Herpes Simplex

("Herpes Simplex"[Mesh]) AND ("Herpes Simplex/drug therapy"[Mesh])

"Drug Therapy"[Mesh]

Acyclovir

("Acyclovir"[Mesh]) OR (Acycloguanosine) OR (9-((2-Hydroxyethoxy)methyl)guanine) OR (Aciclovir) OR (Wellcome-248U) OR (Wellcome 248U) OR (Wellcome248U) OR (Zyclir) OR (Amrad Brand of Aciclovir) OR (Aciclovir Amrad Brand) OR (Aciclovir Alonga) OR (Alonga Brand of Aciclovir Sodium Salt) OR (Bull Brand of Aciclovir) OR (Alonga Brand of Aciclovir) OR (Aci-Sanorania) OR (Aci Sanorania) OR (Sanorania Brand of Aciclovir Sodium Salt) OR (Sanorania Brand of Aciclovir) OR (Aciclovir Sanorania Brand) OR (Aciclovir-Sanorania) OR (Aciclovir Sanorania) OR (Lichtenstein Brand of Aciclovir) OR (Aciclovir Lichtenstein Brand) OR (Acic) OR (Hexal Brand of Aciclovir Sodium Salt) OR (Hexal Brand of Aciclovir) OR (Aciclovir Hexal Brand) OR (Aciclobeta) OR (Betapharm Brand of Aciclovir) OR (Aciclovir Betapharm Brand) OR (Aciclostad) OR (Stada Brand of Aciclovir) OR (Aciclovir Stada Brand) OR (Acifur) OR (Fustery Brand of Aciclovir) OR (Aciclovir Fustery Brand) OR (Acipen Solutab) OR (Solutab, Acipen) OR (Yamanouchi Brand of Aciclovir) OR (Aciclovir Yamanouchi Brand) OR (Acivir) OR (curasan Brand of Aciclovir Sodium Salt) OR (Activir) OR (Warner-Lambert Brand of Aciclovir) OR (Aciclovir Warner-Lambert Brand) OR (Warner Lambert Brand of Aciclovir) OR (Acyclo-V) OR (Acyclo V) OR (Alphapharm Brand of Aciclovir) OR (Aciclovir Alphapharm Brand) OR (Acyclovir Sodium) OR (Sodium, Acyclovir) OR (Antiherpes Creme) OR (ct-Arzneimittel Brand of Aciclovir) OR (Aciclovir ct-Arzneimittel Brand) OR (ct Arzneimittel Brand of Aciclovir) OR (aciclovir von ct) OR (Avirax) OR (Fabrigen Brand of Aciclovir) OR (Aciclovir Fabrigen Brand) OR (Cicloferon) OR (Liomont Brand of Aciclovir) OR (Aciclovir Liomont Brand) OR (Clonorax) OR (Clonmel Brand of Aciclovir) OR (Aciclovir Clonmel Brand) OR (Cusiviral) OR (Britisfarma Brand of Aciclovir) OR (Aciclovir Britisfarma Brand) OR (Britisfarma Brand of Aciclovir Sodium Salt) OR (Alcon Brand of Aciclovir) OR (Aciclovir Alcon Brand) OR (Genvir) OR (Herpetad) OR (TAD Brand of Aciclovir) OR (Aciclovir TAD Brand) OR (Herpofug) OR (Wolff Brand of Aciclovir) OR (Aciclovir Wolff Brand) OR (Herpotern) OR (Rentschler Brand of Aciclovir Sodium Salt) OR (Rentschler Brand of Aciclovir) OR (Aciclovir Rentschler Brand) OR (Herpoviric) OR (Azupharma Brand of Aciclovir) OR (Aciclovir Azupharma Brand) OR (Isavir) OR (Pisa Brand of Aciclovir) OR (Aciclovir Pisa Brand) OR (Laciken) OR (Kendrick Brand of Aciclovir) OR (Aciclovir Kendrick Brand) OR (Mapox) OR (Niddapharm Brand of Aciclovir) OR (Aciclovir Niddapharm Brand) OR (Maynar) OR (Novag Brand of Aciclovir) OR (Aciclovir Novag Brand) OR (Milavir) OR (Zyma Brand of Aciclovir) OR (Aciclovir

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FAMCICLOVIR

("famciclovir "[Substance Name]) OR (9-(4-acetoxy-3-(acetoxymethyl)but-1-yl)-2-aminopurine) OR (Famvir) OR (BRL 42810) OR (BRL-42810)

VALACICLOVIR

("valacyclovir "[Substance Name]) OR (valaciclovir) OR (256U) OR (256U87) OR (BW256U87) OR (valacyclovir, x-hydrochloride, (DL)-isomer) OR (valacyclovir hydrochloride, (DL)-isomer) OR (valacyclovir, (D)-isomer) OR (valacyclovir, (DL)-isomer) OR (valacyclovir, (L)-isomer) OR (acyclovir, L-valyl Ester) OR (L-valylacyclovir) OR (2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)ethyl L-valinate) OR (valacyclovir, x-hydrochloride, (D)-isomer) OR (Valtrex) OR (valacyclovir hydrochloride)

PENCICLOVIR

("penciclovir "[Substance Name]) OR (9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine) OR (Penciclovir Visfarm) OR (Visfarm brand of penciclovir) OR (penciclovir, monosodium salt) OR (penciclovir, monosodium salt, monohydrate) OR (BRL 39123) OR (BRL-39123) OR (Denavir) OR (Vectavir) OR (SB-CH brand of penciclovir) OR (Novartis brand of penciclovir)

Resultado PUBMED

#40	Search **((#24)) AND (#28)** Limits: **Humans, Clinical Trial, Randomized Controlled Trial**	08:55:24	17
#32	Search **((#24)) AND (#28)**	08:55:06	82
#39	Search **((#24)) AND (#27)** Limits: **Humans, Clinical Trial, Randomized Controlled Trial**	08:54:50	41
#31	Search **((#24)) AND (#27)**	08:54:32	231
#38	Search **((#24)) AND (#26)** Limits: **Humans, Clinical Trial, Randomized Controlled Trial**	08:54:03	25
#30	Search **((#24)) AND (#26)**	08:53:38	176
#37	Search **(#24) AND (#25)** Limits: **Humans, Clinical Trial, Randomized Controlled Trial**	08:53:00	345
#29	Search **(#24) AND (#25)**	08:52:08	2080
#36	Search **((#24)) AND (#27)** Limits: **Humans, Systematic Reviews**	08:51:25	10
#35	Search **((#24)) AND (#26)** Limits: **Humans, Systematic Reviews**	08:50:46	8
#34	Search **(#24) AND (#25)** Limits: **Humans, Systematic Reviews**	08:49:47	29
#33	Search **((#24)) AND (#28)** Limits: **Humans, Systematic Reviews**	08:48:24	2
#28	Search **("penciclovir "[Substance Name]) OR (9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine) OR (Penciclovir Visfarm) OR (Visfarm brand of penciclovir) OR (penciclovir, monosodium salt) OR (penciclovir, monosodium salt, monohydrate) OR (BRL 39123) OR (BRL-39123) OR (Denavir) OR (Vectavir) OR (SB-CH brand of penciclovir) OR (Novartis brand of penciclovir)**	08:42:51	303
#27	Search **("valacyclovir "[Substance Name]) OR (valaciclovir) OR (256U) OR (256U87) OR (BW256U87) OR (valacyclovir, x-hydrochloride, (DL)-isomer) OR (valacyclovir hydrochloride, (DL)-isomer) OR (valacyclovir, (D)-isomer) OR (valacyclovir, (DL)-isomer) OR (valacyclovir, (L)-isomer) OR (acyclovir, L-valyl Ester) OR (L-valylacyclovir) OR (2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)ethyl L-valinate) OR (valacyclovir, x-hydrochloride, (D)-isomer) OR (Valtrex) OR (valacyclovir hydrochloride)**	08:42:34	752
#26	Search **("famciclovir "[Substance Name]) OR (9-(4-acetoxy-3-(acetoxymethyl)but-1-yl)-2-aminopurine) OR (Famvir) OR (BRL 42810) OR (BRL-42810)**	08:42:00	620
#25	Search **("Acyclovir"[Mesh]) OR (Acycloguanosine) OR (9-((2-Hydroxyethoxy)methyl)guanine) OR (Aciclovir) OR (Wellcome-248U) OR (Wellcome 248U) OR (Wellcome248U) OR (Zyclir) OR (Amrad Brand of Aciclovir) OR (Aciclovir Amrad Brand) OR (Aciclovir Alonga) OR (Alonga Brand of Aciclovir Sodium Salt) OR (Bull Brand of Aciclovir) OR (Alonga Brand of Aciclovir) OR (Aci-Sanorania) OR (Aci Sanorania) OR (Sanorania Brand of Aciclovir Sodium Salt)**	08:41:27	11793

OR (Sanorania Brand of Aciclovir) OR (Aciclovir Sanorania Brand) OR (Aciclovir-Sanorania) OR (Aciclovir Sanorania) OR (Lichtenstein Brand of Aciclovir) OR (Aciclovir Lichtenstein Brand) OR (Acic) OR (Hexal Brand of Aciclovir Sodium Salt) OR (Hexal Brand of Aciclovir) OR (Aciclovir Hexal Brand) OR (Aciclobeta) OR (Betapharm Brand of Aciclovir) OR (Aciclovir Betapharm Brand) OR (Aciclostad) OR (Stada Brand of Aciclovir) OR (Aciclovir Stada Brand) OR (Acifur) OR (Fustery Brand of Aciclovir) OR (Aciclovir Fustery Brand) OR (Acipen Solutab) OR (Solutab, Acipen) OR (Yamanouchi Brand of Aciclovir) OR (Aciclovir Yamanouchi Brand) OR (Acivir) OR (curasan Brand of Aciclovir Sodium Salt) OR (Activir) OR (Warner-Lambert Brand of Aciclovir) OR (Aciclovir Warner-Lambert Brand) OR (Warner Lambert Brand of Aciclovir) OR (Acyclo-V) OR (Acyclo V) OR (Alphapharm Brand of Aciclovir) OR (Aciclovir Alphapharm Brand) OR (Acyclovir Sodium) OR (Sodium, Acyclovir) OR (Antiherpes Creme) OR (ct-Arzneimittel Brand of Aciclovir) OR (Aciclovir ct-Arzneimittel Brand) OR (ct Arzneimittel Brand of Aciclovir) OR (aciclovir von ct) OR (Avirax) OR (Fabrigen Brand of Aciclovir) OR (Aciclovir Fabrigen Brand) OR (Cicloferon) OR (Liomont Brand of Aciclovir) OR (Aciclovir Liomont Brand) OR (Clonorax) OR (Clonmel Brand of Aciclovir) OR (Aciclovir Clonmel Brand) OR (Cusiviral) OR (Britisfarma Brand of Aciclovir) OR (Aciclovir Britisfarma Brand) OR (Britisfarma Brand of Aciclovir Sodium Salt) OR (Alcon Brand of Aciclovir) OR (Aciclovir Alcon Brand) OR (Genvir) OR (Herpetad) OR (TAD Brand of Aciclovir) OR (Aciclovir TAD Brand) OR (Herpofug) OR (Wolff Brand of Aciclovir) OR (Aciclovir Wolff Brand) OR (Herpotern) OR (Rentschler Brand of Aciclovir Sodium Salt) OR (Rentschler Brand of Aciclovir) OR (Aciclovir Rentschler Brand) OR (Herpoviric) OR (Azupharma Brand of Aciclovir) OR (Aciclovir Azupharma Brand) OR (Isavir) OR (Pisa Brand of Aciclovir) OR (Aciclovir Pisa Brand) OR (Laciken) OR (Kendrick Brand of Aciclovir) OR (Aciclovir Kendrick Brand) OR (Mapox) OR (Niddapharm Brand of Aciclovir) OR (Aciclovir Niddapharm Brand) OR (Maynar) OR (Novag Brand of Aciclovir) OR (Aciclovir Novag Brand) OR (Milavir) OR (Zyma Brand of Aciclovir) OR (Aciclovir Zyma Brand) OR (Novartis Brand of Aciclovir) OR (Aciclovir Novartis Brand) OR (Opthavir) OR (Grin Brand of Aciclovir) OR (Aciclovir Grin Brand) OR (Supraviran) OR (Grünenthal Brand of Aciclovir Sodium Salt) OR (Grünenthal Brand of Aciclovir) OR (Aciclovir Grünenthal Brand) OR (Viclovir) OR (Abello Brand of Aciclovir) OR (Aciclovir Abello Brand) OR (Vipral) OR (Pharma Investi Brand of Aciclovir) OR (Virax-Puren) OR (Virax Puren) OR (ViraxPuren) OR (Isis Brand of Aciclovir) OR (Aciclovir Isis Brand) OR (Virherpes) OR (Pensa Brand of Aciclovir) OR (Aciclovir Pensa Brand) OR

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#24 Search **("Herpes Simplex"[Mesh]) AND ("Herpes Simplex/drug therapy"[Mesh])** 08:40:35 4545

COCHRANE LIBRARY

(herpes and simplex:ti) - 20 encontrado(s)

- Revisões Sistemáticas da Cochrane (4)
  - Revisões completas (2)
  - Protocolos (2)

- Unchanged Antiviral agents for treatment of herpes simplex virus infection in neonates
- Unchanged Interventions for the management of herpes simplex virus in patients being treated for cancer

Antiviral agents for treatment of herpes simplex virus infection in neonates [protocol]

Walker KS, Jones CA, Badawi N

This protocol should be cited as: Walker KS, Jones CA, Badawi N. Antiviral agents for treatment of herpes simplex virus infection in neonates (Protocol for a Cochrane Review). In: *The Cochrane Library,* Issue 2, 2008. Oxford: Update Software.

Background

Herpes simplex virus (HSV) is an important 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 1999). Both type 1 and type 2 HSV can cause neonatal disease, with the predominant type varying around the world (Garland 2001). Neonatal infection can manifest as disease localised to the skin, eye or mouth, as encephalitis, as pneumonitis or as a disseminated infection (Whitley 1993). 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).

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 also a 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 baby and the initiation of antiviral therapy.

The first drugs that had 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, firstly aciclovir, and more recently ganciclovir, famciclovir, and their respective pro-drugs (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, to date 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, with 85% of infants with disseminated HSV infection and 50% of infants with encephalitis dying by one year of age (Whitley 1980). 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). The mortality rate from neonatal HSV disease improved in the 1980s with the availability of the intravenous antiviral agents vidarabine and aciclovir, although there was a less dramatic improvement in the morbidity rate (Whitley 1983). 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 recently redefined the natural history of neonatal HSV disease (Malm 1999, Diamond 1999). Potentially, this technique may have an impact on the classification of neonatal HSV disease in two ways. Firstly, 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. Secondly, 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 commenced on an empirical basis given the high mortality. To date, a systematic review of the therapeutic options for neonatal HSV infection has not been published. Therefore, in light of these recent changes to clinical practice, we propose to systematically evaluate the efficacy of antiviral agents used to treat neonatal HSV disease.

Objectives

The principle objectives will be to assess the efficacy of antiviral agents to treat HSV infections in the neonate with respect to reduction in mortality, progression of disease and prevention of neurodevelopmental sequelae, and to assess the incidence of the major complications associated with the use of these agents, namely nephrotoxicity and bone marrow suppression .

Firstly, the review will compare aciclovir or vidarabine versus placebo or no treatment.
Secondly, it will compare parenteral aciclovir vs vidarabine.
Thirdly, it will compare different durations of treatment, (10 vs 14 vs 21 days) using the one dosing regimen of aciclovir (30mg/kg/day, intravenously, divided into 3 doses).
Fourthly, it will compare different dosing regimens of aciclovir, 30mg/kg/day vs 45 mg/kg/day versus 60 mg/kg/day, all divided in 3 doses, given for the same duration (intravenous infusion for 21 days).

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

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised controlled trials will be included.

Types of participants

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

Types of intervention

Interventions will be parenteral antiviral drug treatments such as aciclovir and vidarabine.
Comparisons will be made between a given parenteral antiviral agent versus 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

The primary outcome measures will be mortality within the first year of life, progression of disease and the development of neurodevelopmental sequelae at approximately one year of age. Progression of disease will be 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 central nervous system disease to disseminated HSV infection.
Neurodevelopmental sequelae will be defined using the definition of abnormality and the standardised infant developmental assessment tool(s) as described by the study authors.

Secondary outcomes measures:
Harms from intervention (nephrotoxicity or marrow suppression) will be defined using the units and range of normal values stated by the study authors.
Adverse clinical reactions to the antiviral agent, namely unexpected side effects not commonly associated with the drug, as defined by the study authors.
Virologically proven recurrences within the first year of life.
CSF examination for cell count, protein, and glucose, using units and age-defined range of normal values as defined by the study authors.
CSF for the presence of HSV DNA as detected by PCR, using the method and lower limit of detection as defined by the study authors.

Search strategy for identification of studies

See: methods used in reviews.

See: Collaborative Review Group search strategy

A systematic and comprehensive literature search will be carried out to identify eligible RCTs using MEDLINE (1966-Sept 2002), EMBASE (1982-Sept 2002), The Oxford Database of Perinatal Trials and the most recent issue of the Cochrane Library using the following search terms as Medical Subject Heading (MeSH) and text words: neonate, infant, HSV, antiviral agents, acyclovir, ganciclovir, valacyclovir, valganciclovir, famciclovir, penciclovir, foscarnet. We will search for human studies in newborn infants with English language reports and reports in foreign languages with an English language abstract. We will hand search abstract books of national, international, American and European paediatric and/or infectious disease research societies January 1990 - December 2002 (Interscience Congress of Antimicrobial Agents and Chemotherapy, Society for Pediatric Research (USA), European Society of Infectious Diseases and Microbiology, Infectious Diseases' Society of America, Pediatric Infectious Diseases Society).

Additional studies will also be located through article reference lists and through contact with local and international experts in the field.

Methods of the review

Standard methods of the Cochrane Neonatal Review Group will be used. Two reviewers will independently screen titles and abstracts retrieved from the searches and identify those trials that meet the inclusion criteria. The RCT's will be selected, analysed and considered for inclusion and graded for methodological quality using concealment of randomisation, blinding of intervention, completeness of follow up and blinding of outcome assessment. Any disagreement will be resolved through discussion and consultation with a third reviewer if needed. Unclear issues regarding the trials will be addressed by contacting the authors where possible.

Data will be extracted independently by two reviewers. The data will be checked and entered into the Cochrane Review Manager (RevMan) computer software by one reviewer. Any missing information or data inconsistencies will be checked with the authors of the study.

Statistical analysis will be performed using the RevMan software using the fixed effects model. Dichotomous outcomes will be expressed as relative risk (RR) with 95% confidence intervals, risk difference (RD) and number needed to treat (NNT) for categorical data. Continuous outcomes will be stated as mean differences for individual trials and weighted mean differences for meta-analyses .

Heterogeneity of treatment effect will be formally tested using Cochran's Q Statistic. To determine whether there is any difference between study results due to the plausible effect modifiers (as defined in the objectives section under pre-specified subgroup analysis), subgroup analysis will be performed, given sufficient numbers for analysis. This analysis will explore the effects of the dose or duration of treatment, the HSV serotype, and the classification of neonatal HSV disease at enrolment.

Acknowledgements

None

Potential conflict of interest

None

Notes

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Additional references

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Cover sheet

Antiviral agents for treatment of herpes simplex virus infection in neonates

Reviewer(s)	Walker KS, Jones CA, Badawi N
Contribution of Reviewer(s)	
Issue protocol first published	2003 issue 2
Date of last minor amendment	Information not supplied by reviewer

Date of last substantive amendment	18 December 2002
Most recent changes	
Review expected to be published in:	Information not supplied by reviewer
Contact address	Ms Walker PO Box 4001 Sydney NSW AUSTRALIA 2115 Telephone: +61 2 9845 2712 Facsimile: +61 2 9845 2251 E-mail: karenw4@chw.edu.au
Cochrane Library number	CD004206
Editorial group	Cochrane Neonatal Group
Editorial group code	HM-NEONATAL

Sources of support

External sources of support

- No sources of support supplied

Internal sources of support

- KW & NB: Grace Neonatal Unit, The Children's Hospital at Westmead AUSTRALIA
- C.A.J is a recipient of the Children's Hospital at Westmead Research Career Development Award AUSTRALIA

Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review (Structured abstract)

SheffieldJ S, HollierL M, HillJ B, StuartG S, WendelG D, . Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. Obstetrics and Gynecology 2003;102(6) :1396-1403.

CRD summary

This review assessed prophylactic acyclovir for pregnant women with genital herpes simplex virus (HSV) near term. The authors concluded that acyclovir at 36 weeks' gestation reduces clinical HSV recurrence at delivery, Caesarean section for recurrent genital herpes and shedding of HSV at delivery. This was a well-conducted and clearly presented review. The authors' conclusions are likely to be reliable.

Record status

This record is a structured abstract written by CRD reviewers. The original has met a set of quality criteria. Since September 1996 abstracts have been sent to authors for comment. Additional factual information is incorporated into the record. Noted as (A:....).

Author's objective

To assess the effects of prophylactic acyclovir administered to pregnant women with genital herpes simplex virus (HSV) near term on HSV recurrence at delivery.

Type of intervention

Category

Specific interventions included in the review

Studies of prophylactic acyclovir were eligible for inclusion. In the included studies, acyclovir was given at a dose of 200 mg four times daily, or 400 mg three times daily. Treatment was started at 36 weeks' gestation in all of the included studies.

Participants included in the review

Studies of pregnant women with HSV were eligible for inclusion. The included studies were of women with recurrent HSV, a first episode of HSV, and any type of HSV. In the studies, HSV was diagnosed clinically using culture or type-specific serology, or combinations of these methods.

Outcomes assessed in the review

Studies were included if they presented adequate data to calculate summary odds ratios (ORs). The review assessed recurrent genital herpes at delivery, Caesarean deliveries performed for clinical HSV recurrence or prodromal symptoms, and HSV detection at delivery. The clinical and virological recurrence of HSV was assessed.

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion.

What sources were searched to identify primary studies?

MEDLINE (from 1966 to March 2003), LILACS and EMBASE were searched. Also searched were conference proceedings available online or in published format, and abstracts of the following forums: Society for Maternal-Fetal Medicine (1966 to 2003), Infectious Diseases Society for Obstetrics and Gynecology (1966 to 2002), and the Society for Gynecological Investigation (1996 to 2003). Bibliographies of relevant studies were reviewed. The register of controlled trials in perinatal medicine complied by the National Perinatal Epidemiology Unit of Oxford University was also searched. No language restrictions were applied to the searches. Only studies reported in full publications or as abstracts in English, French, Spanish, or German were included. For studies published in multiple reports, only the report containing the most information was included.

Criteria on which the validity (or quality) of studies was assessed

Studies were assessed for blinding, the adequacy of allocation concealment, whether sample size estimates were provided, and the use of intention-to-treat analysis. Three reviewers independently assessed validity.

How were the inclusion criteria applied?

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

How were the data extracted from primary studies?

Three reviewers independently extracted the data using a standardised form and resolved any disagreements through consensus. The extracted data included treatment regimen, gestational age at start of treatment, diagnosis of HSV infection, definition of first episode and recurrent HSV infection, and results. The data were extracted on an intention-to-treat basis. Where required, the authors were contacted for further outcomes data.

Number of studies included

Five RCTs (799 women) were included.

How were the studies combined?

The studies were combined in a meta-analysis. Pooled ORs and 95% confidence intervals (CIs) were calculated using a fixed-effect model (Peto) in the absence of statistical heterogeneity, and a random-effects model in its presence. In the meta-analysis, 0.5 was added to any cells with zero events. The possibility of publication bias was explored using a funnel plot.

How were the differences between studies investigated?

Statistical heterogeneity was assessed using the chi-squared statistic. A sensitivity analysis was conducted by analysing the studies according to the adequacy of blinding, type of HSV disease (first episode versus studies that included women with recurrent disease) and dose of acyclovir (800 mg/day versus 1,200 mg/day).

Results of the review

Four RCTs reported an estimation of sample size, but none reached the minimum estimated sample size. One RCT did not report adequate allocation concealment. Four RCTs reported analysis on an intention-to-treat basis.

Acyclovir significantly reduced clinical HSV recurrence at the time of delivery (4% versus 15% for controls). The OR was 0.25 (95% CI: 0.15, 0.40). No statistically significant heterogeneity was detected (P=0.19).

Acyclovir significantly reduced Caesarean section delivery for clinical HSV recurrence (4% versus 14.6% for controls). The OR (random-effects model) was 0.30 (95% CI: 0.13, 0.67). Statistically significant heterogeneity was detected (P=0.02). Acyclovir also significantly reduced Caesarean section delivery for any indication (OR 0.61, 95% CI: 0.43, 0.86). No statistically significant heterogeneity was detected (P=0.86).

Acyclovir significantly reduced the detection of HSV at delivery using viral culture (0% versus 5% for controls). The OR (4 RCTs) was 0.11 (95% CI: 0.04, 0.31). No statistically significant heterogeneity was detected (P=0.99).

Acyclovir significantly reduced asymptomatic shedding at delivery. The OR (4 RCTs) was 0.09 (95% CI: 0.02, 0.39). No statistically significant heterogeneity was detected (P=0.94).

Similar results were obtained for clinical recurrence at delivery when analysing only studies with adequate blinding. The results were similar for both dosing regimens of acyclovir and by type of disease. These results were reported.

None of the studies reported any cases of neonatal herpes.

The funnel plot suggested a low possibility of publication bias.

Was any cost information reported?

No.

Author's conclusions

Prophylactic acyclovir beginning at 36 weeks' gestation reduced clinical HSV recurrence at delivery, Caesarean section for recurrent genital herpes, and shedding of HSV at delivery.

CRD commentary

The review question was clear in terms of the study design, participants, intervention and outcomes. Several relevant sources were searched, the search terms were stated, and studies in any one of four languages were eligible. Unpublished studies were excluded, thus raising the possibility of publication bias. The methods used to select the studies and assess validity were not described, so it is not known whether efforts were made to reduce errors and bias. Methods to minimise bias were used in the data extraction process.

The data were appropriately combined in a meta-analysis, statistical heterogeneity was assessed, and sensitivity analyses were carried out. There was no exploration or discussion of potential reasons for the significant heterogeneity detected for the analysis of Caesarean section rates. This means that, although the direction of effect was consistent among the studies, the size of the effect on Caesarean section rates is uncertain. The evidence presented appears to support the authors' conclusions.

What are the implications of the review?

Practice: The authors did not state any implications for practice.

Research: The authors stated that ongoing trials of other prophylactic antiviral regimens should assess rates of clinical recurrence, asymptomatic shedding and neonatal HSV. Studies should also assess the effects of treatments on exposed neonates and evaluate renal, hepatic and haematological function at follow-up. The authors also stated that research on interventions to reduce genital HSV is required.

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Language of publication

English

Copyright comments

CRD database number

DARE-20032503

Subject index terms

Subject indexing assigned by NLM: Medical Subject Headings (MeSH): Acyclovir [therapeutic use] ; Antiviral Agents [therapeutic use] ; Herpes Simplex [prevention & control] ; Obstetric Labor Complications [prevention & control] [virology] ; Prospective Studies ; Randomized Controlled Trials ; Recurrence

Valacyclovir prophylaxis for the prevention of Herpes simplex virus reactivation in recipients of progenitor cells transplantation (Structured abstract)

Dignani M C, Mykietiuk A, Michelet M, Intile D, Mammana L, Desmery P, Milone G, Pavlovsky S, . Valacyclovir prophylaxis for the prevention of Herpes simplex virus reactivation in recipients of progenitor cells transplantation. Bone Marrow Transplantation 2002;29(3) :263-267.

Record status

This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.

Health technology

The use of valacyclovir (VAL; Valtrex; GlaxoWellcome) compared with intravenous acyclovir (ACY; Filaxis) for the prevention of Herpes simplex virus (HSV) reactivation. VAL was administered orally at a dose of 500 mg twice daily, from day -3 of autologous progenitor cell transplantation (APCT) until recovery from neutropenia, day +30, severe toxicity, or HSV reactivation, which ever came first. Intravenous ACY was administered at a dose of 5 mg/kg twice daily, from day -3 until recovery from neutropenia.

Disease

Virus diseases; Skin and connective tissue diseases; Surgical procedures, operative.

Type of intervention

Secondary prevention.

Hypothesis/study question

The objective of the study was to compare the efficacy and costs of VAL in preventing HSV reactivation. The comparator was intravenous ACY, which was cited as being effective but expensive. Oral ACY was cited to be cheaper, but it requires higher doses and is associated with poor compliance. VAL was chosen as the treatment of interest because it has a higher bioavailability than oral ACY, is cheaper than intravenous ACY, and is effective in other patients. No specific hypothesis was made, although it was clear that VAL had the potential to be a cost-effective alternative. The perspective adopted in the economic analysis was not stated.

Economic study type

Cost-effectiveness analysis.

Study population

The study population comprised HSV seropositive APCT patients.

Setting

The setting was secondary care. It was unclear whether the study was conducted in the USA or Argentina.

Dates to which data relate

The effectiveness evidence was collected between January 1996 and April 1999. The dates when the costs were collected were not reported. A price year was not given.

Source of effectiveness data

The effectiveness data were derived from a single study.

Link between effectiveness and cost data

The costing was carried out retrospectively on the same patient sample as that used in the effectiveness study.

Study sample

The study sample comprised all APCT patients older than 12 years who tested positive for HSV immunoglobulin G antibodies by indirect immunofluorescence during the study period. This sample was

appropriate for the clinical question since it included patients at risk from HSV reactivation. Power calculations, to estimate the impact of chance on the results, were not reported to have been carried out. There were 108 patients in the VAL group, 43 in the ACY group and 38 in the no HSV prophylaxis group. The patients in the VAL group had a median age of 45 years (range: 13 - 65) and 59 were male. In the ACY group, the median age was 43 years (range: 2 - 64) and 23 patients were male). In the no HSV prophylaxis group, the median age was 39 years (range: 7 - 66) and 19 were male. It was not reported whether any patients refused to participate or were excluded for any reason.

Study design

This was a comparative study with historical controls that seems to have been conducted at a single centre. The patients were followed from day-3 of ACPT until a maximum of 30 days post APCT. No loss to follow-up was reported.

Analysis of effectiveness

The analysis appeared to have been conducted on an intention to treat basis, although this was not explicitly stated. The primary health outcome was HSV reactivations (and the associated site), although the number of viral cultures taken was also noted. The authors also noted the median duration of VAL prophylaxis and reasons for discontinuation. The authors compared the groups in terms of diagnosis and median duration of neutropenia. They did not draw the readers' attention to any clinically important differences.

Effectiveness results

There were three (2.7%) HSV reactivations in the VAL group (all genital), one (2%) in the ACY group (oral), and 17 (45%) in the no treatment group (14 oral, 2 genital and 1 both sites).

Forty-four (40%) viral cultures were taken in the VAL group, 5 (12%) in the ACY group, and 23 (60%) in the no treatment group.

The median duration of VAL prophylaxis was 14 days (range: 1 - 26).

Reasons for discontinuation of VAL were end of prophylaxis (84 patients, 78%), oral intolerance (17 patients, 15%), suspected HSV reactivation (5 patients, 5%), toxicity (1 patient, 1%), and other (1 patients, 1%).

Clinical conclusions

The authors concluded that VAL was well tolerated and was as effective as intravenous ACY.

Measure of benefits used in the economic analysis

The authors did not estimate a summary measure of benefit. In effect, a cost-consequences analysis was conducted.

Direct costs

The authors were concerned only with the cost of the actual treatments, that is, a day of intravenous ACY prophylaxis at the given dose and the cost of viral cultures. These estimates seem to have been based on the costs at the study setting, although this was not stated explicitly. The cost estimates do not appear to have included any overheads or staff-related costs. Discounting was not required, owing to the short time horizon during which the patients were treated. The unit costs were not reported separately from the quantities, although the number of days of treatment was reported separately. The exact dates when the unit costs and quantities were collected were not reported, although the authors did state that the costing was carried out retrospectively.

Indirect costs

The indirect costs to the patients or society were not estimated, despite being potentially relevant on account of the age of the patients involved and the possibility of lost earnings due to treatment.

Currency

US dollars ($).

Statistical analysis of costs

The costs were treated deterministically.

Sensitivity analysis

The authors did not report whether sensitivity analyses were carried out.

Estimated benefits used in the economic analysis

See the 'Effectiveness Results' section.

Cost results

VAL cost $200 per patient, ACY cost $1,210 per patient, and no HSV prophylaxis cost $409 per patient.

Synthesis of costs and benefits

Not relevant.

Author's conclusions

Valacyclovir (VAL) can be considered a safe and less expensive alternative to intravenous acyclovir (ACY) for the prophylaxis of Herpex simplex virus (HSV) in autologous progenitor cells transplantation (APCT) patients.

CRD commentary

Selection of comparators:

The authors compared VAL with intravenous ACY in preventing HSV reactivation. There was a full discussion of the available prophylaxis and a comparison of existing cost and effectiveness evidence. Intravenous ACY appears to have been current practice in the authors' setting. You should decide if this represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness:

The analysis was based on a comparative study with historical controls. This enabled a comparison of the treatments in a true to life setting, but meant that there was no control of potentially confounding variables. The authors stated, "all the groups had the same risk of developing the study endpoint". However, in defining the no prophylaxis group they also reported that these patients did not receive prophylaxis because "they were expected to develop less severe mucositis". This factor introduced a systematic difference between the groups, suggesting a source of bias. The study sample was representative of the study population since it included patients at risk from HSV reactivation. The study might have been improved by a statistical analysis to test for significant differences between the groups, and sensitivity analyses to assess whether the results might be transferable to other settings. Given the nature of the study design, the internal validity is likely to be low.

Validity of estimate of measure of benefit:

The authors did not derive a summary measure of health benefit. Therefore the analysis was categorised as a cost-consequence study.

Validity of estimate of costs:

Very few details of the cost analysis were reported. The authors suggested that the costing was carried out retrospectively and the study was not designed to be a cost-effectiveness analysis. The perspective of the study was not reported, making it difficult to assess the quality of the costing. However, the inclusion of only two sources of costs (prophylaxis and culture) suggests that a number of important cost sources were omitted, irrespective of the perspective taken. From a provider perspective, for instance,

overheads and staff costs should have been included. These problems suggest that the costs reported should be considered as no more than an indicative source of information, and that until further evidence on the cost is available, these results should not be used to inform clinical decision-making.

Other issues:

The authors made some limited comparisons of their findings with those from other authors, particularly results pertaining to oral ACY. However, as the authors did not report results for oral ACY, this comparison is not clear. The authors considered the issue of generalisability by suggesting that VAL savings might be higher in settings with a greater incidence of HSV reactivation. Broader issues of generalisability that might have been addressed through sensitivity analyses were not discussed. The conclusions were an accurate reflection of the scope of the analysis, in relation to the study population, and were indicative of the results presented.

Implications of the study

The authors did not make any recommendations for policy or practice, although they suggested that their findings should be confirmed in a "prospective trial directed towards assessing efficacy, safety, and appropriate dosing".

Country codes

USA

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Source of funding

Partly financed by an educational grant from GlaxoSmithKline, Argentina.

Language of publication

English

Copyright comments

CRD database number

NHSEED-20026548

Subject index terms

Subject indexing assigned by NLM: Medical Subject Headings (MeSH): Acyclovir [administration & dosage] [analogs & derivatives] [economics] [standards] ; Adolescent ; Antiviral Agents [administration & dosage] [economics] [standards] ; Costs and Cost Analysis ; Hematopoietic Stem Cell Transplantation [adverse effects] [methods] ; Herpes Simplex [drug therapy] [prevention & control] ; Research Support, Non-U.S. Gov't ; Simplexvirus [drug effects] [growth & development] ; Transplantation, Autologous [adverse effects] [methods] ; Treatment Outcome ; Valine [administration & dosage] [analogs & derivatives] [economics] [standards] ; Virus Activation [drug effects]

Antiviral therapy for neonatal herpes simplex virus: a cost-effectiveness analysis (Structured abstract)

Mennemeyer S T, Cyr L P, Whitley R J, . Antiviral therapy for neonatal herpes simplex virus: a cost-effectiveness analysis. American Journal of Managed Care 1997;3(10) :1551-1558.

Record status

This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.

Health technology

The subject of this study was antiviral therapy for neonatal herpes simplex virus. The two types of antiviral therapy considered were vidarabine and acyclovir as opposed to no drug treatment.

Disease

Virus diseases.

Type of intervention

Treatment.

Hypothesis/study question

The general objective of the study was to assess the cost-effectiveness of antiviral drug treatment for neonates with the herpes simplex virus, as opposed to no drug treatment.

Economic study type

This was primarily a cost-effectiveness analysis although a cost-utility approach was used in the sensitivity analysis.

Study population

Little information was given in this paper about the study population except that they were neonates and had virological confirmation of the disease regardless of severity. Several references were cited for further information on the original studies on which this paper was based.

Setting

The effectiveness study was based in community care and hospital settings. The economic study was conducted at the University of Alabama, Birmingham, USA.

Dates to which data relate

Effectiveness data related to trial data collected in four trials with the following dates: 1974-1979; 1979-1983; 1984-1989; and 1989-1997. Information from these trials was compared with a historical database of non-treated neonates for which other references were given. Resource use data derived from data collected between 1974 and 1989. 1995 US dollar prices were used.

Source of effectiveness data

The evidence on treatment outcomes was based on a series of previously conducted trials (NIAID CASG trials), the results of which were reported to be already pooled in another study, supplemented by information from other sources. The source of evidence relating to the comparator (i.e. no treatment) was a historical database.

Modelling

Decision tree analysis was used to consider the outcome effects of treatment and no treatment on the three main forms of neonatal herpes simplex virus, listed in increasing order of severity: SEM (skin, ear and mouth), CNS (central nervous system) and DIS (disseminated multiorgan)

Link between effectiveness and cost data

The costing appears to have been undertaken on a separate sample of patients from that used in the effectiveness studies and it is not clear whether it was undertaken retrospectively or prospectively.

Outcomes assessed in the review

Although the authors used data from different sources, there was no specific review of the literature. In terms of outcomes the authors considered lives saved, including those of future generations, and disease occurrence as the main measures of effectiveness.

Study designs and other criteria for inclusion in the review

Data from the NSAID CASG therapeutic trial series were included in the analysis of effectiveness of treatment; these studies were a mixture of placebo-controlled trials, dose-comparison studies and controlled trials. For information concerning the distribution of outcomes in neonates treated and not treated with antiviral therapy, a further source was used, the nature of which is not clear but a reference was provided. Data on the comparator group were obtained from a historical database.

Sources searched to identify primary studies

There does not appear to have been a search of sources.

Criteria used to ensure the validity of primary studies

It does not seem that criteria were used to ensure the validity of the studies included.

Methods used to judge relevance and validity, and for extracting data

There was no systematic review of the literature.

Number of primary studies included

Data on outcomes for patients receiving treatment was reported to have been obtained from four NIAID CASG studies involving a total of 323 patients. The source of data on outcomes for those not receiving treatment was obtained from a historical database of 235 untreated neonates. A further source was given for data on the distribution of outcomes in neonates treated and not treated with antiviral therapy, for which no details are given.

Method of combination of primary studies

It was stated that outcome data from the NIAID CASG were previously pooled and another paper was referenced for this.

Investigation of differences between primary studies

An analysis of differences in the results of primary studies was not carried out, despite the fact that the authors stated that differences in drug toxicity were found.

Results of the review

The authors presented data on the progression of the herpes simplex virus infection in untreated neonates and the distribution of outcomes in neonates treated and not treated, although with regards to the latter, not all the patients in the four NIAID CASG trials seem to have been included. The authors found that a larger percentage of treated infants were considered to have normal outcomes than untreated neonates (56% versus 25%) and a smaller percentage of treated neonates died compared to those not treated (17% versus 47%). These values were not tested for statistical significance. The relative proportions of those with mild, moderate or severe outcomes did not differ greatly. Survival data

were not presented separately from the model and are therefore summarised in the measure of benefits below.

Measure of benefits used in the economic analysis

In the base-line analysis, life years gained were the main outcome measure, although quality-adjusted lives (QALYs) saved were imputed in the sensitivity analysis. QALYs were calculated using the EuroQol scale which ranks death at 0 and normal life at 1. The clinical team rated patients according to the following dimensions: mobility, self-care, usual activity, pain and anxiety using a scale of 1 (normal) to 3 (very dysfunctional).

Direct costs

Direct medical costs were evaluated by comparing the data from the historical database with data on 93 patients treated with antiviral drugs at a US hospital (University of Alabama, Birmingham) between 1974 and 1989. Costs were based on 74% of the daily hospital charges for a stay in a semi-private room and the paediatric intensive care unit (PICU) (since the authors stated that many payers were able to negotiate discounts) and an estimate of the expenses for a 10 day drug regimen of acyclovir with associated use of intravenous fluids and pumps. Data were presented on days of use of hospital ward and PICU by neonates treated and not treated. It was assumed in the cost analysis that survivors with a severe outcome do not live beyond 19 years of age. The base case analysis also included the costs of institutional care for those with severe outcomes (based on a survey of 22 families with a child under treatment at the University of Alabama at Birmingham) and the costs of special education for those with moderate outcomes (another paper was referenced as the source of this data). The analysis did not consider the costs for the patient beyond 20 years of age as the authors stated that most patients with severe outcomes will not live beyond this age and that after this age it is difficult to apportion the costs of health care purely to HSV sequelae. All costs were converted to 1995 dollars and discounted by 3%.

Indirect costs

Indirect costs were not included in the analysis in this paper, although the authors stated that they examined this issue and did not find it to be at odds with the base case analysis presented here (no reference was provided).

Currency

US dollars ($).

Statistical analysis of costs

No statistical analysis was performed on costs.

Sensitivity analysis

One-way sensitivity analyses were performed on discount rates (at 5% and 10%) and the cost of drug treatment (increased and decreased by a factor of two). To examine alternative measures of life, a sensitivity analysis was performed using quality-adjusted life years saved (as described above).

Estimated benefits used in the economic analysis

In the base case analysis, marginal lives saved were calculated. In terms of the societal perspective (which includes lives saved in future generations discounted at 3%), treatment for neonates with SEM saved 0.8 lives per case, treatment for neonates with CNS saved 0.7 lives per case and treatment for neonates with DIS saved 0.4 lives per case. When the impact on future generations was excluded, 0.4 lives per case were saved in the SEM and the CNS groups whilst 0.2 lives per case were saved in the DIS group. In the sensitivity analysis, quality adjusted life years (QALYs) were used as an outcome measure. The authors applied the EuroQol scale to derive QALY values of 1.0, 0.82, 0.52, 0.16 and 0 for normal, mild, moderate, severe and dead outcomes respectively. It was reported that without treatment an average of 28 lives were saved per SEM case whereas with treatment 58 QALYs were saved so that the marginal gain from treatment was 30 QALYs per case treated. Turning to the case of CNS, without treatment 16 QALYs were saved and with treatment 33 (a gain of 17 QALYs) were saved. Lastly, without treatment for DIS, 9 QALYs were gained and with treatment, 20 QALYs (for a gain of 11 QALYs) were gained.

Cost results

When all costs were included (i.e. medical, special education and institutional care) for a duration of 20 years,the cost per patient with SEM treated with antiviral therapy was reported to be $19,873 and without treatment, $98,474. For neonates with CNS, the cost of treatment was $172,808 per patient whilst no treatment cost $120,859. Finally, for neonates with DIS, the cost of treatment was $86,714 per patient whilst the cost of no treatment was $69,054. When only direct medical costs were included and the costs of future care and education ignored, drug treatment for neonates with SEM cost $13,638 and without treatment, $35,870. For CNS patients, the cost of drug treatment was $50,858 whilst no treatment cost $42,717. And for patients with DIS, drug treatment cost $32,107 per patient whilst no treatment cost $32,736.

Synthesis of costs and benefits

When the societal perspective was considered (all special education and institutional costs plus the benefits to future generations of survivors in this generation), the authors found that when neonatal herpes simplex virus appears in the SEM form, treatment with antiviral drugs is a dominant strategy, i.e. lives were saved at reduced cost. Considering the CNS form, the additional cost per additional life saved was $75,125 whilst for the case of DIS, the additional cost per additional life saved was $46,619. When the narrower health care perspective was considered and the future generations ignored, antiviral therapy for neonatal HSV in the SEM form was again found to be a dominant strategy. For the CNS case, the additional cost per additional life saved was $19,975, whilst giving antiviral therapy to neonates with HSV with a DIS presentation was also found to be a dominant strategy. The costs and benefits in terms of the stream of future lives were all discounted at 3%. The sensitivity analysis on the discount rates did not change the nature of the findings and the authors stated that only small changes in the results were found to occur when the cost of drug treatment was varied (no details given).

Author's conclusions

The authors concluded that antiviral therapy can save lives and reduced costs when the disease was discovered in the SEM form. When the disease had progressed to the CNS and DIS forms saving lives was associated with increased costs, although treatment was more cost-effective when considered from only a health service perspective. The prospect of home administration of antiviral therapy has the potential to make antiviral therapy a dominant form for all presentations of neonatal HSV.

CRD commentary

Selection of comparators:

The comparator in this case was standard treatment which did not include drug therapy. It would have been helpful to know how widespread the use of drug therapy really is and whether the option of not giving drug therapy actually exists.

Validity of estimate of measure of benefit:

The estimate of the benefit from antiviral therapy was derived from several studies which did not form part of an overall review of literature so results may be biased. Results from these trials were stated to have been pooled elsewhere and no summary statistics of this pooling were provided here. In addition a historical database was used to derive information on patients not treated which may again contain biases. In addition data does not seem to have been presented on all cases treated (table 2 shows the outcome of 235 patients treated rather than the 323 referred to in the earlier section on data sources). Utility data were derived from the clinical team which may not be representative.

Validity of estimate of costs:

This paper considered the costs of institutional care and special education which is very commendable. The cost data presented would have been rather more transparent if it had been broken down into these elements and it is not clear how the summary measures of costs in tables 5 and 6 were calculated.

Other issues:

The authors did mention that the clinical trials reported statistical a difference between the two types of treatment for neonatal HSV in terms of drug-toxicity which however did not form part of the authors' model. Cost data may not be generalisable to other settings.

Country codes

USA

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Source of funding

Supported by awards from the NIAID N01-A1-65306, NC1 CA RO-1-13148, Division of Research Resource (DRR) RR-032 and the State of Alabama.

Language of publication

English

Copyright comments

CRD database number

NHSEED-980021

Subject index terms

Subject indexing assigned by NLM: Medical Subject Headings (MeSH): Acyclovir [therapeutic use] ; Antiviral Agents [adverse effects] [therapeutic use] ; Cost-Benefit Analysis ; Eye Infections, Viral ; Eye Infections, Viral virology ; Herpes Genitalis cerebrospinal fluid ; Herpes Simplex [drug therapy] ; Infant, Newborn ; Morbidity ; Mouth Diseases ; Skin Diseases, Viral ; Vidarabine [therapeutic use]

Acyclovir prophylaxis for pregnant women with a known history of herpes simplex virus: a cost-effectiveness analysis (Structured abstract)

Little S E, Caughey A B, . Acyclovir prophylaxis for pregnant women with a known history of herpes simplex virus: a cost-effectiveness analysis. American Journal of Obstetrics and Gynecology 2005;193(Supplement 3) :1274-1279.

Record status

This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.

Health technology

The study examined prophylactic antiviral (acyclovir) therapy for women with a history of herpes simplex virus (HSV) but without recurrence during pregnancy.

Disease

Virus diseases; Skin and connective tissue diseases; Female genital diseases and pregnancy complications.

Type of intervention

Secondary prevention.

Hypothesis/study question

The objective of the study was to perform a cost-effectiveness analysis of acyclovir prophylaxis (at 36 weeks' gestation) in women with a history of HSV but without recurrence in pregnancy. The current clinical practice was to offer acyclovir prophylaxis only to those women who had experienced an HSV recurrent outbreak during pregnancy. The authors' hypothesis was that providing acyclovir prophylaxis to women with a diagnosed history of HSV, even if they did not have recurrence during pregnancy, might prove clinically beneficial and cost-effective. The comparator was no medical therapy. The perspective adopted in the study was that of the health care provider.

Economic study type

Cost-utility analysis.

Study population

The study population comprised a hypothetical cohort of pregnant women with a history of diagnosed HSV but without recurrence during pregnancy.

Setting

The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate

The effectiveness data came from studies published between 1983 and 2004. The price year was 2005.

Source of effectiveness data

The effectiveness data were derived from a review of published studies, augmented by some authors' assumptions.

Modelling

A decision tree model was developed, using TreeAge Pro software, to estimate the clinical benefits and costs of acyclovir prophylaxis in the study population. The model considered the probability of experiencing side effects with acyclovir therapy. In case of HSV transmission, the health outcomes included were normal neonate, moderately impaired neonate, severely impaired neonate and neonatal death. A moderately impaired neonate was defined as a child who could perform the activities of daily living on his own, free from pain, and who performed schoolwork more slowly than his peers. A severely impaired neonate was defined as a child who needed assistance with eating, bathing or using the toilet, was very slow at schoolwork, was in moderate to no physical pain, and was blind, deaf or unable to talk. The time horizon of the model seems to have been the child's lifetime, although it was not explicitly reported.

Outcomes assessed in the review

The effectiveness outcomes assessed for use in the model were:

the genital HSV infection because of HSV Type 1;

the probability of side effects because of acyclovir therapy;

the probability of a Caesarean delivery if no lesions were present;

the maternal mortality rate;

the probability of lesions at delivery;

the probability of shedding asymptomatically at delivery;

the probability of neonatal transmission if shedding ;

the outcomes of neonatal transmission (probabilities of moderate or severe neurologic disability and probability of neonatal death); and

the effectiveness of acyclovir.

Study designs and other criteria for inclusion in the review

Not stated.

Sources searched to identify primary studies

Not reported.

Criteria used to ensure the validity of primary studies

Not reported.

Methods used to judge relevance and validity, and for extracting data

Not reported.

Number of primary studies included

Ten primary studies were included in the review.

Method of combination of primary studies

The authors used composite odds ratios determined by meta-analysis to reduce the probabilities of either having lesions or asymptomatic shedding with acyclovir prophylaxis. No more information was given about the method of combining primary studies for the rest of the probabilities obtained in the review. However, combination was not necessary in most cases since each probability was derived from only one source.

Investigation of differences between primary studies

Not reported.

Results of the review

The probability of genital HSV infection because of HSV Type 1 was 0.150.

The probability of side effects because of acyclovir therapy was 0.020.

The probability of a Caesarean delivery if no lesions were present was 0.244.

The probability of maternal death was 0.000092 with vaginal delivery, 0.000350 with Caesarean delivery not for lesions, and 0.000239 with Caesarean delivery for lesions.

The probability of lesions at delivery was 0.0037 with HSV-1 and 0.0110 with HSV-2.

The probability of shedding asymptomatically at delivery was 0.0018 with HSV-1 and 0.0055 with HSV-2.

The probability of neonatal transmission if shedding was 0.00 with Caesarean delivery for lesion. For all other deliveries, the probability was 0.028 for neonatal HSV-1 if maternal HSV-1, 0.113 for neonatal HSV-2 if maternal HSV-1, 0.000 for neonatal HSV-1 if maternal HSV-2, and, 0.040 for neonatal HSV-2 if maternal HSV-2.

The probability of moderate neurologic disability was 0.01 for HSV-1 and 0.14 for HSV-2.

The probability of severe neurologic disability was 0.02 for HSV-1 and 0.17 for HSV-2.

The probability of neonatal death was 0.28 for HSV-1 and 0.20 for HSV-2.

The effectiveness of acyclovir in reducing lesions was 0.75.

The effectiveness of acyclovir in reducing asymptomatic shedding was 0.91.

The effectiveness of acyclovir in reducing transmission was 0.89.

Methods used to derive estimates of effectiveness

The authors made an assumption in order to complete all the probabilities of the model.

Estimates of effectiveness and key assumptions

It was assumed that if lesions were present at time of delivery, every child would be delivered by Caesarean.

Measure of benefits used in the economic analysis

The measure of benefit was the quality-adjusted life-years (QALYs). The QALYs were obtained from the literature. Only the mothers' and children's QALYs estimates were taken into consideration. In calculating the mothers' QALYs, the USA average maternal age and life expectancy were used. To calculate the maternal utility decrease when a child had either moderate or severe neurologic impairment, the authors used the estimated utility for having a child with Down syndrome. For a neonate with neurologic disability, the life expectancy of a child with either severe or moderate cerebral palsy was used. For the utility of being a child with either severe or moderate neurologic disability, the estimates from Saigal et al. (see 'Other Publications of Related Interest' below for bibliographic details.) were used. Discounting was applied at a rate of 3%. Moreover, the number-needed-to-treat was calculated for several outcomes (Caesarean deliveries, neonatal deaths and severely neurologically impaired children).

Direct costs

The direct costs included were for acyclovir prophylaxis, vaginal delivery, Caesarean delivery, Caesarean delivery for lesions, the initial hospital treatment for neonate with HSV, and the lifetime treatment of a child with moderate or severe neurologic disability. For the lifetime cost of having a child with severe neurologic disability, the cost of a child with cerebral palsy was used. The costs, which were obtained from the literature, reflected real costs rather than charges. The costs and the quantities were not reported separately. The price year was 2005. It was not reported whether discounting was applied.

Indirect costs

The indirect costs were not considered.

Currency

US dollars ($).

Statistical analysis of costs

The costs were treated deterministically in the base-case.

Sensitivity analysis

The robustness of the model results were tested by varying every variable of the model (univariate sensitivity analysis). Moreover, threshold analyses were performed over particularly sensitivity inputs. Finally, a Monte Carlo simulation was used to test the robustness to simultaneous multivariable changes in a theoretic cohort of 160,000 women. Triangular distributions were used for the Monte Carlo simulations.

Estimated benefits used in the economic analysis

The average composite QALY for mother and child was 56.7117 with acyclovir versus 56.7074 with 'no acyclovir'. The total number of QALYs (in thousands) in the 160,000 women cohort was 9,074 with acyclovir versus 9,073 with 'no acyclovir'.

The clinical outcomes showed that 22,286 women needed to be treated to prevent 1 neonatal death, 8,985 women needed to be treated to prevent 1 affected child, and 177 women needed to be treated to prevent 1 Caesarean delivery.

Cost results

The average cost per woman was $6,102 with acyclovir and $6,122 with 'no acyclovir'.

The respective figures for the 160,000 women cohort were $976 million (with acyclovir) versus $979 million (without acyclovir).

Synthesis of costs and benefits

Acyclovir prophylaxis was a dominant strategy since it was both less expensive and more effective than the option of no prophylaxis. Therefore, cost-effectiveness ratios were not calculated. Acyclovir prophylaxis saved approximately $20 per person and increased the total QALYs by 0.01. By providing acyclovir prophylaxis to a hypothetical cohort of 160,000 women, approximately $3 million were saved and 1,000 QALYs were gained. Moreover, it prevented approximately 6 severely neurologically impaired children, 7 neonatal deaths and 1,000 Caesarean deliveries.

These results proved to be robust in the univariate sensitivity analyses. Threshold analyses showed that acyclovir was the dominant strategy up to a cost estimate of $67 (150% of baseline). The Monte Carlo simulation demonstrated acyclovir to be cost-effective (at a cost of <$20,000 per QALY) 100% of the time and cost-saving greater than 99% of the time.

Author's conclusions

Acyclovir prophylaxis was not only cost-effective but also cost-saving for pregnant women with a diagnosed history of genital herpes who do not experience recurrence during pregnancy.

CRD commentary

Selection of comparators:

The comparator was standard care which did not include drug therapy. However, it would have been interesting to have compared acyclovir with other antiviral therapies available on the market. You should decide if the options evaluated (acyclovir prophylaxis versus no prophylaxis) are relevant in your own setting.

Validity of estimate of measure of effectiveness:

The effectiveness evidence was derived from the literature. As a systematic review of the literature was not reported, it was not clear whether all of the relevant studies were included. However, every effectiveness input used in the model was tested in the sensitivity analyses, which to some extent enhance the validity of the results obtained. Despite this, given the lack of detail on the methods used to identify and select the studies from which the model inputs were derived, it was difficult to ascertain if the best available evidence had been used in the analysis

Validity of estimate of measure of benefit:

The use of QALYs as a measure of benefit enables the results to be compared with those of other studies. The utilities rates were obtained from the literature and most of them were not specific for the health states analysed in the model (i.e. the utilities for having a child with Down syndrome or the life expectancy of a child with cerebral palsy were used). The QALYs were discounted appropriately. As the authors stated, it is most likely that the QALYs estimates were underestimated because they only included the mother and the child and ignored the impact of other members of the family.

Validity of estimate of costs:

It seems that all the categories of costs relevant to the perspective adopted have been considered in the study. The quantities and the costs were not reported separately. However, the price year was stated and comprehensive sensitivity analyses were performed. These, in some degree, enhance the possibility of replicating the study in other settings. It was unclear whether the costs were discounted, although it would have been appropriate since lifetime costs were considered in the model. Real costs rather than charges were used.

Other issues:

The issue of generalisability was not explicitly addressed, although the results obtained seem to have been quite specific to the setting where the study was carried out. Further details on resource use and the costing methodology would have been helpful (it would have been particularly useful to have had evidence that the costs were discounted). The authors made some comparisons of their findings with those of other studies and it seems that similar conclusions were found.

Implications of the study

The study findings suggested that, compared with no treatment, the use of acyclovir prophylaxis for pregnant women with a diagnosed history of genital herpes who do not experience recurrence during pregnancy is cost-effective over a wide range of assumptions. The authors recommended that further studies should be done on other populations, since most neonatal infections were not addressed in this study. Most of the neonates who are born with HSV are delivered by women without a known history of genital HSV.

Other publications of related interest

Saigal S, Stoskopf BL, Feeny D, Furlong W, Burrows E, et al. Differences in preferences for neonatal outcome among health care professionals, parents and adolescents. JAMA 1999;281:1991-7.

Country codes

United States

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Source of funding

Supported by the National Institute of Child Health and Human Development.

Language of publication

English

CRD database number

NHSEED-20051462

Subject index terms

Subject indexing assigned by NLM: Medical Subject Headings (MeSH): Acyclovir [economics] [therapeutic use] ; Cost-Benefit Analysis ; Cost Savings ; Decision Support Techniques ; Herpes Genitalis [economics] [prevention & control] ; Monte Carlo Method ; Pregnancy Complications, Infectious [economics] [prevention & control] ; Quality-Adjusted Life Years ; Research Support, N.I.H., Extramural ; Research Support, U.S. Gov't, P.H.S. ; United States

CRD database number: NHSEED20051462

Therapeutic interventions for herpes simplex virus epithelial keratitis

Wilhelmus KR

This review should be cited as: Wilhelmus KR. Therapeutic interventions for herpes simplex virus epithelial keratitis (Cochrane Review). In: *The Cochrane Library,* Issue 2, 2008. Oxford: Update Software.

A substantive amendment to this systematic review was last made on 29 October 2007. Cochrane reviews are regularly checked and updated if necessary.

Abstract

Background

Many clinical trials have been performed on the acute treatment of dendritic epithelial keratitis. Surveys of ocular antiviral pharmacology and of herpes simplex virus (HSV) eye disease have evaluated different interventions, but a systematic review of all comparative clinical studies has not previously been undertaken.

Objective

The objective of this review was to compare the effects of various therapeutic interventions for dendritic or geographic HSV epithelial keratitis.

Search strategy

We searched the Cochrane Central Register of Controlled Trials - CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) in The Cochrane Library (Issue 3, 2007), MEDLINE (1966 to September 2007), EMBASE (1980 to September 2007), LILACS (up to September 2007), SIGLE (1980 to September 2007), ZETOC (21 September 2007), BIOSIS (up to 2005), JICT-EPlus (up to 2005), Index Medicus (1960 to 1965), Excerpta Medica Ophthalmology (1960 to 1973), reference lists of primary reports and review articles, and conference proceedings pertaining to ocular virology.

Selection criteria

This review included comparative clinical trials that assessed one-week or two-week healing rates of topical ophthalmic or oral antiviral agents and or physical or chemical debridement in people with active epithelial keratitis.

Data collection and analysis

The review author extracted data and assessed trial quality. Interventions were compared by the proportions of participants healed at seven days and at fourteen days after trial enrolment.

Main results

This review included data from 99 trials that randomised a total of 5363 participants. The topical application of vidarabine, trifluridine, acyclovir or ganciclovir resulted in a high proportion of participants healing within one week of treatment. Among these antiviral agents, no treatment emerged as significantly better for the therapy of dendritic epithelial keratitis. Insufficient placebo-controlled studies were available to assess debridement and other physical or physicochemical methods of treatment. Interferon monotherapy had a slight beneficial effect on dendritic epithelial keratitis but was not better than other antiviral agents. Interferon was very effective when combined with another antiviral agent such as trifluridine.

Reviewers' conclusions

Currently available antiviral agents are effective and nearly equivalent. The combination of a nucleoside antiviral with either debridement or with interferon seems to speed healing. Future trials of the acute treatment of HSV epithelial keratitis must aim to achieve adequate statistical power for assessing the primary outcome of epithelial healing and should consider the effect of lesion size and other characteristics on treatment response.

Synopsis

Antiviral, interferon, and debridement treatments for herpes simplex eye disease

Herpes simplex is the most common virus acquired by humans, and ocular herpes is a prevalent and recurrent infection. Several treatments, ranging from eye medications to wiping or scraping, aim to shorten the course of herpetic eye disease when infection of the corneal surface, known as a dendrite, occurs. To examine the effectiveness of treatment options, the review author included 99 clinical trials from Europe, North America, Asia, Australia, and Africa that involved 5,363 participants who had a corneal dendrite. Healing rates at one week and two weeks were compared using different treatments, including placebo, antivirals, interferon, and ocular surface removal known as debridement. Placebo was not very effective since only 25% of corneal dendrites healed spontaneously within one week and slightly less than half by two weeks. During the 1960s, the first nucleoside antiviral drug idoxuridine (IDU) was discovered and was shown to lead to faster healing of herpetic corneal infection compared to placebo. Randomized trials subsequently found that antiviral drugs such as trifluridine and acyclovir were better than IDU; about 5 times as many patients healed within one week with trifluridine or acyclovir as with IDU. Further trials showed that trifluridine and acyclovir were equivalently effective and led to healing in two thirds of treated patients by one week and in approximately 90% by two weeks. Ganciclovir gel appeared equivalent to acyclovir ointment. Small trials with bromovinyldeoxyuridine (BVDU) or foscarnet suggested similar effectiveness as trifluridine or acyclovir. In one trial, acyclovir taken by mouth was as good as acyclovir applied to the eye. Interferon was better than placebo and as effective as other antiviral drugs. The combination of interferon-alfa eye drops and either trifluridine or acyclovir resulted in faster healing of dendritic keratitis than treatment with trifluridine or acyclovir alone; 90% of eyes healed within one week with combined interferon-antiviral therapy. Debridement by heat, chemicals, swabbing, or abrasion was commonly used before the development of antiviral drugs; the joint use of debridement and antiviral therapy seemed to speed healing and reduced recrudescent infection. Unfortunately, undue inconsistency among too few studies precluded knowing whether patients who had their infected corneal surface wiped off and then received antiviral treatment healed faster than those treated only with an antiviral medication. This review was limited by the many different therapies that have been studied and could not include 63 other trials that used inadequate methods or reported insufficient information

Background

Herpes simplex virus (HSV) is an important cause of infectious eye disease (Wilhelmus 1998). A prevalence study revealed a history of ocular HSV disease in 149 people per 100,000 population (Liesegang 1989a). Worldwide, up to 10 million people are estimated to have a history of herpetic eye disease.

The incidence of ocular HSV is 21 to 31 per 100,000 people per year (Labetoulle 2005; Liesegang 1989a) although both lower and higher estimates have been made (Kaiserman 2005; Mortensen 1979; Norn 1970; Ribaric 1976). Epithelial keratitis is the most common form of ocular HSV disease, accounting for approximately 70% to 80% of all cases (Labetoulle 2005; Liesegang 1989a). Dendritic epithelial keratitis, a branching pattern of epithelial infection and erosion, is the typical configuration of HSV epithelial keratitis. Geographic epithelial keratitis is a less common, macroulcerative form of HSV corneal epithelial infection. The incidence of HSV epithelial keratitis is approximately 15 to 20 per 100,000 people per year (Labetoulle 2005; Liesegang 1989b; Mortensen 1979). No triggers for herpes simplex epithelial keratitis have been established (HEDS Group 2000a; HEDS Group 2001). The recurrence rate of HSV epithelial keratitis may be greater in atopes, diabetics, corneal transplant recipients and people with immunosuppression (Hodge 1997; Kaiserman 2005; Remeijer 1997; Rezende 2006).

Herpes simplex virus type 1 is the cause for nearly all cases of dendritic and geographic epithelial keratitis, although other viruses are implicated on rare occasions (for example HSV type 2) (Neumann-Haefelin1978). The prospective Herpetic Eye Disease Study examined the risk of recurrent HSV disease (HEDS Group 2001). Few triggering factors are known (HEDS Group 2000a) largely because of recall bias (Kip 2001). Topical (Romano 1988; Wilhelmus 1983) and oral (HEDS Group 2000b; Luzi 1983) agents can suppress recurrent HSV epithelial keratitis and other avenues for prophylaxis are feasible (Jones 1977; Kaufman 2002).

This review focuses on treatment of HSV epithelial keratitis rather than diagnostic evaluation of infection, management of stromal inflammation, or prevention of recurrences. Many physical, chemical, and antiviral agents for treating HSV epithelial keratitis have been introduced (Gordon 2000; Sundmacher 1983). In the first half of the twentieth century corneal epithelial debridement and cauterization came into widespread use. In 1962, Kaufman reported the use of idoxuridine in HSV epithelial keratitis (Kaufman 1962). Idoxuridine's success led to the development of other nucleoside analogues such as vidarabine (Whitley 1980) and trifluridine (Carmine 1982). Acyclovir was subsequently developed in both topical and oral formulations (Richards 1983; Wagstaff 1994). Interferons have also been tested for use in therapy and prevention (Cantell 1995). Ganciclovir, foscarnet, bromovinyldeoxyuridine, cidofovir, and other drugs have been recently evaluated for dendritic

epithelial keratitis. Idoxuridine was removed from the marketplace in the early 1990s because of low demand, but several antivirals are widely available for the treatment of HSV epithelial keratitis.

Controversies persist about the effectiveness of debridement methods, the optimal antiviral agent, and the role of interferon. Complex decision-making is involved in selecting appropriate therapy for ocular herpes (Kastner 1984). This systematic review summarizes the clinical trials that have been performed on the acute treatment of HSV epithelial keratitis.

Objectives

The objective of this review was to assess the relative effects of physical and pharmacological interventions for treating dendritic or geographic epithelial keratitis due to herpes simplex virus.

Criteria for considering studies for this review

Types of studies

This review included controlled clinical trials that assessed the effects of one or more therapeutic interventions on the corneal epithelial healing of participants with presumed herpes simplex virus epithelial keratitis.

Types of participants

Participants were people with active dendritic, dendrogeographic, or geographic epithelial keratitis. Studies of people with stromal keratitis were excluded if epithelial keratitis was not present.

Types of intervention

Interventions were physical debridement, chemical cauterization, topical ophthalmic antiviral nucleoside agents, topical interferon, and oral antiviral agents and were compared to control or placebo, to each other, or to combinations of these interventions.

Types of outcome measures

The primary outcome was the proportion of participants healed at seven days after study entry. To evaluate that the speed of healing correlated with overall treatment effectiveness, the secondary outcome was the proportion healed at 14 days after study entry.

Search strategy for identification of studies

See: Cochrane Eyes and Vision Group search strategy

See: methods used in reviews.

Electronic searches
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) in The Cochrane Library, MEDLINE, EMBASE, LILACS (Latin American and Caribbean Literature on Health Sciences), ZETOC, SIGLE (System for Information on Grey Literature), BIOSIS, and JICT-EPlus. All databases except for SIGLE, BIOSIS and JICT-EPlus were last searched on 21st September 2007.

We used the following strategy to search CENTRAL Issue 3 2007.
#1 MeSH descriptor Keratitis, Herpetic
#2 MeSH descriptor Keratitis, Dendritic
#3 (herpes* or simplex) near (cornea* or kerati* or dendr* or epithel* or endothel* or stroma* or uveiti* or ocular)
#4 (#1 OR #2 OR #3)

We used the following strategy to search MEDLINE on OVID to September 2007.
1. exp clinical trial/ [publication type]
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.

5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp keratitis herpetic/
14. exp keratitis dendritic/
15. ((herpe$ or simplex) adj4 (cornea$ or kerati$ or dendr$ or epithel$ or endothel$ or stroma$ or uveiti$ or ocular)).tw.
16. or/13-15
17. 12 and 16

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

We used the following strategy to search EMBASE on OVID to September 2007.
1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp herpes simplex keratitis/
34. ((herpe$ or simplex) adj4 (cornea$ or kerati$ or dendr$ or epithel$ or endothel$ or stroma$ or uveiti$ or ocular)).tw.
35. or/33-34
36. 32 and 35

We searched LILACS on 21st September 2007 using the following terms herpe$ or simplex and cornea$ or kerati$ or dendr$ or ocular.

We searched ZETOC on 21st September 2007 using the following terms herpes simplex kerati* and random* or trial*.

We searched SIGLE to 2005/03 using the following string:
(herpe* or simplex) near (cornea* or kerati* or dendr* or ocular)

We searched BIOSIS and JICT-EPlus to 2005 using the terms HERPE$ or SIMPLEX in combination with CORNEA$ or KERATI$ or DENDR$.

Other sources
Manual searching included Index Medicus from 1960 through 1965 and Excerpta Medica Ophthalmology from 1960 to 1973, using the terms 'cornea', 'herpes', and 'keratitis'. Other sources included the indices of Ophthalmic Literature to 1999, and the reference lists of primary reports, review articles, and corneal textbooks for additional relevant articles that included the word 'herpes' or 'herpetic'.

Titles and abstracts of meetings held between 1980 and 2006 of the Association for Research in Vision and Ophthalmology (ARVO), the American Academy of Ophthalmology (AAO), the Ocular Microbiology and Immunology Group, and the International Conference on Herpetic Eye Diseases were searched for clinical studies of herpetic keratitis.

Methods of the review

Selection of studies
Articles retrieved by the searches were copied and translated as needed. Studies were selected that had an unbiased allocation of two or more interventions to participants with herpes simplex virus (HSV) epithelial keratitis and that reported the status of participants by seven or 14 days after study entry. For multiple publications using all or part of the same study population the most detailed report with the largest sample was used.

Assessment of methodological quality of included studies
Relevant studies were assessed on the reported study design, analysis, and presentation (Chalmers 1981). Studies were assessed for internal validity, as noted in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006). Major sources of systematic bias that were appraised included selection bias, performance bias, detection bias, and attrition bias. Selection bias was evaluated by the use of randomization in treatment allocation using a concealed assignment schedule. Performance bias and detection bias were evaluated by noting the use of masking of participants, trialists (who were the eligibility determiners, treatment providers, and outcome evaluators in all trials), and analysts. Detection bias was also evaluated by noting the use of slit-lamp biomicroscopy and of stains such as fluorescein and rose-Bengal in the determination of corneal epithelial healing. Attrition bias was evaluated by the extent of withdrawals and number of censored individuals.

Each study was rated by the degree of plausible biases. The level of possible bias was based on three criteria: the use of concealed randomised allocation of the intervention, the use of masking of participants and providers, and the use of slit-lamp biomicroscopy for determining eligibility and outcome. Studies that met all criteria were ranked as having a low risk of bias (A). Studies that met at least two criteria were ranked as having a moderate risk of bias (B). Studies that did not meet two or more criteria were ranked as having a high risk of possible bias (C). Studies that did not provide sufficient information, either in the published report or by making direct contact with the investigators, were ranked as having an uncertain risk of bias (D).

Data extractionand management
One unmasked person extracted data using a data collection form. Data were extracted from the full articles to describe the population, the method of treatment allocation, any co-interventions or adjunctive treatment, and the examination method used to evaluate healing.

Information from all participants was extracted for trials that enrolled people with either dendritic or geographic epithelial keratitis. Data from trials enrolling exclusively people with geographic epithelial keratitis were evaluated separately. Data for participants with only geographic epithelial keratitis were also recorded separately when the published report provided outcome information on these patients.

The cumulative number of participants who were healed in each intervention group was recorded for each day of follow up. For reports providing only graphs of healing curves, a millimeter ruler was used to find the proportion healed, by projecting the curve onto the ordinate axis for each day.

Corresponding authors were contacted, when feasible, if insufficient data were provided in the published report.

Analysis
A time point of one week was chosen as the primary treatment day for comparison, since this was a time when patients with herpes simples virus keratitis were commonly re-evaluated. While the median time to corneal epithelial healing in an intervention group was considered as another outcome measure, the discrete number of follow-up observations limited using survival analysis in this review (that is occasionally only the proportion healed at one week was known rather than on a day-by-day basis). Treatment comparisons based on the mean or median times to resolution were, therefore, not presented because antiviral treatments did not all yield similar healing distributions and because some interventions (for example minimal wiping debridement) were complicated by recrudescent epithelial

infection. A masked review of the 49 trials that provided survival graphs showed that the maximum separation of the healing curves for different treatments occurred at a mode of seven days, a mean of six days (± two days), and a median of six days (25% and 75% quartiles of four and seven days, respectively).

Standard fourfold tables were constructed with columns for treatment groups and rows for presence or absence of healing at seven days and at 14 days after trial enrolment. This overview summarizes all accessible direct treatment comparisons. Studies comparing more than two interventions were recombined into appropriate pairs of interventions in the data tables. The data also permitted indirect comparisons to be made for interventions that were not directly compared but were compared to another commutual intervention (Bucher 1997). Relative effect measures were presented as the more effective therapy compared to the less effective therapy.

Interventions that were considered sufficiently similar to allow data pooling were: photoinactivation and carbolization; cryotherapy and carbolization; thermomechanical debridement and thermomechanical debridement with interferon-alpha 62,500 international units per millilitre (IU/ml), a dosage probably too low to exert clinical effects; debridement with interferon-alpha at either 11 million IU/ml or 33 million IU/ml; and trifluridine with interferon-alpha at either one million IU/ml or 30 million IU/ml. While ganciclovir 0.05% appeared similar to ganciclovir 0.15%, only the 0.15% gel was examined since this was the commercially available concentration.

Some placebo controlled trials used the vehicle of the relevant study drug for the placebo control. Other agents also classified as a placebo in this review included neomycin, albumin, nonspecific gamma globulin, and low-dose interferon preparations.

Description of studies

The electronic searches identified a total of 1228 reports of clinical trials of herpes simplex virus (HSV) epithelial keratitis. Ninety-nine trials, published in 95 primary reports between 1963 and 2007, were retained for data analysis.

Of the 99 included trials, 70 (71%) took place in Europe, 12 (12%) in North America (including one performed in both the United States and the United Kingdom), 15 (15%) in Asia, one (1%) in Africa, and one (1%) in Australia. Seventy-seven (78%) of the trials were published in the English language. Eighty-two (83%) of the trials took place at a single center; the multicenter trials involved between two and 60 sites.

A total of 5363 participants were enrolled and analyzed in the 99 trials. The median (25%, 75% quartiles) and mean (standard deviation) number of participants per study were 42 (32, 61) and 53 (37) respectively (range 15 to 287). Study sizes were skewed toward smaller trials: 91 (92%) enrolled 100 or fewer participants, and 56 (57%) enrolled 50 or fewer participants. None of the studies reported pretrial sample size estimation, although one trial did plan to enrol a certain number of participants based on an outcome other than epithelial healing (HEDS Group 1997).

Of the 39 trials that provided average age of enrolled participants, the median was 46 years. Of the 46 trials reporting the gender of enrolled participants, the mean male-female ratio was 2.0 and the median male-female ratio was 1.8.

Sixty-one trials were limited to dendritic epithelial keratitis; 34 trials enrolled participants with either dendritic or geographic epithelial keratitis; two trials were restricted to geographic keratitis; and two trials provided insufficient information to classify participant groups. Use of a cycloplegic agent was reported in 41 trials (atropine in 19, scopolamine in six, homatropine in five, and a nonspecified mydriatic or cycloplegic agent in 11). Nine trials reported using a concomitant topical antibiotic.

Endpoint
Outcome evaluation was judged by direct observation of the corneal surface in all trials. Fifty-eight trials used fluorescein as the primary method to assess corneal epithelial status; eight trials used rose-Bengal staining; and 11 trials used both fluorescein and rose-Bengal. Ten trials assessed epithelial healing without mentioning use of a stain. The method of outcome assessment was not specified in 12 trials.

The assessment of healing within the trials required subjective assessments by study investigators. Fluorescein or rose-Bengal staining determined the day of resolution of infection in most trials, although one group of investigators reported both the time to initial re-epithelialization and the day of re-establishment of a normal corneal surface. The day of healing in this review was determined by the time to initial re-epithelialization that resulted in no confluent staining.

Despite the large number of included trials, the variety of interventions resulted in relatively few trials for each treatment comparison. The largest number of trials in one comparison was 10 (included in the idoxuridine-placebo comparison). Other comparisons involved seven or fewer trials, and often only one trial for a given treatment comparison was available.

Methodological quality

Sixty-nine of the included studies specifically mentioned the use of a randomized allocation scheme. Methodological quality was graded A for 70 trials, B for 26 trials, and C for three trials. Attrition bias was uncommonly encountered as the primary endpoint occurred within two weeks of enrolment.

Results

Nucleoside antiviral versus placebo (Analysis 01)
Idoxuridine was statistically significantly better than placebo at seven days (odds ratio (OR) 4.05, 95% confidence interval (CI) 2.60 to 6.30) and at 14 days (OR 4.17, 95% CI 1.33 to 13.04). Vidarabine was better than placebo at 14 days (OR 5.40, 95% CI 1.42 to 20.52) but not at seven days.

Nucleoside antiviral versus another nucleoside antiviral (Analysis 02)
Trifluridine was statistically significantly better than idoxuridine at seven days (OR 4.77, 95% CI 2.66 to 8.58) and at 14 days (OR 4.26, 95% CI 2.20 to 8.23). Acyclovir was better than idoxuridine at seven days (OR 4.69, 95% CI 3.13 to 7.02) and at 14 days (OR 4.18, 95% CI 2.48 to 7.03). Bromovinyldeoxyuridine was significantly better than idoxuridine. Vidarabine was equivalent to idoxuridine at seven days (OR 1.24, 95% CI 0.72 to 2.00) and at 14 days (OR 1.24, 95% CI 0.65 to 2.37). Older agents, such as fluorophenylalanine, had minimal effect compared to idoxuridine.

Trifluridine and acyclovir appeared equivalent to one another at seven days and 14 days. Trifluridine was not statistically significantly better than vidarabine when all groups of participants were considered, but one study found that trifluridine was statistically significantly better than vidarabine at 14 days in the subgroup of people with geographic epithelial keratitis. Acyclovir was not better than vidarabine in any group. Ganciclovir gel appeared equivalent to acyclovir ointment. Other topical antiviral agents including bromovinyldeoxyuridine, iododeoxycytidine, foscarnet and cidofovir appeared equivalent in clinical antiviral effectiveness to trifluridine or to acyclovir, but few trials evaluated these comparisons and those that did were small.

Oral versus topical nucleoside antiviral (Analysis 03)
Oral acyclovir was equivalent to topical antiviral therapy in a single trial.

Combined nucleoside antivirals versus single nucleoside antiviral (Analysis 04.01 and 04.02)
The combination of oral acyclovir and topical trifluridine was similar in effect to topical trifluridine alone. The combination of topical acyclovir and vidarabine was similar to acyclovir alone.

Supplemental agents combined with nucleoside antiviral (Analysis 04.03 and 04.04)
Neither epidermal growth factor nor a nonsteroidal antiinflammatory agent (oxyphenbutazone) added significantly to an antiviral agent's effect on corneal epithelial healing.

Physicochemical methods (Analysis 05, 06 and 07)
Physicochemical debridement was not statistically better than no treatment. Debridement appeared similar to topical antiviral therapy; however, recrudescent epithelial keratitis occurred in some debridement-treated eyes and limited the use of this intervention by itself. One trial found a significant benefit from debridement compared to antiviral therapy, but this finding appeared to be an outlier. Different methods of debriding the corneal epithelium produced similar rates of subsequent re-epithelialization.

Combined physicochemical method and nucleoside antiviral (Analysis 08, 09 and 10)
The combination of physicochemical treatment with an antiviral agent was statistically significantly better than physicochemical treatment alone at seven days (OR 2.08, 95% CI 1.17 to 3.71) and at 14 days (OR 10.81, 95% CI 1.81 to 64.50). Combined treatment was also better than antiviral treatment alone at seven days (OR 2.01, 95% CI 1.21 to 3.34) but not at 14 days. The heterogeneous cauterization and curettage techniques and the various treatment combinations limited valid quantitative summary effect measures. One trial comparing acyclovir with debridement to idoxuridine with debridement showed no statistically significant difference in the proportion of participants healed at seven or 14 days.

Interferon versus placebo (Analysis 11)
Topical interferons were better than placebo at seven days (OR 2.09, 95% CI 1.15 to 3.81) and at 14 days (OR 3.43, 95% CI 1.30 to 9.02).

Interferon versus another interferon (Analysis 12, 13, 14 and 15)
Low interferon concentrations (less than 1 million units per millilitre) were slightly less effective than higher concentrations though this was not statistically significant. Leukocyte-derived interferon (alpha-interferon), fibroblast-derived interferon (beta-interferon), and gamma-interferon were equivalent at similar concentrations but few trials compared these products. Recombinant interferon was similar to naturally derived interferon.

Interferon versus nucleoside antiviral (16 and 17)
No difference was found between topical interferon and topical antiviral agents at seven days (OR 1.18, 95% CI 0.29 to 4.75) but the difference was statistically significant at 14 days (OR 3.48, 95% CI 1.06 to 11.40). Only one study compared a topical interferon inducer with a topical antiviral agent and found no difference at seven days but showed the topical antiviral to be better at 14 days (OR 0.11, 95% CI 0.01 to 0.84).

Combined interferon and nucleoside antiviral versus nucleoside antiviral (Analysis18)
The combination of interferon and an antiviral agent was significantly better than a single antiviral agent (usually trifluridine) at seven days (OR 13.31, 95% CI 7.41 to 23.89) but not at 14 days. The higher concentrations of interferon in the interferon-trifluridine trials seemed more effective than lower concentrations but none of these trials found statistically significant differences in outcome.

Immune modulator versus placebo
Oral isoprinosine was not statistically significantly different than placebo at seven or 14 days in one trial; however, few participants were studied.

Discussion

Nucleoside antiviral therapy
Idoxuridine appeared significantly better than placebo. Variable formulations and dosages of idoxuridine were likely to have contributed to heterogeneity among the placebo-controlled trials.

Antiviral agents have not been adequately compared to the physicochemical methods used in the preantiviral era. The use of antiviral therapy following minimal debridement prevents recrudescent epithelial keratitis during the subsequent two weeks but any healing advantage of combined physical and antiviral treatment is uncertain (Wilhelmus 1989).

Most clinical trials of the antiviral treatment of herpes simplex virus (HSV) epithelial keratitis compared different antiviral agents but no single treatment was used as a standard referent. Compared to idoxuridine, the topical application of vidarabine, trifluridine, acyclovir or ganciclovir generally resulted in a significantly greater proportion of participants healing within one week of treatment. Among these four antiviral agents no treatment emerged as significantly better for the therapy of dendritic epithelial keratitis.

Sufficient data were not available to adequately assess topical bromovinyldeoxyuridine or oral acyclovir although these agents appeared equivalent to topical trifluridine or topical acyclovir. The addition of an adjunctive agent such as topical vidarabine or oral acyclovir to topical antiviral therapy did not significantly improve epithelial healing. Short-term, therapeutic use of a topical or oral antiviral agent did not reduce the risk of recurrent epithelial or stromal keratitis following treatment of dendritic epithelial keratitis (HEDS Group 1997; Wilhelmus 1981a).

Physicochemical therapy
For convenience and power, all physical and chemical methods were assumed to be equivalent and were grouped together. Differences among these methods, however, could limit their comparability and result in discordant combinations. For example, the extent of physicochemical de-epithelialization varied from wiping loosened, infected epithelial cells by minimal debridement to thermomechanical or cryomechanical curettage and chemical cauterization that ablated a large zone of epithelium surrounding the dendrite. Minimal wiping debridement without antiviral co-treatment was often followed by recrudescent epithelial keratitis while more aggressive physicochemical methods apparently removed all infected epithelial cells. An unproved benefit of debridement was a reduced risk of subsequent HSV stromal keratitis (Maudgal 1979; Wilhelmus 1981b). Reported shortcomings of physicochemical debridement were the time and effort needed for the procedure, the risk of damaging Bowman's layer, the enhancement of corneal inflammation or scarring, and the occurrence of recrudescent epithelial keratitis if additional antiviral therapy was not provided (Coster 1977b).

Interferon therapy
This overview demonstrated that interferon monotherapy had a slight beneficial effect on dendritic epithelial keratitis but was not better than other antiviral agents. Topical interferon was useful with debridement. A compelling observation was the significantly improved treatment success produced by a combination of a topical interferon with a topical nucleoside antiviral agent such as trifluridine or acyclovir. Previous literature surveys have also noted the apparent benefit of interferon-antiviral treatment (Cantell 1995; Sundmacher 1982; Sundmacher 1984b). Combined interferon-nucleoside therapy may emerge as an improvement over currently available treatment for HSV epithelial keratitis.

Geographic epithelial keratitis
Several studies noted that larger epithelial lesions healed more slowly. The treatment of geographic epithelial keratitis, therefore, might present a more challenging way to evaluate antiviral therapy. Geographic epithelial keratitis is less common than dendritic keratitis, accounting for only five per cent of HSV epithelial keratitis in a population-based study (Liesegang 1989a) and six per cent of participants in this meta-analysis. Only two trials were restricted to geographic epithelial keratitis (Collum 1985; Coster 1979). Even when these data were combined with stratified treatment results for the subcategory of geographic epithelial disease reported by other studies the optimal therapy of geographic epithelial keratitis could not be determined from the available evidence.

Prognostic factors
There were insufficient numbers of trials for each treatment comparison to productively undertake meta-regression. Except for lesion size, the effects of prognostic variables on re-epithelialization time were derived from retrospective subgroup analyses. The following were reported in individual studies to prolong the healing time of HSV epithelial keratitis: larger size of the epithelial defect, longer duration of symptoms, peripheral corneal location, presence of stromal inflammation and viral resistance. The roles of these and other possible prognostic factors in corneal epithelial healing remain to be evaluated from a priori hypotheses. The prognostic importance of suspected risk factors should be considered in the design and analysis of future trials of HSV epithelial keratitis when developing eligibility criteria, planning baseline measurements and performing stratified comparisons.

Limitations
Randomization reduced selection bias within most trials but the method of treatment allocation was unclear in some studies. The methodological quality varied among the trials but gradually improved over time. Sensitivity analyses showed minimal changes in summary effect measures when studies with a moderate or high risk of bias were excluded.

Information bias was addressed by using a standard format to abstract information from journal articles and other sources and by applying a uniform outcome measure for all studies. Extrapolations were necessary since many studies provided healing curves without corresponding lifetables. Furthermore, studies that reported mean but not median healing times were not usable for this review if sufficient data were not included.

Heterogeneity limited pooling of selected treatment comparisons. A lack of homogeneity was noted among trials comparing idoxuridine and placebo, idoxuridine and acyclovir, vidarabine and acyclovir, physicochemical-antiviral combinations, and interferon and placebo. The variable treatment dosages and formulations and the inconsistent use of cycloplegic and other adjunctive agents could affect the summary measures of treatment effect.

The large number of participants, exceeding 5,000 individuals, who were enrolled in these comparative clinical trials enhanced external validity, although several treatment comparisons involved relatively few participants. Few trials had eligibility criteria that might limit generalizability. Men outnumbered women, perhaps because males are more likely to be treated for HSV epithelial keratitis (Gundersen 1936; HEDS Group 1997; Wilhelmus 1981b) but it is also possible that females may have been selectively excluded from trials of antiviral chemotherapy.

All of the trials focused on the time until complete corneal healing during the first few weeks of acute therapy. Insufficient trials evaluated long-term outcomes to enable a systematic review of treatment comparisons, although the largest trial (HEDS Group 1997) and a cohort study (Wilhelmus 1981b) found no benefit of acute therapy on subsequent recurrences. Cost and toxicity are important considerations in determining optimal therapy. Unfortunately, these issues were addressed in too few trials to enable treatment comparisons.

Interpretation
This systematic review aimed to provide a critical, quantitative overview of previous clinical research and to yield, where possible, summary effect measures with increased statistical power by combining multiple small clinical trials.

Most studies were too small to confirm either significant differences or equivalence between treatments. Trials of HSV dendritic epithelial keratitis showing no significant difference between treatments were often inconclusive because of inadequate sample size. A minority of trials in this meta-analysis achieved adequate statistical power, but none provided pretrial estimates of sample size based on anticipated epithelial healing times. Since the pooled data from published trials suggest that nearly 90% of treated eyes heal within two weeks, subsequent trials comparing nearly equivalent treatments should plan to enrol large numbers of participants.

Besides treatment, other clinical factors were likely to have affected epithelial healing during HSV infection. Most reports, however, did not provide outcome information for different categories of participants. Prognostic factors that were reported to modify the rate of corneal epithelial healing during antiviral therapy of HSV epithelial keratitis included the size, duration and location of the epithelial lesion, the presence of stromal inflammation and the susceptibility of the viral strains. Whether these or other factors such as diabetes (Kaiserman 2005) or atopy (Rezende 2006) modify relative treatment response has not been determined.

Reviewers' conclusions

Implications for practice

Based on this systematic review, both currently available and investigational antiviral agents are effective and nearly equivalent. The combination of an antiviral nucleoside with either debridement or interferon speeds healing. A nucleoside-interferon preparation may emerge as an alternative treatment for clinically resistant cases.

Implications for research

This review suggests guidelines for how to plan and to report clinical studies on the therapy of dendritic or geographic epithelial keratitis. Since no single antiviral agent is clearly superior with regard to corneal epithelial healing, the choice of an appropriate comparison for evaluating new agents depends on other factors. Reported trials should provide cumulative healing curves or lifetables to enable between-study comparisons. Secondary endpoints, other than resolution of epithelial keratitis, that could be considered are early recrudescence of HSV epithelial keratitis, later occurrence or recurrence of HSV epithelial keratitis or stromal keratitis, extent of residual subepithelial opacification or corneal topographic changes, and visual acuity. Information on cost, adverse effects, and quality of life are needed. While there is insufficient evidence that any acute therapy alters the risk of subsequent recurrences, prolonged observation after re-epithelialization is needed to establish the natural history of herpetic eye disease.

Acknowledgements

The Cochrane Eyes and Vision Group editorial team developed and executed the electronic searches for this review and facilitated translations. This work was originally prepared in partial fulfillment of the requirements for membership in the American Ophthalmological Society.

Potential conflict of interest

None known.

Notes

Tables

Characteristics of included studies

Study	Abe 1987
Methods	Allocation method: not givenMasking: single (partial)Number of centers: one
Participants	Country: JapanNumber enrolled: 27Average age (range): 35 (2-77)Sex: 17 males, 10 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=9): idoxuridineTreatment two (n=18): acyclovir ointment

Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: JapaneseStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Altinisik 1987**
Methods	Allocation method: not givenMasking: singleNumber of centers: one
Participants	Country: TurkeyNumber enrolled: 19 (of 27)Average age (range): 38 (4-73)Sex: 16 males, 11 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=9): idoxuridine 0.5% ointment 5 times per dayTreatment two (n=10): acyclovir 3% ointment 5 times per day
Outcomes	Epithelial healing
Notes	Nonstudy interventions: atropineReport language: TurkishStudy date: 1985-1986Financial support: not given
Allocation concealment	B - Unclear
Study	**Austin 1974**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 41Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=16): iodinizationTreatment two (n=25): idoxuridine
Outcomes	'When no corneal staining remained'
Notes	Nonstudy interventions: mydriatic, antibiotic (iodinization group), padReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Bartholomew 1977**
Methods	Allocation method: randomizedMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 21Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=6): photodynamic inactivation(neutral red 1% solution x 2 then blue light for 15 minutes)Treatment two (n=7): carbolizationTreatment three (n=8): idoxuridine ointment 6 times per day
Outcomes	'When the ulcerated area no longer stained with fluorescein (scattered superficial punctate erosions were ignored)'
Notes	Nonstudy interventions: chloramphenicol ointment, corneal scrapingReport language: EnglishStudy date: not givenFinancial support: private foundation
Allocation concealment	A - Adequate
Study	**Behrens-Baumann 1992**

Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 20Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one: (n=10): trifluridine 1% solution 5 times per dayTreatment two (n=10): foscarnet 3% solution 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: scopolamineReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Blake 1977**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: IrelandNumber enrolled: 30Average age (range): 45 (7-75)Sex: 16 males, 14 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=13): idoxuridine ointment 0.5% 4 times dailyTreatment two (n=17): vidarabine ointment 3% 4 times daily
Outcomes	Not given
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Burns 1963**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: several (42 sites in entire study)
Participants	Country: USANumber enrolled: 38Average age (range): not givenSex: not givenInclusion criteria: acute epithelial keratitis
Interventions	Control (n=15): distilled water hourly day, 2-hourly nightTreatment one (n=23): idoxuridine solution hourly day, 2-hourly night
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: not givenReport language: EnglishStudy date: 1962-1963Financial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Carmassi 1993**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: ItalyNumber enrolled: 15Average age (range): 44 (25-71)Sex: 7 males, 8 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=5): acyclovir 3% ointment 5 times per dayTreatment two (n=5): interferon solution 8 times per day (total of 200,000 units)Treatment three (n=5): acyclovir 3% ointment 5 times per day and interferon solution 8 times per day

Outcomes	'Corneal reepithelialization and negativity of the fluorescein test'
Notes	Nonstudy interventions: noneReport language: ItalianStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Cellini 1994**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: ItalyNumber enrolled: 40Average age (range): 43 (19-70)Sex: 24 males, 16 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=20): acyclovir 3% ointment 4 times per dayTreatment two (n=20): acyclovir 3% ointment 4 times per day and murine epidermal growth factor 10 mg/ml 4 times per day
Outcomes	'Negativity of the fluorescein staining test'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Colin 1981**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: FranceNumber enrolled: 46Average age (range): 49 (8-84)Sex: 25 males, 21 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=21): idoxuridine 0.5% ointment 5 times per dayTreatment two (n=25): acyclovir 3% ointment 5 times per day
Outcomes	'The absence of epithelial ulceration after instillation of fluorescein'
Notes	Nonstudy interventions: atropineReport language: FrenchStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Colin 1983**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: FranceNumber enrolled: 45Average age (range): not givenSex: 36 males, 9 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=21): acyclovir 3% ointment 5 times per day and albumin once per dayTreatment two (n=24): acyclovir 3% ointment 5 times per day and human leukocyte interferon 30 million units/ml once per day
Outcomes	'The absence of fluorescein staining in the area of the previous corneal ulceration'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate

Study	Colin 1984
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: FranceNumber enrolled: 32Average age (range): 48 (7-79)Sex: 20 males, 12 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=17): iododeoxycytidine 1% ointment 5 times per dayTreatment two (n=15): acyclovir 3% ointment 5 times per day
Outcomes	'The absence of epithelial ulceration after the instillation of fluorescein, using the biomicroscope'
Notes	Nonstudy interventions: atropineReport language: FrenchStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Colin 1987**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: FranceNumber enrolled: 32Average age (range): 49 (8-77)Sex: 19 males,23 femalesInclusion criteria: dendritic or geographical epithelial keratitis
Interventions	Treatment one (N=16): acyclovir 3% ointment 4 times per day and placebo ointment 3 times per day Treatment two (n=16): acyclovir 3% ointment 4 times per day and vidarabine 3% ointment 3 time per day
Outcomes	'The absence of fluorescein staining in the area of previous corneal ulceration'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: governmental agency
Allocation concealment	A - Adequate
Study	**Colin 1997a**
Methods	Allocation method: randomizedMasking: noneNumber of centers: three
Participants	Country: Mali and TunisiaNumber enrolled: 67Average age (range): 41Sex: 37 males, 30 femalesInclusion criteria: dendritic (51) or geographic (16) epithelial keratitis
Interventions	Treatment one (n=22): acyclovir 3% ointment 5 times per dayTreatment two (n=23): ganciclovir 0.15% gel 5 times per dayTreatment three (n=22): ganciclovir 0.05% gel 5 times per day
Outcomes	'Absence of fluorescein staining at ulcer site'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: 1990-1992Financial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Colin 1997b**
Methods	Allocation method: randomizedMasking: noneNumber of centers: four
Participants	Country: France, Switzerland, and United KingdomNumber enrolled: 37Average age (range): 48Sex: 26 males, 11 femalesInclusion criteria: dendritic (36) or geographic (1) epithelial keratitis

Interventions	Treatment one (n=18): acyclovir 3% ointment 5 times per dayTreatment two (n=19): ganciclovir 0.15% gel 5 times per day
Outcomes	'Absence of fluorescein staining at ulcer site'
Notes	Nonstudy interventions: noneReport language; EnglishStudy date: 1990-1992Financial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Colin 2007a**
Methods	Allocation method: randomizedMasking: noneNumber of centers: multiple
Participants	Country: PakistanNumber enrolled: 109Average age (range): not givenSex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=38): acyclovir 3% ointment 5 times per dayTreatment two (n=36): ganciclovir 0.15% gel 5 times per dayTreatment three (n=35): ganciclovir 0.05% gel 5 times per day
Outcomes	'Lack of fluorescein staining'
Notes	Nonstudy interventions: noneReport language; EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Colin 2007b**
Methods	Allocation method: randomizedMasking: noneNumber of centers: 28
Participants	Country: 28 European centersNumber enrolled: 164Average age (range): 45Sex: not givenInclusion criteria: dendritic (138) or geographic (26) epithelial keratitis
Interventions	Treatment one (n=80): acyclovir 3% ointment 5 times per day (n=67 dendrites)Treatment two (n=84): ganciclovir 0.15% gel 5 times per day (n=71 dendrites)
Outcomes	'When there was no fluorescein uptake'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: 1992-1994Financial support: not given
Allocation concealment	A - Adequate
Study	**Collum 1980**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: IrelandNumber enrolled: 60Average age (range): 41 (4-79)Sex: 44 males, 16 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=30): idoxuridine 0.5% ointment 5 times per dayTreatment two (n=30): acyclovir 3% ointment 5 times per day
Outcomes	'No fluorescein uptake'
Notes	Nonstudy interventions: homatropine, padReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry

Allocation concealment	A - Adequate
Study	**Collum 1985**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: two
Participants	Country: Ireland and UKNumber enrolled: 51Average age (range): 55 (range not given)Sex: 29 males, 22 femalesInclusion criteria: geographic epithelial keratitis
Interventions	Treatment one (n=26): vidarabine 3% ointment 5 times per dayTreatment two (n=25): acyclovir 3% ointment 5 times per day
Outcomes	'No further staining of the ulcer area'
Notes	Nonstudy interventions: pad "as appropriate"Report language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Collum 1986**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: IrelandNumber enrolled: 56Average age (range): 47 (range not given)Sex: 45 males, 11 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=29): acyclovir 3% ointment 5 times per day and oral placebo 5 times per dayTreatment two (n=27): placebo ointment 5 times per day and oral acyclovir 400 mg 5 times per day
Outcomes	'When there was no further staining with fluorescein, though slight irregularity or cystic change in the epithelium might still exist'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Coster 1976**
Methods	Allocation method: randomizedMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 102Average age (range): not givenSex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=48): vidarabine 3.3% ointment 5 times per dayTreatment two (n=54): trifluridine 1% solution 5 times per day
Outcomes	'Absence of staining with fluorescein'
Notes	Nonstudy interventions: atropineReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Coster 1977a**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: UKNumber enrolled: 78Average age (range): not givenSex: not

	givenInclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=22): minimal wiping debridement and placebo solution once per dayTreatment one (n=26): minimal wiping debridement and human leukocyte interferon 11 million units/ml once per dayTreatment two (n=30): minimal wiping debridement and human leukocyte interferon 33 million units/ml once per day
Outcomes	Not given
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Coster 1979**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: UKNumber enrolled: 30Average age (range): not givenSex: not givenInclusion criteria: geographic epithelial keratitis
Interventions	Treatment one (n=17): vidarabine 3.3% ointment 5 times per dayTreatment two (n=13): trifluridine 1% solution 5 times per day
Outcomes	'The absence of staining with fluorescein'
Notes	Nonstudy interventions: atropineReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Coster 1980**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: UKNumber enrolled: 59Average age (range): not givenSex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=30): idoxuridine 1% ointment 5 times per dayTreatment two (n=29): acyclovir 3% ointment 5 times per day
Outcomes	'No epithelial defect was demonstrable with rose-Bengal and fluorescein staining'
Notes	Nonstudy interventions: atropineReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Daniel 1972**
Methods	Allocation method: alternate patientsMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 54Average age (range): not givenSex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=25): idoxuridine ointment 5 times per dayTreatment two (n=29): idoxuridine ointment 5 times per day and ultraviolet (2536A) light for 2-4 minutes once or twice
Outcomes	Fluorescein and rose-Bengal staining

Notes	Nonstudy interventions: mydriatic, padReport language: EnglishStudy date: 1970-1971Financial support: not given
Allocation concealment	C - Inadequate
Study	**Davidson 1964**
Methods	Allocation method: randomized with tableMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 75Average age (range): not givenSex: not givenInclusion criteria: not given
Interventions	Control (n=25): gamma globulin 1% solution hourly during day, 2-hourly during nightTreatment one (n=25): debridement (with orange stick) and iodinization (with alcohol solution of iodine and potassium iodide on soaked cotton wool)Treatment two (n=25): idoxuridine 0.1% solution hourly during day, 2-hourly during night
Outcomes	'The absence of staining with two per cent fluorescein'
Notes	Nonstudy interventions: pad, atropine (debridement group), chloramphenicol ointment (debridement group)Report language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**De Koning 1982**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: NetherlandsNumber enrolled: 53Average age (range): not givenSex: 33 males, 20 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=28): trifluridine 1% solution 5 times per day and albumin solutionTreatment two (n=25): trifluridine 1% solution 5 times per day and human leukocyte interferon 10 million units/ml
Outcomes	'No staining with fluorescein' and 'closure of the epithelial wound without any epithelial edema or cystic change in the area of the previous dendrite'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**De Koning 1983**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: NetherlandsNumber enrolled: 51Average age (range): not givenSex: 30 males, 21 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=26): acyclovir 3% ointment 5 times per day and albumin solution every morningTreatment two (n=25): acyclovir 3% ointment 5 times per day and human leukocyte interferon 30 million units/ml every morning
Outcomes	'No staining with fluorescein' and 'absence of epithelial edema and cystic changes'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation	A - Adequate

concealment	
Study	**Denis 1983**
Methods	Allocation method: randomizedMasking: singleNumber of centers: one
Participants	Country: FranceNumber enrolled: 23Average age (range): not givenSex: not givenInclusion criteria: not given
Interventions	Treatment one (n=9): vidarabine 3% ointment 5 times per dayTreatment two (n=14): acyclovir 3% ointment 5 times per day
Outcomes	Not given
Notes	Nonstudy interventions: mydriatic, antibiotic (rarely)Report language: FrenchStudy date: 1980-1981Financial support: not given
Allocation concealment	A - Adequate
Study	**Fulhorst 1972**
Methods	Allocation method: randomizedMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 90Average age (range): not givenSex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=26): idoxuridine ointment 5 times per dayTreatment two (n=18): cryotherapy (multiple applications at -70° to -80° C) and idoxuridine ointment 5 times per dayTreatment three (n=18): cryotherapy (multiple applications at -70° to -80° C) and idoxuridine ointment 5 times per day and placebo 5 times per dayTreatment four (n=13): carbolization (debridement with orange stick followed by touching epithelial edge with phenol) and idoxuridine ointment 5 times per dayTreatment five (n=15): carbolization (debridement with orange stick followed by touching epithelial edge with phenol) and placebo ointment 5 times per day
Outcomes	'When the lesion no longer stained with rose-Bengal'
Notes	Nonstudy interventions: scopolamine, chloramphenicol ointment, patching for 48 hoursReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Genee 1987**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 28Average age (range): not givenSex: 21 males, 7 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=14): acyclovir 3% ointment 5 times per dayTreatment two (n=14): vidarabine 3% ointment 5 times per day
Outcomes	Epithelial healing
Notes	Nonstudy interventions: noneReport language: GermanStudy date: 1981-1984Financial support: not given
Allocation concealment	A - Adequate
Study	**Graupner 1966**

Methods	Allocation method: not givenMasking: double (partial)Number of centers: one
Participants	Country: GermanyNumber enrolled: 32Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=12): idoxuridine 0.1% solution every 2 hoursTreatment two (n=20): para-fluorophenylalanine 0.1% solution every 2 hours
Outcomes	Epithelial healing
Notes	Nonstudy interventions: atropineReport language: GermanStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Graupner 1968**
Methods	Allocation method: not givenMasking: singleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 53Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=27): idoxuridine 0.1% ointment 5 times per dayTreatment two (n=26): para-fluorophenylalanine 0.1% ointment 5 times per day
Outcomes	Epithelial healing
Notes	Nonstudy interventions: atropineReport language: GermanStudy date: note givenFinancial support: pharmaceutical industry
Allocation concealment	B - Unclear
Study	**Graupner 1969**
Methods	Allocation methods: not givenMasking: singleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 33Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=18): iodinization /debridement plus idoxuridine 0.1% ointment every 4 hoursTreatment two (n=15): iodinization /debridement plus para-fluorophenylalanine 0.1% ointment every 4 hours
Outcomes	Epithelial healing
Notes	Nonstudy interventions: atropineReport language: GermanStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Guerra 1979**
Methods	Allocation method: randomized by tableMasking: singleNumber of centers: one
Participants	Country: ItalyNumber enrolled: 20Average age (range): 46 (9-76)Sex: 13 males, 7 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=10): poly IC 1000 ug/ml hourlyTreatment two (n=10): idoxuridine 0.2% solution hourly
Outcomes	Not given

Notes	Nonstudy interventions: atropineReport language: ItalianStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**HEDS Group 1997**
Methods	Allocation method: randomized by permuted blocksMasking: doubleNumber of centers: 60
Participants	Country: USANumber enrolled: 287Average age (range): 48 (range not given)Sex: 179 males, 108 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=134): trifluridine 1% solution 8 times per day and oral placebo 5 times per dayTreatment two (n=153): trifluridine 1% solution 8 times per day and oral acyclovir 400 mg 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: 1992-1995Financial support: governmental agency
Allocation concealment	A - Adequate
Study	**Hart 1965**
Methods	Allocation method: randomized by tableMasking: doubleNumber of centers: one
Participants	Country: AustraliaNumber enrolled: 32Average age (range): 48 (14-80)Sex: only given for healed patients (20 males, 6 females)Inclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=13): neomycin 0.3% solution hourly day, 2-hourly nightTreatment one (n=19): idoxuridine 0.1% solution hourly day, 2-hourly night
Outcomes	'The absence of discrete fluorescein staining of the corner'
Notes	Nonstudy interventions: mydriatic, padReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Haut 1983**
Methods	Allocation method: not givenMasking: doubleNumber of centers: one
Participants	Country: FranceNumber enrolled: 26Average age (range): not givenSex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Control (n=12): oral placeboTreatment one (n=14): oral isoprinosine 500 mg 6 times per day
Outcomes	Not given
Notes	Nonstudy interventions: atropine, antibioticReport language: FrenchStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Hoang-Xuan 1984**

Methods	Allocation method: randomizedMasking: noneNumber of centers: one
Participants	Country: FranceNumber enrolled: 29Average age (range): not givenSex: only given for total group with herpetic keratitis (28 males, 9 females)Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=11): trifluridine 1% solution 6 times per dayTreatment two (n=18): acyclovir 3% ointment 5 times per day
Outcomes	'No fluorescein staining'
Notes	Nonstudy interventions: cycloplegic, antibiotic, timololReport language: FrenchStudy date: 1980-1982Financial support: not given
Allocation concealment	A - Adequate
Study	**Hung 1984**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: UKNumber enrolled: 29Average age (range): 56 (range not given)Sex: 23 males, 6 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=14): minimal wiping debridement and oral placebo 5 times per dayTreatment two (n=15): minimal wiping debridement and oral acyclovir 400 mg 5 times per day
Outcomes	'Ulcer stained with rose-Bengal to assess healing'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Høvding 1989**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: NorwayNumber enrolled: 50Average age (range): 46 (range not given)Sex: 27 males, 23 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=25): trifluridine 2% ointment 5 times per dayTreatment two (n=25): acyclovir 3% ointment 5 times per day
Outcomes	'Disappearance of epithelial ulceration(s) staining with fluorescein'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Jackson 1984**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: three
Participants	Country: CanadaNumber enrolled: 66Average age (range): 45 (12-80)Sex: 39 males, 27 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=34): vidarabine 3% ointment 5 times per dayTreatment two (n=32): acyclovir 3% ointment 5 times per day

Outcomes	Not given
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Jensen 1982**
Methods	Allocation method: randomizedMasking: noneNumber of centers: one
Participants	Country: DenmarkNumber enrolled: 43Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=20): acyclovir 3% ointment 6 times per dayTreatment two (n=23): acyclovir 3% ointment 6 times per day and debridement
Outcomes	'No epithelial defect was demonstrated after staining'
Notes	Nonstudy interventions: cycloplegic, chloramphenicol ointmentReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Jepson 1964**
Methods	Allocation method: not givenMasking: doubleNumber of centers: one
Participants	Country: USANumber enrolled: 24Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=12): distilled water with thimerosal hourly day, 2-hourly nightTreatment one (n=12): idoxuridine 0.1% solution hourly day, 2-hourly night
Outcomes	'Absence of fluorescein staining pattern'
Notes	Nonstudy interventions: scopolamineReport language: EnglishStudy date: 1962-1963Financial support: not given
Allocation concealment	B - Unclear
Study	**Kato 1979**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: JapanNumber enrolled: 27Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=10): minimal wiping debridementTreatment two (n=17): idoxuridine
Outcomes	'Fluorescein staining'
Notes	Nonstudy interventions: pad (debridement group)Report language: JapaneseStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Kitano 1983**
Methods	Allocation method: randomizedMasking: single (partial)Number of centers: 21

Participants	Country: JapanNumber enrolled: 55Average age (range): not givenSex: 34 males, 21 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=25): idoxuridine every 1 or 2 hoursTreatment two (n=30): interferon-beta 20,000 IU/ml 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: JapaneseStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Kitano 1985**
Methods	Allocation method: randomizedMasking: double
Participants	Country: JapanNumber enrolled: 109 (excluding 5 withdrawals)Average age (range): not givenSex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n = 55, excluding 3 drop outs): idoxuridine 0.25% ointment 5 times per dayTreatment two: (n=54, excluding 2 drop outs): acyclovir 3% ointment 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: JapaneseStudy date: August 1981 - May 1982Financial support: not given
Allocation concealment	A - Adequate
Study	**Klauber 1982**
Methods	Allocation method: not givenMasking: doubleNumber of centers: one
Participants	Country: DenmarkNumber enrolled: 38Average age (range): 51 (range not given)Sex: 25 males, 13 femalesInclusion criteria: epithelial keratitis without or with stromal keratitis
Interventions	Treatment one (n=20): idoxuridine 0.5% ointment 5 times per dayTreatment 2 (n=18): acyclovir 3% ointment 5 times per day
Outcomes	'Fluorescein and rose-Bengal staining'
Notes	Nonstudy interventions: scopolamineReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Kumar 1987**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: IndiaNumber enrolled: 36Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=17): idoxuridine 0.5% ointment 5 times per dayTreatment two (n=19): acyclovir 3% ointment 5 times per day
Outcomes	'Fluorescein staining'

Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**La Lau 1982**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: four
Participants	Country: NetherlandsNumber enrolled: 59Average age (range): not givenSex: 34 males, 25 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=28): trifluridine 2% ointment 5 times per dayTreatment two (n=1): acyclovir 3% ointment 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Laibson 1964**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: USANumber enrolled: 100Average age (range): 45 (range not given)Sex: 72 males, 28 femalesInclusion criteria: dendritic or geographic epithelial keratitis, without or with stromal keratitis
Interventions	Control one (n=53): distilled water hourly day, 2-hourly nightTreatment one (n=47): idoxuridine 0.1% solution hourly day, 2-hourly night
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: 1962-1963Financial support: governmental agency
Allocation concealment	A - Adequate
Study	**Laibson 1977**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: USANumber enrolled: 33Average age (range): not givenSex: 25 males, 8 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=17): idoxuridine solution hourly day, 2-hourly nightTreatment two (n=16): trifluridine solution hourly day, 2-hourly night
Outcomes	Epithelial healing
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Luntz 1963**
Methods	Allocation method: alternate patientsMasking: noneNumber of centers: one

Participants	Country: UKNumber enrolled: 22Average age (range): 49 (20-83)Sex: 15 males, 7 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=11) neomycin 1% ointment 2 times dailyTreatment one (n=11): idoxuridine 0.1% solution hourly
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: atropine, pad, small scrapingReport language: EnglishStudy date: 1962Financial support: not given
Allocation concealment	C - Inadequate
Study	**MacKenzie 1964**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 80Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=27): carbolizationTreatment two (n=25): idoxuridine 0.1% solution hourly day, 2-hourly nightTreatment three (n=28): idoxuridine 0.5% ointment 4 times per day
Outcomes	'The disappearance of staining with 2 per cent fluorescein'
Notes	Nonstudy interventions: mydriaticReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Markham 1977**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: UKNumber enrolled: 64Average age (range): 51 (18-87)Sex: 44 males, 20 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Control (n=20): placebo ointment 4 times per dayTreatment one (n=21): idoxuridine 0.5% ointment 4 times per dayTreatment two (n=23): vidarabine 3% ointment 4 times per day
Outcomes	Rose-Bengal staining
Notes	Nonstudy interventions: homatropineReport language: EnglishStudy date: not givenFinancial support: governmental agency
Allocation concealment	A - Adequate
Study	**Matthaus 1970**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: GermanyNumber enrolled: 120Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=33): iodinization plus panthenol ointmentTreatment two (n=27): iodinization plus para-fluorophenylalanine 0.1% ointmentTreatment three (n=26): cryotherapy plus panthenol ointmentTreatment 4 (n=34): cryotherapy plus para-fluorophenylalanine 0.1% ointment

Outcomes	Not given
Notes	Nonstudy interventions: atropineReport language: GermanStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Maychuk 1988**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: RussiaNumber enrolled: 138Average age (range): not givenSex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=63): idoxuridine 0.1% solutionTreatment two (n=39): acyclovir 3% ointmentTreatment three (n=36): acyclovir 3% ointment and leukocyte interferon 10,000 u/ml
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: RussianStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**McCulley 1982**
Methods	Allocation method: randomized by tableMasking: doubleNumber of centers: five
Participants	Country: USANumber enrolled: 64Average age (range): 46 (15-80)Sex: 43 males, 21 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=34): idoxuridine 0.5% ointment 5 times per dayTreatment two (n=30): acyclovir 3% ointment 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**McGill 1974**
Methods	Allocation method: randomizedMasking: singleNumber of centers: one
Participants	Country: UKNumber enrolled: 20Average age (range): 48 (21-79)Sex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=9): trifluridine 1% aqueous solution 5 times per dayTreatment two (n=11): trifluridine 1% viscous solution 5 times per day
Outcomes	Not given
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Meurs 1985**

Methods	Allocation method: not givenMasking: doubleNumber of centers: one
Participants	Country: NetherlandsNumber enrolled: 93Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=45): acyclovir ointment 5 times per day and albumin solution every morningTreatment two (n=24): acyclovir ointment 5 times per day and recombinant human alpha-2 interferon 30 million units/ml every morningTreatment three (n=24): acyclovir ointment 5 times per day and recombinant human alpha-2 interferon rod every morning
Outcomes	Partial healing (closure of epithelial wound) and complete healing (no edematous or cystic changes in epithelium)
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Norn 1973**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: DenmarkNumber enrolled: 29Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=14): idoxuridine 1% solution hourly and idoxuridine 2% ointment at bedtime and placebo ointment 6 times per dayTreatment two (n=15): idoxuridine 1% solution hourly and idoxuridine 2% ointment at bedtime and oxyphenbutazone 10% ointment 6 times per day
Outcomes	Fluorescein and rose-Bengal staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: 1990-1993Financial support: not given
Allocation concealment	A - Adequate
Study	**O'Day 1975**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 17Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=9): idoxuridine 0.5 % ointment 5 times per dayTreatment two (n=8): proflavine hemisulphate 0.1% solution with fluorescent light exposure daily for 3 or more days
Outcomes	Rose-Bengal staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Panda 1995**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: IndiaNumber enrolled: 80Average age (range): not givenSex: not

	givenInclusion criteria: dendritic epithelial keratitis (first episode)
Interventions	Treatment one (n=20): idoxuridine 1% ointment 5 times per dayTreatment two (n=20): trifluridine 2% ointment 5 times per dayTreatment three (n=20): acyclovir 3% ointment 5 times per dayTreatment four (n=20): bromovinyldeoxyuridine 1% ointment 5 times per day
Outcomes	"Fluorescein staining and reduced corneal sensitivity"
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: 1988-1993Financial support: not given
Allocation concealment	A - Adequate
Study	**Parlato 1985**
Methods	Allocation method: randomized by tableMasking: single (partial)Number of centers: one
Participants	Country: USANumber enrolled: 34Average age (range): 46 (15-80)Sex: 25 males, 9 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=8): minimal wiping debridementTreatment two (n=14): trifluridine 1% solution 9 times per dayTreatment three (n=12): minimal wiping debridement and trifluridine 1% solution 9 times per day (beginning on second day)
Outcomes	'The disappearance of dendritic staining, despite the occasional persistence of fine superficial punctate keratitis'
Notes	Nonstudy interventions: cycloplegic, patch (debridement group)Report language: EnglishStudy date: 1981-1984Financial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Patterson 1963a**
Methods	Allocation method: not givenMasking: doubleNumber of centers: one
Participants	Country: UKNumber enrolled: 23Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=13): 199 tissue-culture medium hourly day, 2-hourly nightTreatment one (n=10): idoxuridine 0.1% solution hourly day, 2-hourly night
Outcomes	Fluorescein and rose-Bengal staining
Notes	Nonstudy interventions: atropine, padReport language: EnglishStudy date: 1962Financial support: not given
Allocation concealment	B - Unclear
Study	**Patterson 1963b**
Methods	Allocation method: not givenMasking: doubleNumber of centers: one
Participants	Country: UKNumber enrolled: 32Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=15): placebo hourly day, 2-hourly nightTreatment one (n=17): idoxuridine 0.1% solution hourly day, 2-hourly night

Outcomes	Fluorescein and rose-Bengal staining
Notes	Nonstudy interventions: atropine, padReport language: EnglishStudy date: 1962Financial support: not given
Allocation concealment	B - Unclear
Study	**Patterson 1963c**
Methods	Allocation method: not givenMasking: doubleNumber of centers: one
Participants	Country: UKNumber enrolled: 30Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=14): placebo hourly day, 2-hourly nightTreatment one (n=16): idoxuridine 0.1% solution hourly day, 2-hourly night
Outcomes	Fluorescein and rose-Bengal staining
Notes	Nonstudy interventions: atropine, padReport language: EnglishStudy date: 1962Financial support: not given
Allocation concealment	B - Unclear
Study	**Patterson 1967a**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 77Average age (range): 33 (1-66)Sex: 54 males, 23 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Control (n=39): carbolizationTreatment one (n=38): idoxuridine ointment 5 times per day
Outcomes	Rose-Bengal staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Patterson 1967b**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 28Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis with disciform keratitis
Interventions	Control (n=11): carbolizationTreatment one (n=17): idoxuridine ointment 5 times per day
Outcomes	Rose-Bengal staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Pavan-Langston 1976**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: several

Participants	Country: United StatesNumber enrolled: 169Average age (range): 47 (2-85)Sex: 115 males, 54 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=82): idoxuridine ointment 5 times per dayTreatment two (n=87): vidarabine ointment 5 times per day
Outcomes	Epithelial healing
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Pavan-Langston 1981**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: two
Participants	Country: USANumber enrolled: 41Average age (range): not given (16-82)Sex: 23 males, 18 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=21): vidarabine 3% ointment 5 times per dayTreatment two (n=20): acyclovir 3% ointment 5 times per day
Outcomes	Epithelial healing
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry and governmental agency
Allocation concealment	A - Adequate
Study	**Power 1991**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: IrelandNumber enrolled: 60Average age (range): 45 (9-72)Sex: 43 males, 17 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=30): trifluridine 1% solution 5 times per dayTreatment two (n=30): bromovinyldeoxyuridine 0.1% solution 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Richter 1986**
Methods	Allocation method: randomizedMasking: noneNumber of centers: one
Participants	Country: GermanyNumber enrolled: 57Average age (range): not given (11-71)Sex: 34 males, 23 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=32): bromovinyldeoxyuridine solutionTreatment two (n=25): bromovinyldeoxyuridine solution and epithelial abrasion
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: cycloplegic, antibioticReport language: GermanStudy date: not givenFinancial support: not given

Allocation concealment	A - Adequate
Study	**Serifoglu 1987**
Methods	Allocation method: randomizedMasking: singleNumber of centers: one
Participants	Country: TurkeyNumber enrolled: 25Average age (range): 36 (4-78)Sex: 17 males, 8 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=12): minimal wiping debridement and idoxuridine 0.5% ointment 5 times per dayTreatment two (n=13): minimal wiping debridement and acyclovir 3% ointment 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: TurkishStudy date: 1985-1986Financial support: not given
Allocation concealment	A - Adequate
Study	**Srinivas 1993**
Methods	Allocation method: not statedMasking: noneNumber of centers: one
Participants	Country: IndiaNumber enrolled: 40Average age (range): not givenSex: 18 males, 14 females, 8 childrenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=20): idoxuridine solution 5 times per dayTreatment two (n=20): idoxuridine solution 5 times per day and oral acyclovir 200 mg 3 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: cycloplegicReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Struck 1989**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: GermanyNumber enrolled: 109Average age (range): not given (1-89)Inclusion criteria: dendritic epithelial keratitis without or with stromal keratitis
Interventions	Control (n=34): debridement, debridement with iodinisation, cryoapplication, or otherTreatment one (n=28): idoxuridane 0.1% solution 5 times per dayTreatment two (n=16): trifluridine 1% solution 5 times per dayTreatment three (n=31): bromovinyldeoxyuridine 0.1% solution
Outcomes	Fluorescein and rose-Bengal straining
Notes	Nonstudy interventions: noneReport language: GermanStudy date: 1981-1985Financial support: not given
Allocation concealment	C - Inadequate
Study	**Sugar 1980**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: six

Participants	Country: USANumber enrolled: 61Average age (range): 46 (range not given)Sex: 43 males, 18 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=27): idoxuridine 0.1% solution 19 times per dayTreatment two (n=34): trifluridine 1% solution 9 times per day
Outcomes	Not given
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Sundmacher 1976a**
Methods	Allocation method: randomizedMasking: single (partial)Number of centers: one
Participants	Country: GermanyNumber enrolled: 55Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=17): thermomechanical debridement and placebo solution 3 times per dayTreatment two (n=22): thermomechanical debridement and human leukocyte interferon 62,500 units/ml 3 times per dayTreatment three (n=16): human leukocyte interferon 62,500 units/ml 3 times per day
Outcomes	'Fluorescein-negative healing of the corneal epithelium, which was defined as complete closure of all erosions except for some single dye-positive micropunctuations'
Notes	Nonstudy interventions: scopolamine, lubricating ointment, padReport language: EnglishStudy date: not givenFinancial support: governmental agency
Allocation concealment	A - Adequate
Study	**Sundmacher 1976b**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 40Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=18): thermomechanical debridement and human albumin 2 times per dayTreatment two (n=22): thermomechanical debridement and human leukocyte interferon 3 million units/ml 2 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: homatropine, lubricating ointment, padReport language: EnglishStudy date: not givenFinancial support: governmental agency
Allocation concealment	A - Adequate
Study	**Sundmacher 1978a**
Methods	Allocation method: randomizedMasking: noneNumber of centers: one
Participants	Country: GermanyNumber enrolled: 42Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=18): thermomechanical debridement plus human leukocyte interferon 6 million units/ml once per dayTreatment two (n=24): minimal wiping debridement plus human leukocyte interferon 6 million units/ml once per day

Outcomes	Fluorescein staining
Notes	Nonstudy interventions: homatropineReport language: EnglishStudy date: not givenFinancial support: governmental agency
Allocation concealment	A - Adequate
Study	**Sundmacher 1978b**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 38Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=18): thermomechanical debridement plus human leukocyte interferon 1 million units/ml once per dayTreatment two (n=20): thermomechanical debridement plus human fibroblast interferon 1 million units/ml once per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: homatropineReport language: EnglishStudy date: not givenFinancial support: governmental agency
Allocation concealment	A - Adequate
Study	**Sundmacher 1981a**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 51Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=24): trifluridine 1% solution 5 times per day plus human leukocyte interferon 10 million units/ml once per dayTreatment two (n=27): trifluridine 1% solution 5 times per day plus human leukocyte interferon 30 million units/ml once per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Sundmacher 1981b**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 70Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=20): trifluridine 1% solution 5 times per day and albumin solution once per dayTreatment two (n=24): trifluridine 1% solution 5 times per day and human leukocyte interferon 1 million units/ml once per dayTreatment three (n=26): trifluridine 1% solution 5 times per day and human leukocyte interferon 30 million units/ml once per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given

Allocation concealment	A - Adequate
Study	**Sundmacher 1984**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 36Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=17): trifluridine 1% solution 5 times per day plus human leukocyte interferon 30 million units/ml once per dayTreatment two (n=19): trifluridine 1% solution 5 times per day plus human leukocyte interferon 100 million units/ml once daily
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Sundmacher 1985**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 32Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=17): trifluridine 1% solution 5 times per day plus human alpha-interferon 30 million units/ml once per dayTreatment two (n=15): trifluridine 1% solution 5 times per day plus recombinant alpha-2- interferon 23 million units/ml once per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Sundmacher 1987**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: GermanyNumber enrolled: 45Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=16): trifluridine 1% solution 5 times per day plus recombinant alpha-interferon 30 million units/ml once per dayTreatment two (n=14): trifluridine 1% solution 5 times per day plus recombinant gamma- interferon 30 million units/ml once per dayTreatment three (n=8): trifluridine 1% solution 5 times per day plus recombinant alpha- interferon 0.3 million units/ml once per day and gamma-interferon 0.3 million units/ml once per dayTreatment four (n=7): trifluridine 1% solution 5 times per day plus recombinant alpha- interferon 1.5 million units/ml once per day and gamma- interferon 1.5 million units/ml once per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given

Allocation concealment	A - Adequate
Study	**Travers 1978**
Methods	Allocation method: not givenMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 100Average age (range): 50 (range not given)Sex: 52 males, 48 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=50): vidarabine ointment 5 times per dayTreatment two (n=50): trifluridine solution 5 times per day
Outcomes	Rose-Bengal staining
Notes	Nonstudy interventions: mydriatic, antiglaucoma agents ("as necessary")Report language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Uchida 1981**
Methods	Allocation method: randomized by codeMasking: doubleNumber of centers: eight
Participants	Country: JapanNumber enrolled: 54Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=17): minimal wiping debridement and human albumin 4 times per dayTreatment one (n=17): minimal wiping debridement and idoxuridine solution hourly day, 2-hourly nightTreatment two (n=20): minimal wiping debridement and fibroblast interferon 1 million units/ml 4 times per day
Outcomes	'Disappearance of gross staining areas with fluorescein'
Notes	Nonstudy interventions: gentamicin solutionReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Uchida 1982**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: JapanNumber enrolled: 68 (5 others disqualified)Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=32): human fibroblast interferon 1000 units/ml 4 times per dayTreatment two (n=36): human fibroblast interferon 1 million units/ml 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: JapaneseStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Van Bijsterveld 1980**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one

Participants	Country: NetherlandsNumber enrolled: 56Average age (range): 46 (range not given)Sex: 36 males, 28 femalesInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=28): vidarabine 3% ointment 5 times per dayTreatment two (n=28): trifluridine 2% ointment 5 times per day
Outcomes	Fluorescein and rose-Bengal staining; 'no epithelial edema and cystic changes were present in the epithelium covering the site of the original ulcer'
Notes	Nonstudy interventions: scopolamineReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Van Bijsterveld 1989**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: NetherlandsNumber enrolled: 41Average age (range): 39 (7-81)Sex: 22 males, 19 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=22): bromovinyldeoxyuridine 1% ointment 5 times per day and albumin rod dailyTreatment two (n=19): bromovinyldeoxyuridine 1% ointment 5 times per day and recombinant alpha-2 interferon rod (1.5 million units) daily
Outcomes	'Wound closure'
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Vannini 1986**
Methods	Allocation method: randomizedMasking: singleNumber of centers: one
Participants	Country: ItalyNumber enrolled: 20Average age (range): 41 (18-76)Sex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=10): idoxuridine solution 7 times per dayTreatment two (n=10): beta-interferon 1 million units/ml 7 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate
Study	**Wellings 1972**
Methods	Allocation method: randomized by tableMasking: doubleNumber of centers: two
Participants	Country: UK and USANumber enrolled: 78Average age (range): not givenSex: not givenInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=38): idoxuridine 0.1% solution 5 times per dayTreatment two (n=40): trifluridine 1% solution 5 times per day
Outcomes	Fluorescein and rose-Bengal staining

Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: governmental agency
Allocation concealment	A - Adequate
Study	**Wilhelmus 1981a**
Methods	Allocation method: randomized by tableMasking: noneNumber of centers: one
Participants	Country: UKNumber enrolled: 50Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=25): minimal wiping debridement and acyclovir 3% ointment 5 times per dayTreatment two (n=25): acyclovir 3% ointment 5 times per day
Outcomes	'Disappearance of specific Bengal-rose staining of the precise site of the healing dendritic ulceration'
Notes	Nonstudy interventions: atropineReport language: EnglishStudy date: not givenFinancial support: private foundation
Allocation concealment	A - Adequate
Study	**Yamazaki 1984a**
Methods	Allocation method: not givenMasking: singleNumber of centers: one
Participants	Country: JapanNumber enrolled: 40Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=21): minimal wiping debridement and idoxuridine 0.1% solutionTreatment two (n=19): minimal wiping debridement and fibroblast interferon 20,000 units/ml
Outcomes	Not given
Notes	Nonstudy interventions: not givenReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Yamazaki 1984b**
Methods	Allocation method: not givenMasking: singleNumber of centers: one
Participants	Country: JapanNumber enrolled: 74Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=41): albumin solution 4 times per dayTreatment two (n=33): human leukocyte interferon 20 million units/ml 4 times per day
Outcomes	Not given
Notes	Nonstudy interventions: not givenReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Yamazaki 1984c**

Methods	Allocation method: not givenMasking: singleNumber of centers: one
Participants	Country: JapanNumber enrolled: 36Average age (range): not givenSex: not givenInclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=16): recombinant alpha-interferon 1000 units/ml 4 times per dayTreatment two (n=20): recombinant alpha-interferon 10 million units/ml 4 times per day
Outcomes	Not given
Notes	Nonstudy interventions: not givenReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	B - Unclear
Study	**Yeakley 1981**
Methods	Allocation method: randomized by codeMasking: doubleNumber of centers: one
Participants	Country: USANumber enrolled: 40Average age (range): 49 (7-81)Sex: 27 males, 13 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=21): vidarabine 3% ointment 5 times per dayTreatment two (n=19): acyclovir 3% ointment 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: noneReport language: EnglishStudy date: not givenFinancial support: not given
Allocation concealment	A - Adequate
Study	**Young 1982**
Methods	Allocation method: randomizedMasking: doubleNumber of centers: one
Participants	Country: UKNumber enrolled: 93Average age (range): 51 (range not given)Sex: 62 males, 31 femalesInclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=45): vidarabine 3% ointment 5 times per dayTreatment two (n=48): acyclovir 3% ointment 5 times per day
Outcomes	Not given
Notes	Nonstudy interventions: atropineReport language: EnglishStudy date: not givenFinancial support: pharmaceutical industry
Allocation concealment	A - Adequate

Characteristics of excluded studies

Study	Reason for exclusion
Abboud 1967	Nonconcurrent treatment allocation
Akberova 2000	Nonconcurrent treatment allocation
Assetto 1981	Insufficient data provided
Babushkin 1993	Insufficient data provided

Bianchetti 1964	Nonconcurrent treatment allocation
Butikova 1990	Nonconcurrent treatment allocation
Corina 1998	Outcome not based on epithelial healing
Corina 1999	Insufficient data provided
Dundarov 1998	Nonconcurrent treatment allocation
Elze 1979	Nonconcurrent treatment allocation
Fellinger 1980	Insufficient data provided
Galin 1976	Insufficient data provided
Gilkes 1963	Nonconcurrent treatment allocation
Gundersen 1936	Nonconcurrent treatment allocation
Guo 2003	No mention of randomization
Herbort 1987	Nonconcurrent treatment allocation
Hilsdorf 1969	Insufficient data provided
Horodenscy 1979	Nonconcurrent treatment allocation
Hua 1997	Insufficient data provided
Inocencio 1982	Insufficient data provided
Jin 1992	Insufficient data provided
Jones 1979	Outcome not based on epithelial healing
Kasparov 1974	Insufficient data provided
Kasparov 1990	Nonconcurrent treatment allocation
Kasparov 1991	Insufficient data provided
Kolomiets 1986	Insufficient data provided
Kuyama 1979	Insufficient data provided
Leopold 1965	Insufficient data provided
Ma 1982	Nonconcurrent treatment allocation
Mal'khanov 1991	Varied eligibility criteria
Marquardt 1971	Nonconcurrent treatment allocation
Martenet 1979	Nonconcurrent treatment allocation
Matalia 1987	Nonconcurrent treatment allocation
Mathur 1984	Insufficient data provided
Maychuk 1990	Varied eligibility criteria
McGill 1981	Insufficient data provided
Mohan 1987	Insufficient data provided
Morimoto 1986	Nonconcurrent treatment allocation
Pavan-Langston 1972	Insufficient data provided
Pavan-Langston 1977	Insufficient data provided

Pietruschka 1968	Insufficient data provided
Pintér 1973	Nonconcurrent treatment allocation
Pivetti-Pezzi 1985	Insufficient data provided
Prost 1986	Insufficient data provided
Reim 1965	Nonconcurrent treatment allocation
Scialdone 1986	Insufficient data provided
Sellitti 1982	Insufficient data provided
Shimomura 1987	Insufficient data provided
Shiota 1979	Nonconcurrent treatment allocation
Shiota 1988	Insufficient data provided
Sozen 2006	Varied eligibility criteria
Stambuk 1995	Outcome not based on epithelial healing
Tamburi 1990	Insufficient data provided
Tarakji 1978	Insufficient data provided
Tommila 1963	Nonconcurrent treatment allocation
Topciu 1992	Insufficient data provided
Tormey 1981	Insufficient data provided
Whitcher 1976	Insufficient data provided
Yamamoto 1984	Nonconcurrent treatment allocation
Yu 1999	Insufficient data provided
Zagaigora 1971	Nonconcurrent treatment allocation
Zajacz 1968	Nonconcurrent treatment allocation
Zhang 1995	Outcome not based on epithelial healing
Zirm 1981	Nonconcurrent treatment allocation

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** indicates the major publication for the study*

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Graphs

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

ANTIVIRAL VERSUS PLACEBO				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Idoxuridine versus			Odds Ratio (Fixed) 95% CI	Subtotals

placebo				only
02 Vidarabine versus placebo			Odds Ratio (Fixed) 95% CI	Subtotals only
03 Oral isoprinosine versus placebo			Odds Ratio (Fixed) 95% CI	Subtotals only

ANTIVIRAL A VERSUS ANTIVIRAL B

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Trifluridine versus idoxuridine			Odds Ratio (Fixed) 95% CI	Subtotals only
02 Acyclovir versus idoxuridine			Odds Ratio (Fixed) 95% CI	Subtotals only
03 Vidarabine versus idoxuridine			Odds Ratio (Fixed) 95% CI	Subtotals only
04 Trifluridine versus acyclovir			Odds Ratio (Fixed) 95% CI	Subtotals only
05 Trifluridine versus vidarabine			Odds Ratio (Fixed) 95% CI	Subtotals only
06 Acyclovir versus vidarabine			Odds Ratio (Fixed) 95% CI	Subtotals only
07 Acyclovir versus bromovinyldeoxyuridine			Odds Ratio (Fixed) 95% CI	Subtotals only
08 Trifluridine versus bromovinyldeoxyuridine			Odds Ratio (Fixed) 95% CI	Subtotals only
09 Idoxuridine versus bromovinyldeoxyuridine			Odds Ratio (Fixed) 95% CI	Subtotals only
10 Acyclovir versus iododeoxycytidine			Odds Ratio (Fixed) 95% CI	Subtotals only
11 Acyclovir versus ganciclovir			Odds Ratio (Fixed) 95% CI	Subtotals only
12 Trifluridine versus foscarnet			Odds Ratio (Fixed) 95% CI	Subtotals only
13 Trifluridine (aqueous) versus trifluridine (viscous)			Odds Ratio (Fixed) 95% CI	Subtotals only
14 Panthenol versus fluorophenylalanine			Odds Ratio (Fixed) 95% CI	Subtotals only
15 Idoxuridine versus fluorophenylalanine			Odds Ratio (Fixed) 95% CI	Subtotals only

ORAL VERSUS TOPICAL ANTIVIRAL

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

COMBINED VERSUS SINGLE ANTIVIRAL

Outcome title	No. of studies	No. of participants	Statistical method	Effect size

01 Oral/topical versus topical alone			Odds Ratio (Fixed) 95% CI	Subtotals only
02 Acyclovir/vidarabine versus acyclovir			Odds Ratio (Fixed) 95% CI	Subtotals only
03 Acyclovir/epidermal growth factor versus acyclovir			Odds Ratio (Fixed) 95% CI	Subtotals only
04 Idoxuridine/oxyphenbutazone versus idoxuridine			Odds Ratio (Fixed) 95% CI	Subtotals only

PHYSICOCHEMICAL METHOD VERSUS CONTROL				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

PHYSICOCHEMICAL METHOD VERSUS ANTIVIRAL AGENT				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

THERMAL DEBRIDEMENT/ INTERFERON VERSUS WIPING DEBRIDEMENT/ INTERFERON				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

PHYSICOCHEMICAL/ ANTIVIRAL VERSUS PHYSICOCHEMICAL ALONE				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

PHYSICOCHEMICAL/ ANTIVIRAL VERSUS ANTIVIRAL ALONE				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

ACYCLOVIR/DEBRIDEMENT VERSUS IDOXURIDINE/ DEBRIDEMENT				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

INTERFERON VERSUS PLACEBO				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

INTERFERON VERY LOW DOSE VERSUS INTERFERON LOW DOSE				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

INTERFERON LOWER DOSE VERSUS INTERFERON HIGHER DOSE				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Low dose versus high dose			Odds Ratio (Fixed) 95% CI	Subtotals only
02 Moderate dose versus high dose			Odds Ratio (Fixed) 95% CI	Subtotals only
03 High dose versus very high dose			Odds Ratio (Fixed) 95% CI	Subtotals only

DEBRIDEMENT/ LEUKOCYTE INTERFERON VERSUS DEBRIDEMENT/ FIBROBLAST INTERFERON				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

TRIFLURIDINE/ NATURAL INTERFERON VERSUS TRIFLURIDINE/ RECOMBINANT INTERFERON				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

INTERFERON VERSUS ANTIVIRAL AGENT				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

INTERFERON INDUCER VERSUS ANTIVIRAL AGENT				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

INTERFERON/ANTIVIRAL VERSUS ANTIVIRAL ALONE				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Healing			Odds Ratio (Fixed) 95% CI	Subtotals only

Cover sheet

Therapeutic interventions for herpes simplex virus epithelial keratitis

Reviewer(s)	Wilhelmus KR
Contribution of Reviewer(s)	KRW developed the protocol, selected and appraised the trials, extracted data, and wrote the review.
Issue protocol first published	2001 issue 1
Issue review first published	2001 issue 1
Date of last minor amendment	08 November 2007
Date of last substantive amendment	29 October 2007
Most recent changes	Issue 1 2008: 1 new study (Colin 2007a) has been added.
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	Information not supplied by reviewer
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Cochrane Library number CD002898

Editorial group Cochrane Eyes and Vision Group

Editorial group code HM-EYES

Sources of support

External sources of support

- National Eye Institute, National Institutes of Health USA
- Research to Prevent Blindness, Inc USA
- Sid W Richardson Foundation USA

Internal sources of support

- No sources of support supplied

Keywords

Humans; Administration, Oral; Administration, Topical; Antiviral Agents[*administration & dosage]; Combined Modality Therapy[methods]; Debridement[*methods]; Keratitis, Herpetic[*therapy]; Randomized Controlled Trials as Topic

Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection

Hollier Lisa M, Wendel George D

This review should be cited as: Hollier Lisa M, Wendel George D. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection (Cochrane Review). In: *The Cochrane Library,* Issue 2, 2008. Oxford: Update Software.

Abstract

Background

Genital herpes simplex virus (HSV) infection is one of the most common viral sexually transmitted infections. The majority of women with genital herpes will have a recurrence during pregnancy. Transmission of the virus from mother to fetus typically occurs by direct contact with virus in the genital tract during birth.

Objective

To assess the effectiveness of antenatal antiviral prophylaxis for recurrent genital herpes on neonatal herpes and maternal recurrences at delivery.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (January 2007), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2006, Issue 4), MEDLINE (January 1966 to February 2007) and EMBASE (January 1974 to February 2007; handsearched conference proceedings; reviewed bibliographies of all relevant articles for further references; and contacted experts in the field.

Selection criteria

Randomized controlled trials which assessed the effectiveness of antivirals compared to placebo or no therapy, on neonatal herpes and maternal disease endpoints among pregnant women with genital herpes.

Data collection and analysis

Two authors independently applied study selection criteria and extracted data.

Main results

Seven randomized controlled trials (1249 participants) which met our inclusion criteria compared acyclovir to placebo or no treatment (five trials) and valacyclovir to placebo (two trials). The effect of antepartum antiviral prophylaxis on neonatal herpes could not be estimated. There were no cases of symptomatic neonatal herpes in the included studies in either the treatment or placebo groups. Women who received antiviral prophylaxis were significantly less likely to have a recurrence of genital herpes at delivery (relative risk (RR) 0.28, 95% confidence interval (CI) 0.18 to 0.43, I2 = 0%). Women who received antiviral prophylaxis were also significantly less likely to have a cesarean delivery for genital herpes (RR 0.30, 95% CI 0.20 to 0.45, I2 = 27.3%). Women who received antiviral prophylaxis were significantly less likely to have HSV detected at delivery (RR 0.14, 95% CI 0.05 to 0.39, I2 = 0%).

Reviewers' conclusions

Women with recurrent genital herpes simplex virus should be informed that the risk of neonatal herpes is low. There is insufficient evidence to determine if antiviral prophylaxis reduces the incidence of neonatal herpes. Antenatal antiviral prophylaxis reduces viral shedding and recurrences at delivery and reduces the need for cesarean delivery for genital herpes. Limited information exists regarding the neonatal safety of prophylaxis. The risks, benefits, and alternatives to antenatal prophylaxis should be discussed with women who have a history and prophylaxis initiated for women who desire intervention.

Synopsis

The incidence of herpes, a sexually transmitted disease, varies across the world. Among pregnant women with herpes, nearly 75% can expect at least one flare-up during their pregnancy. Transmission of the virus from mother to baby typically occurs by direct contact with the virus during birth. It is often recommended that a cesarean should be offered to women with active lesions to reduce the risk of transmission to the baby. In addition, several antiviral agents are available for use both for therapy and for preventing a flare-up. These antiviral drugs include acyclovir, penciclovir, valacyclovir, and famciclovir. The review assessed whether antiviral drugs given to pregnant women with herpes before a recurrence might be effective in reducing transmission to the baby. Seven studies were identified involving 1249 women. Giving antiviral drugs reduces viral shedding and recurrences at labor and birth. They also reduced the use of cesarean, but there is no evidence of reduction in neonatal herpes. Women should also be informed that the risk of the baby getting herpes during birth is low.

Background

Genital herpes simplex virus (HSV) infection is one of the most common viral sexually transmitted infections in the United States (US), now affecting an estimated 45 million adolescents and adults (Corey 2000; Fleming 1997). The seroprevalence (the frequency of individuals in a population that have a particular element (as antibodies to HSV) in their blood serum) is higher among women than among men across various populations (Cowan 2004; Wutzler 2000). A very large serologic (the science dealing with the immunological properties and actions of serum) study in the US found that approximately 23% of women had serologic evidence of HSV-2 infection (Xu 2006). The seroprevalence of HSV-2 in western and southern Europe appears to be lower than in northern Europe and North America (Smith 2002).

Among women with recurrent genital HSV, nearly 75% can expect at least one recurrence during pregnancy, and about 14% of women will have prodromal symptoms (early symptoms indicating the onset of an attack) or clinical recurrence at delivery (Sheffield 2006; Watts 2003). Transmission of the virus from mother to fetus typically occurs by direct contact with the virus in the genital tract during delivery. The risk of vertical transmission is related to the gestational age at delivery, the presence of maternal antibodies to HSV and the route of delivery (Baker 1999; Brown 2003). To reduce neonatal transmission, it is currently recommended that a cesarean delivery be offered to all women with active genital lesions or prodromal symptoms at delivery (Baker 1999; NGC 2002).

The estimated incidence of neonatal herpes infection is broad, ranging from 5 to 80 per 100,000 live births (Kropp 2006; Mahnert 2007; Whitley 2007). Infection can be classified as disseminated disease (25%), central nervous system disease (30%), or disease limited to the skin, eyes, or mouth (45%) (Whitley 1988). About 30% of infants with disseminated disease and 4% of infants with CNS disease will die from their infection. Long-term neurologic sequelae occur in about 20% of survivors (Kimberlin 2001).

There are several antiviral agents that have been used both for therapy and for prophylaxis in the management of women with genital herpes virus infections. Acyclovir and penciclovir are nucleoside analogs. These drugs become active only after initial phosphorylation (addition of a phosphorus group) that is carried out only by viral thymidine kinase (a viral-specific enzyme) (Elion 1993; Larsson 1986). In this way, the drugs become active only in cells that are infected with the herpes virus. In these cells, the phosphorylated drug (nucleoside analog) is incorporated into the replicating viral DNA and this terminates the growth of the DNA chain. Valacyclovir is a prodrug (inactive form) of acyclovir that is rapidly metabolized to acyclovir (Weller 1993). Famciclovir is converted to penciclovir. Among non-pregnant women, daily oral acyclovir, valacyclovir, and famciclovir have been shown to reduce the frequency of recurrent genital herpes (Mertz 1988; Mertz 1997; Reitano 1998). Additionally, oral valacyclovir has been shown to reduce the risk of symptomatic transmission of genital herpes (Corey 2004).

Oral antiviral agents are used in pregnancy to treat genital herpes infections. Acyclovir in pregnancy is well tolerated, with minimal fetal drug accumulation (Haddad 1993). The Acyclovir in Pregnancy Registry included data from more than 1200 women exposed to acyclovir. No increase in drug-related fetal abnormalities was ascribed to acyclovir, although long-term developmental outcomes were not evaluated (Stone 2004).

In an effort to reduce neonatal transmission of HSV and to reduce the number of cesarean deliveries performed for genital herpes infections, a number of studies have investigated whether antiviral therapy in the last month of pregnancy would decrease HSV recurrence at delivery among women with genital herpes diagnosed before or during pregnancy (Andrews 2006; Braig 2001; Brocklehurst 1998; Scott 1996; Scott 2002; Sheffield 2006; Stray-Pedersen 1990; Watts 2003). The findings of these studies

have been controversial: several studies finding evidence of benefit and others finding no reduction in recurrent HSV or cesarean delivery. A previous meta-analysis found reduction in recurrences and cesarean delivery, but did not address adverse effects (Sheffield 2003). Although the American College of Obstetricians and Gynecologists states that the use of acyclovir to suppress recurrent HSV infection in pregnancy is acceptable, some reports note that there are insufficient data to recommend this prophylaxis. (Baker 1999; Brown 2003; Handsfield 1999; IHMF 2003; Smith 1998).

Objectives

To estimate the effect of prophylactic antiviral medication provided to pregnant women near term on:

the rate of neonatal HSV transmission;

the rate of recurrent genital herpes at delivery;

the number of cesarean deliveries performed for clinical herpes simplex virus (HSV) recurrences or prodromal symptoms;

the prevalence of HSV detection at delivery.

Criteria for considering studies for this review

Search strategy for identification of studies

See: Cochrane Pregnancy and Childbirth Group search strategy

Methods of the review

Description of studies

Methodological quality

Results

Discussion

We found insufficient evidence to evaluate the effect of antiviral prophylaxis given to pregnant women with a history of recurrent genital herpes on the incidence of neonatal herpes. There were no cases of neonatal herpes in the seven included trials, which included over 1200 infants. The estimated incidence of neonatal herpes in North America ranges from 5 to 80 per 100,000 live births (Brown 2003; Kropp 2006; Mahnert 2007; Whitley 2007). Corresponding to the lower prevalence of herpes simplex virus (HSV) in women outside the United States, the incidence of neonatal herpes is significantly lower in the United Kingdom - estimated at 1.6/100,000 (Tookey 1996). Approximately 70% to 80% of infected infants are born to mothers with no reported history of HSV infection (Tookey 1996; Whitley 1988). Because the outcome of neonatal herpes is expected to be infrequent in this population, the total sample size included in the meta-analysis is inadequate to detect even large relative reductions in neonatal infection. Neutropenia is a recognized, transient complication of acyclovir treatment of neonatal HSV infection (Kimberlin 2001). Data were available on a limited number of infants, but no adverse fetal/neonatal effects were identified. Continued assessment of the neonatal safety of maternal prophylaxis is important.

Surrogate outcomes are often measured in situations where an important outcome is rare. Samples from mucosal surfaces of neonates in several trials were taken and tested for the presence of HSV both by culture and by polymerase chain reaction. Three infants, two treatment-exposed and one placebo-exposed, had detectable virus. Thus, we did not find evidence that prophylactic antivirals given to pregnant women reduced the frequency of detectable HSV.

Antiviral prophylaxis was associated with a significant reduction in recurrence at the time of delivery. Because the practice of performing a cesarean delivery when women present with active genital herpes is relatively common, there was also a significant reduction in cesarean delivery for genital HSV. These findings are similar to a previous meta-analysis, which included only trials involving the use of acyclovir (Sheffield 2003) and showed significant reductions in recurrence at delivery, cesarean delivery for HSV and in total cesarean deliveries. The effectiveness in reducing recurrences was consistent for acyclovir and for valacyclovir.

Cesarean delivery has been shown to reduce the risk of transmission of HSV to the neonate (Brown 2003). One potential concern of using prophylactic antivirals would be that suppression of viral activity would be incomplete and women might have asymptomatic shedding rather than an active lesion, and hence would not have a cesarean delivery. In our analysis and in a previous analysis, prophylaxis was effective in significantly reducing the detection of virus at delivery (Sheffield 2003).

Reviewers' conclusions

Implications for practice

Women with recurrent genital herpes simplex virus should be informed that the risk of neonatal herpes is low. There is insufficient evidence to determine if antiviral prophylaxis for women with a history of genital herpes reduces the incidence of neonatal herpes. Antenatal antiviral prophylaxis reduces viral shedding and recurrences at delivery and reduces the need for cesarean delivery for genital herpes. Limited information exists regarding the neonatal safety of prophylaxis. The risks, benefits, and alternatives to antenatal prophylaxis should be discussed with women who have a history and prophylaxis initiated in women who desire intervention.

Implications for research

Because neonatal HSV is an infrequent complication in this population, other interventions will be needed to significantly reduce the overall incidence of neonatal herpes. Continued assessment of the safety of antepartum antiviral prophylaxis is important to inform the woman's decision made based on the risks and benefits of the intervention.

Acknowledgements

We would like to thank the authors of the studies who responded to our requests for additional information and clarification.

As part of the pre-publication editorial process, this review has been commented on by two peers (an editor, and a referee who is external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

Potential conflict of interest

Notes

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** indicates the major publication for the study*

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Graphs

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

Antenatal antiviral prophylaxis versus placebo				
Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
1 Neonatal herpes	7	1240	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Genital herpes simplex virus recurrence at delivery	7	1249	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.18, 0.43]
2.1 Acyclovir	5	799	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.15, 0.43]
2.2 Valacyclovir	2	450	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.17, 0.68]
3 Cesarean delivery	7	1249	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.20, 0.45]
3.1 Acyclovir	5	799	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.16, 0.46]

3.2 Valacyclovir	2	450	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.17, 0.70]
4 Genital herpes simplex virus detection at delivery	5	887	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.05, 0.39]
4.1 Acyclovir	4	632	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.45]
4.2 Valacyclovir	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 0.85]
5 Neonatal viral detection	4	737	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.22, 12.13]

Cover sheet

Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection

Reviewer(s)	Hollier Lisa M, Wendel George D
Contribution of Reviewer(s)	
Issue protocol first published	2004 issue 4
Issue review first published	2008 issue 1
Date of last minor amendment	Information not supplied by reviewer
Date of last substantive amendment	Information not supplied by reviewer
Most recent changes	
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	Information not supplied by reviewer
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Cochrane Library number CD004946

Editorial group Cochrane Pregnancy and Childbirth Group

Editorial group code HM-PREG

Keywords