applicable Test for overall effect: Z=0.63(P=0.53)					
Favours aciclovir 0.5 0.7 1 1.5 2 Favours vidarabine					

Analysis 2.11. Comparison 2 Aciclovir vs vidarabine, Outcome 11 Cerebral palsy in CNS HSV neonatal infection up to three years by HSV serotype.

Study or subgroup	Aciclovir n/N	Vidarabine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.11.1 HSV-1					
Whitley 1991	0/5	0/4			Not estimable
Subtotal (95% CI)	5	4			Not estimable
Total events: 0 (Aciclovir), 0 (Vidarabine) Heterogeneity: Not applicable Test for overall effect: Not applicable					
2.11.2 HSV-2					
Whitley 1991	4/6	5/8		100%	1.07[0.49,2.33]
Subtotal (95% CI)	6	8		100%	1.07[0.49,2.33]
Total events: 4 (Aciclovir), 5 (Vidarabine) Heterogeneity: Not applicable Test for overall effect: Z=0.16(P=0.87)					
Favours aciclovir 0.5 0.7 1 1.5 2 Favours vidarabine					

Analysis 2.12. Comparison 2 Aciclovir vs vidarabine, Outcome 12 Developmental delay in CNS HSV neonatal infection up to three years by HSV serotype.

Analysis 2.13. Comparison 2 Aciclovir vs vidarabine, Outcome 13 Leucopenia.

Analysis 2.14. Comparison 2 Aciclovir vs vidarabine, Outcome 14 Thrombocytopenia.

Analysis 2.15. Comparison 2 Aciclovir vs vidarabine, Outcome 15 Aspartate transaminase elevation.

Analysis 2.16. Comparison 2 Aciclovir vs vidarabine, Outcome 16 Total bilirubin elevation.

Analysis 2.17. Comparison 2 Aciclovir vs vidarabine, Outcome 17 Adverse clinical events.

Analysis 2.18. Comparison 2 Aciclovir vs vidarabine, Outcome 18 Virologically proven recurrences.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 3, 2009

Date	Event	Description
17 February 2009	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

KW- co-wrote protocol, searched for studies, extracted data, entered data into RevMan, co-wrote review.

CAJ- wrote protocol, searched for studies, extracted data, co-wrote review.

NB- edited protocol.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- KW & NB: Grace Centre for Newborn Care, The Children's Hospital at Westmead, Australia.
- CAJ: Discipline of Paediatrics & Child Health, University of Sydney, Australia.
- CAJ is a recipient of the Children's Hospital at Westmead Research Career Development Award, Australia.

External sources

- Syliva & Charles Viertel Clinical Investigator Award to CAJ, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Acyclovir [adverse effects] [*therapeutic use]; Antiviral Agents [adverse effects] [*therapeutic use]; Developmental Disabilities [*prevention & control] [virology]; Disease Progression; Herpes Simplex [complications] [*drug therapy] [mortality]; Randomized Controlled Trials as Topic; Vidarabine [adverse effects] [*therapeutic use]

MeSH check words

Humans; Infant, Newborn