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Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

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Abstract

Background—Eye disease due to herpes simplex virus (HSV) commonly presents as epithelial keratitis.

Objectives—To compare the relative effectiveness of antiviral agents, interferon, and corneal débridement in the treatment of acute HSV epithelial keratitis.

Search methods—We searched CENTRAL (*The Cochrane Library* 2010, Issue 4), MEDLINE (January 1950 to October 2010), EMBASE (January 1980 to October 2010), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to October 2010), Zetoc (British Library's Electronic Table of Contents), System for Information on Grey Literature in Europe (openSIGLE), Biosciences Information Service (BIOSIS), the *meta*Register of Controlled Trials (*mRCT*) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), Japan Information Center of Science and Technology (JICST-EPlus), and China Academic Journals database (CAJ) via China National Knowledge Infrastructure (CNKI) with citations confirmed using China/Asia On Demand (COAD). There were no language or date restrictions in the search for trials. All databases except CNKI and COAD were last searched on 27 October 2010, CNKI and COAD were searched on 1 April 2010. We also searched literature digests, conference proceedings and reference lists.

Selection criteria—Of 152 eligible studies, 106 comparative treatment trials involving 5872 eyes with dendritic or geographic epithelial keratitis were analysed for corneal healing over two weeks.

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CONTRIBUTIONS OF AUTHORS

KRW developed the protocol, selected and appraised the trials, extracted data, and wrote the review.

DECLARATIONS OF INTEREST

None known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This updated review uses 14 days, rather than seven days, as the primary treatment outcome time and estimates risk ratios and hazard ratios instead of odds ratios.

NOTES

Issue 12 2010: This review was substantively updated and the original title of 'Therapeutic interventions for herpes simplex virus epithelial keratitis' was changed.

Data collection and analysis—Interventions were compared at 14 days after trial enrolment by calculating a risk ratio (RR) that was adjusted with indirect RR, assessed by an inconsistency index (I^2) and supplemented by a seven-day RR and a hazard ratio (HR).

Main results—Idoxuridine, though uncertainly better in healing outcome than control because of few trials with 14-day follow up, allowed earlier corneal re-epithelialisation. Vidarabine resulted in a significantly better outcome than placebo in one trial (RR 1.96; 95% CI 1.10 to 3.49). Compared to idoxuridine, in combined direct and indirect analyses, vidarabine (RR 1.11; 95% CI 1.03 to 1.19), trifluridine (RR 1.31; 95% CI 1.20 to 1.42), acyclovir (RR 1.23; 95% CI 1.16 to 1.31), brivudine (RR 1.38; 95% CI 1.18 to 1.61), and ganciclovir (RR 1.40; 95% CI 1.25 to 1.57) were significantly more effective. Trifluridine (RR 1.12; 95% CI 1.04 to 1.21) and acyclovir (RR 1.11; 95% CI 1.05 to 1.19) appeared more effective than vidarabine. No significant differences in healing were found in comparisons between acyclovir, trifluridine and brivudine. The comparison of ganciclovir to acyclovir was limited by heterogeneity and possible publication bias. The joint use of two topical antivirals (RR 1.00; 95% CI 0.89 to 1.12) and the use of oral acyclovir alone (RR 0.92; 95% CI 0.79 to 1.07) or combined with a topical antiviral (RR 1.08; 95% CI 0.99 to 1.17) appeared as effective as topical antiviral therapy. Compared to antiviral monotherapy, the combination of an antiviral with interferon (RR 1.03; 95% CI 0.99 to 1.07) or with débridement (RR 1.04; 95% CI 0.95 to 1.14) did not yield significantly better outcomes but may have accelerated healing. The corneal epithelial healing outcome was improved when antiviral therapy followed débridement (RR 1.21; 95% CI 1.04 to 1.42).

Authors' conclusions—Trifluridine and acyclovir are more effective than idoxuridine or vidarabine and similar in therapeutic effectiveness. Brivudine and ganciclovir are at least as effective as acyclovir. While not improving outcome, the combination of interferon and an antiviral agent may speed healing. The effectiveness of corneal epithelial débridement is improved by an antiviral agent.

INDEX TERMS: Medical Subject Headings (MeSH)

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

MeSH check words

Humans

PLAIN LANGUAGE SUMMARY

Antivirals, interferon, and débridement treatments for herpes simplex eye disease

Ocular herpes is a prevalent and recurrent eye infection. Without therapy, only one half of non-complicated herpetic corneal surface infections resolve in two weeks. Several treatments, ranging from medications to superficial wiping, aim to shorten the course of herpetic infection of the corneal surface. This review provides evidence-based guidance on the comparative effectiveness of interventions for herpes simplex virus (HSV) epithelial keratitis, by systematically analysing clinical trials from Europe, North America, Asia,

Australia, and Africa. Corneal healing rates were examined during treatment with antivirals, interferon, or corneal surface débridement. The first topical nucleoside antiviral drugs, idoxuridine and vidarabine, were moderately effective but newer antiviral drugs such as trifluridine and acyclovir were better. Ophthalmic preparations of trifluridine, acyclovir, ganciclovir, and brivudine were nearly equivalently effective and allowed approximately 90% of treated eyes to heal within two weeks. In parallel with the development of nucleoside antiviral drugs, interferon, which is an antiviral protein of the immune defence system, was studied in trials that indicated effectiveness of topical formulations. Compared with antiviral treatment, the combination of interferon with a nucleoside antiviral agent seemed to facilitate early healing. Ocular allergic and toxic effects were infrequent and transitory. Before the introduction of antiviral drugs and interferon, the corneal surface was removed by physical scraping or chemical erosion, but evidence is lacking that establishes the efficacy and safety of physicochemical methods of débridement. The joint use of débridement and antiviral therapy promoted corneal recovery but was not better than single antiviral medications on corneal epithelial healing.

BACKGROUND

Herpes simplex virus (HSV) is a human herpes virus that affects most people. After initial exposure, usually during early childhood or adolescence, HSV type 1 may produce a primary viral syndrome but more often remains subclinical and establishes latency within neurons of the trigeminal ganglia (Toma 2008). Years later reactivation leads to viral shedding that, while commonly asymptomatic, occasionally leads to ocular inflammation (Wald 2007).

Description of the condition

Reactivation and recurrence—Ultraviolet light and temperature reactivate experimental HSV keratitis (Laycock 1991; Varnell 1995); but sunlight exposure, climatic conditions, febrile illnesses, and psychological stressors have not been proven as triggering factors (HEDS Group 2000a; HEDS Group 2001; Kip 2001; Stan 2000). HSV epithelial keratitis has occurred after contact lens wear (Mucci 2009), corneal injury (Sundmacher 1986), intraocular or periocular injections (Hashizume 2009; Khalili 2009), anterior segment surgery (Patel 2009), corneal transplantation (Borderie 2004; Hassan 2009; Rezende 2004; Robert 2005), and the use of some topical medications such as prostaglandin analogues (Alm 2008; Villegas 2008). Herpetic recurrences may become more common with ageing (Young 2010). HSV epithelial keratitis may be more prevalent or severe in atopes, corneal transplant recipients, patients using corticosteroids (Williams 1977), people with immune suppression (Hodge 1997; Kaiserman 2006; Prabripataloong 2006; Remeijer 1997; Rezende 2006), and malnourished children with measles (Ukety 1991).

Epidemiology of ocular herpes—Recurrent HSV is an epidemiologically important cause of infectious and inflammatory eye disease affecting children, adolescents, adults, and the elderly (Liesegang 2001; Wilhelmus 2008a). The estimated prevalence of ocular HSV disease is 15 per 10,000 population (Liesegang 1989a). The incidence of first-episode ocular HSV at centres in Europe and North America is 4 to 13 per 100,000 person-years

(Labetoulle 2005; Liesegang 1989a; Mortensen 1979; Ribaric 1976; Young 2010). The incidence of further episodes of HSV keratitis is 12 to 18 per 100,000 person-years (Labetoulle 2005; Liesegang 1989a). Worldwide, an estimated 10 million persons have had herpetic eye disease, with approximately two million individuals left with impaired vision of their affected eye.

Epithelial keratitis—Epithelial keratitis is the most common form of HSV eye disease, accounting for 50% to 80% of ocular herpes (Labetoulle 2005; Liesegang 1989a; Uchio 1994; Young 2010). The incidence of new or recurrent HSV epithelial keratitis is estimated at 12 to 22 people per 100,000 person-years (Labetoulle 2005; Liesegang 1989b; Mortensen 1979). On a global scale, about one million new or recurrent episodes of HSV epithelial keratitis occur each year.

Dendritic epithelial keratitis, a branching pattern of painful infection affecting the corneal surface, is the customary configuration (Tabery 2010). Geographic epithelial keratitis is a macrolcerative form of corneal infection that complicates corticosteroid use or immunosuppression. HSV epithelial keratitis is typically unilateral. The contralateral eye is infrequently affected either simultaneously or subsequently (Liesegang 2001), although people with atopy or an immune deviation may be predisposed to HSV epithelial keratitis of both eyes (Souza 2003; Wilhelmus 1981c). Besides HSV-1, much less common causes of dendritic epithelial keratitis are HSV-2 (Kaneko 2008; Neumann-Haefelin 1978; Vannini 1986), varicella-zoster virus (Bierly 1994; Hu 2010; Pavan-Langston 1973), co-infection with HSV-1 and human herpes virus 6 (Okuno 2011) and, very rarely, cytomegalovirus (Wilhelmus 1996b), Epstein-Barr virus (Pflugfelder 1990), or adenovirus (Chodosh 1995). Laboratory testing can help to establish the etiology of atypical cases (Chanzy 2002).

Description of the intervention

Many interventions have been used in the treatment of HSV epithelial keratitis (Wilhelmus 2000). Curettage and cauterization of the ocular surface came into use in 1890 (Kipp 1890) followed by the application of cytotoxic reagents in 1900 (Friedenwald 1900). Corneal epithelial débridement, iodination, and carbolic acid were customary remedies for superficial ulcerative keratitis during the first half of the 20th century.

With the recognition that dendritic keratitis was associated with a herpetic syndrome (Verhoeff 1909) and was due to a virus (Grüter 1920), various anti-infective compounds were screened as potential treatments (Bauer 1985; Graupner 1969). A pyrimidine analogue, idoxuridine (iododeoxyuridine, IDU), that was originally developed as an anticancer drug, became the first antiviral agent in 1962 (Kaufman 1962). In the following decade a purine analogue, vidarabine (adenine arabinoside, ARA-A), also entered ophthalmic practice (Whitley 1980). Both were subsequently replaced by other nucleoside analogues that were marketed as ophthalmic solutions, gels, or ointments. These include trifluridine (trifluorothymidine, TFT) (Carmine 1982), acyclovir (acycloguanosine, ACV) (Richards 1983; Wagstaff 1994), brivudine (bromovinyldeoxyuridine, BVDU) (De Clercq 2005), and ganciclovir (dihydroxypropoxymethylguanine, DHPG) (Croxtall 2011; Tabbara 2010).

In parallel with studies on nucleoside antivirals, interferon was discovered in 1957, tested against HSV in 1960, and evaluated for treatment of HSV epithelial keratitis in 1963 (Tommila 1963). Interferon emerged as a distinct management strategy for viral eye disease (Jones 1967). Comparative treatment trials of topical interferon that began in 1976 showed interferon to be clinically effective for treating HSV epithelial keratitis. Several formulations and dosages of interferon were tested. Interferon was used alone, with an antiviral nucleoside, and after débridement (Cantell 1995; Sundmacher 1982; Sundmacher 1983). While interferon eye drops can be prepared extemporaneously, a topical preparation is not widely available for clinical use.

How the intervention might work

Treatment of HSV epithelial keratitis aims to halt active viral infection of the cornea, quickly and safely, thereby controlling symptoms and allowing a normal ocular surface to become re-established. Antiviral nucleosides include purine analogues such as vidarabine, acyclovir, and ganciclovir; and pyrimidine analogues such as idoxuridine, trifluridine, and brivudine. These agents inhibit HSV replication by interfering with viral DNA synthesis during transcription of the viral genome. Acyclovir, ganciclovir, and brivudine are potentially less toxic than the other antivirals because they are processed by a virus-encoded enzyme, thymidine kinase, to inhibit viral DNA polymerase. Although occurring infrequently in immunocompetent people with herpetic eye disease, sporadic mutations in viral genes encoding thymidine kinase or DNA polymerase can confer antiviral resistance. Interferon- α and interferon- β are cytokines capable of activating an intracellular pathway that upregulates host genes affecting antiviral responses. Interferon and a nucleoside antiviral may have an additive or synergistic interaction. Other topical ophthalmic agents such as nonsteroidal anti-inflammatory drugs have variable effects on the replication of herpes simplex virus. Corneal epithelial débridement or chemical cauterization removes or destroys virus-infected cells of the corneal surface and is followed by corneal epithelial regeneration if residual virus does not cause recrudescence of ocular infection.

Why it is important to do this review

An antiviral agent is a favoured treatment for herpes simplex virus epithelial keratitis (Sundmacher 2009). However, controversies persist about the optimal antiviral agent, the role of interferon, and the effectiveness of débridement methods (Epstein 1989; Guess 2007; Kastner 1984). Surveys among ophthalmologists revealed some differences of opinion in treatment preferences for HSV epithelial keratitis (Guess 2010; Labetoulle 2005; McAllum 2003). To provide an evidence-based analysis of the comparative benefits among therapeutic options used in patient-centred eye care, this systematic review summarizes the results of comparative clinical trials that evaluated the acute treatment of HSV epithelial keratitis.

OBJECTIVES

The objective of this review was to assess the relative effectiveness of pharmacological and non-pharmacological interventions, but not herbal medicinals, on the acute treatment of HSV dendritic or geographic epithelial keratitis.

METHODS

Criteria for considering studies for this review

Types of studies—This review included clinical trials that compared the relative effectiveness of two or more therapeutic interventions on the corneal epithelial healing of participants who had clinically diagnosed or virologically confirmed HSV epithelial keratitis.

Types of participants—Participants had active dendritic or geographic epithelial keratitis. Punctate, stellate, or linear epithelial keratitis was considered to be a form of dendritic epithelial keratitis. Studies of herpetic keratouveitis were excluded if epithelial keratitis was not present.

Types of interventions—Antiviral agents included idoxuridine, vidarabine, trifluridine, acyclovir, ganciclovir, brivudine, foscarnet, and cidofovir. Interferon preparations included interferon- α , interferon- β , and interferon- γ as well as interferon inducers. Débridement of the corneal epithelium was done by wiping, scraping, chemical corrosion, cryotherapy, thermal application, or photoinactivation. Supplemental agents included growth factors, anti-inflammatory medications, and immunomodulators. Interventions were compared to inactive controls, to each other, or to combinations of interventions.

Types of outcome measures—Healing of the corneal epithelium was evaluated by slit-lamp biomicroscopy, with or without the use of fluorescein or rose-Bengal staining.

Primary outcomes: The primary outcome was the proportion of participants healed at 14 days after study entry.

Secondary outcomes: To evaluate the pace of healing, two secondary outcomes were used: the proportion healed at seven days after study entry, and the rate of healing as estimated by logrank analysis of survival curves or life tables.

Search methods for identification of studies

We attempted to identify all relevant trials, regardless of language or publication status, using search strategies recommended by The Cochrane Collaboration.

Electronic searches—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (2010, Issue 4), part of *The Cochrane Library* www.thecochranelibrary.com (accessed 27 October 2010), MEDLINE (January 1950 to October 2010), EMBASE (January 1980 to October 2010), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to October 2010), Zetoc (British Library's Electronic Table of Contents), System for Information on Grey Literature in Europe (openSIGLE), Biosciences Information Service (BIOSIS), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), Japan Information Center of Science and Technology (JICST-EPlus) and China Academic Journals database (CAJ) via China National Knowledge Infrastructure (CNKI) with citations confirmed using China/Asia On

Demand (COAD). There were no language or date restrictions in the search for trials. All databases except CNKI and COAD were last searched on 27 October 2010, CNKI and COAD were last searched on 1 April 2010.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), openSIGLE (Appendix 6), BIOSIS (Appendix 7), mRCT (Appendix 8), ClinicalTrials.gov (Appendix 9), JICST-EPlus (Appendix 10), and CNKI/COAD (Appendix 11).

Searching other resources

Handsearching: Manual searching of printed databases, using the terms ‘cornea’, ‘herpes’, and ‘keratitis’, was undertaken for *Index Medicus* (from 1960 through 1965), *Excerpta Medica Ophthalmology* (from 1960 to 1973), and *Ophthalmic Literature* (from 1947 to 1998).

Grey literature: Titles and abstracts of presentations and posters that were scheduled at meetings (held between 1980 and 2010) of the Association for Research in Vision and Ophthalmology (ARVO), the International Congress of Ophthalmology/World Ophthalmology Congress, the American Academy of Ophthalmology, the Ocular Microbiology and Immunology Group (OMIG), and the International Conference on Herpetic Eye Diseases were searched for clinical reports of herpetic keratitis. The websites of the US Food and Drug Administration, the UK National Institute for Health and Clinical Excellence, and European Medicines Agency were searched for clinical trials on herpetic keratitis. Web-based sources were traced with the Google search engine.

Reference lists: The bibliographies of primary reports, ocular virology review articles, and corneal textbooks were surveyed for relevant publications that included the word ‘herpes’ or ‘herpetic’ in the article title.

Correspondence: Selected authors were contacted, when feasible, if insufficient data were provided in the published report.

Data collection and analysis

The search for studies was performed with the assistance of the Cochrane Eyes and Vision Group. The author selected potentially relevant studies by reviewing the titles and abstracts of studies found by the searches. The full text was obtained for any report considered to include a relevant clinical trial. Articles were translated as needed. The sequence of searching and assessment of studies was described in accordance with PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher 2009).

Selection of studies—Studies were selected based on study design and types of participants, interventions, and outcome measures. Included studies had an impartial allocation of two or more interventions to participants who were clinically diagnosed or virologically confirmed with HSV epithelial keratitis and who were evaluated for corneal healing at seven or 14 days, or both, after study entry. Trials on the relative effectiveness of

botanical or herbal preparations were not included in this review. For multiple publications that described all or part of the same study population the most detailed report with the largest sample was used (Wilhelmus 2007a).

Data extraction and management—The author recorded relevant information onto a data collection form. Data extracted from the full articles categorized attributes of the study participants, the method of treatment allocation, any co-interventions or adjunctive treatment, and the examination method used to evaluate healing. Data from trials restricted to geographic epithelial keratitis were incorporated into pooled comparisons but also tabulated separately.

The cumulative number of participants who healed in each intervention group was recorded for each day of follow up, including data for days seven and 14. For reports providing only graphs of healing curves, an assistant geometer (KRH) projected the curve onto the ordinate axis for each day along the abscissa to estimate the daily proportion healed in each treatment group. Since few patients were withdrawn or lost to follow up, and since trials did not consistently identify when these patients exited the study, adjustment for censoring in the estimation of risk ratios was not routinely performed.

Assessment of risk of bias in included studies—Relevant studies were appraised on the reported study design, analysis, and presentation (Chalmers 1981). This assessment sought to evaluate potential sources of systematic bias such as selection bias, performance bias, detection bias, and attrition bias. Selection bias was evaluated by examining the use of randomisation in treatment allocation, using a concealed assignment schedule. Performance bias and detection bias were evaluated by noting the use of masking of participants and trialists and the method for ascertaining corneal epithelial healing. Attrition bias was evaluated by the extent of withdrawals and other losses to follow up. Studies were assessed for internal validity, as noted in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008), using the following six components: sequence generation, allocation concealment, masking (blinding), completeness of outcome data, outcome reporting, and other sources of bias. Each component was assigned a judgement of the risk of bias categorized as low risk of bias, unclear risk of bias, or high risk of bias.

Measures of treatment effect—Healing was analysed with risk ratios at seven and 14 days and with hazard ratios, both with 95% confidence intervals. Time-to-event data were extracted from tables and cumulative healing curves.

Unit of analysis issues—Data from trials with multiple treatment groups were evaluated by selecting paired comparisons of two interventions or by combining data from similar treatment groups. Reports of treatment comparisons that provided only the mean time to resolution were not used in estimating survival rates because all interventions did not yield consistently similar healing distributions (Michiels 2005).

Dealing with missing data—Whenever possible, data on all participants were extracted from studies that reported sufficient information for an intention-to-treat analysis.

Censoring, assumed to be non-informative and to occur at a constant rate during the initial two weeks of treatment, was incorporated when reported.

Assessment of heterogeneity—Heterogeneity among trials evaluating similar interventions was investigated using forest plots. The I^2 statistic was used as an inconsistency index to evaluate pooled comparisons of interventions (Higgins 2002). $I^2 > 50\%$ was considered to indicate substantial heterogeneity. Risk ratios were explored using random-effects models for comparisons having high heterogeneity.

Assessment of reporting biases—Publication bias was explored by funnel plots for treatment comparisons that had at least 10 trials.

Data synthesis

Treatment comparisons: Some placebo-controlled trials used the vehicle of the relevant study drug for the inactive control. Other topical agents, also classified as inactive controls in this review, included tissue-culture medium, neomycin solution, albumin, non-specific gamma-globulin, and low-dose interferon preparations.

Interventions that were considered sufficiently similar to allow data pooling within studies were: photoinactivation and carbolization; cryotherapy and carbolization; thermomechanical débridement and thermomechanical débridement with interferon- α 62,500 international units per millilitre (IU/ml), a dosage probably too low to exert clinical effects; débridement with interferon- α at either 11 million IU/ml or 33 million IU/ml; and trifluridine with interferon- α at either one million IU/ml or 30 million IU/ml. Different formulations but similar drug concentrations of the same nucleoside antiviral agent (for example acyclovir ointment and acyclovir solution; ganciclovir gel and ganciclovir solution) were also combined in pooled analyses. Data for ganciclovir 0.15% gel rather than ganciclovir 0.05% gel were tabulated for comparison to topical acyclovir since ganciclovir 0.15% is the commercially available concentration. Multi-arm studies comparing more than two interventions were recombined into appropriate pairs of interventions in the data tables.

Statistical estimation

Direct risk ratio: Tables were constructed of the cumulative number of eyes healed after trial enrolment for each treatment group. Direct comparisons between interventions estimated risk ratios (Deeks 2002) at seven days and at 14 days using a fixed-effect model with the Mantel-Haenszel method.

Indirect risk ratio: In addition to direct comparisons of antiviral agents, indirect comparisons adjusted by way of shared comparators can yield a combined estimate with improved statistical power (Song 2009). To evaluate the network of antiviral treatment trials, indirect risk ratios were performed when different antivirals were directly compared with a mutual antiviral agent (Bucher 1997; Glenny 2005). Using formulae (Wells 2009) implemented in an on-line calculator from the Canadian Agency for Drugs and Technologies in Health, indirect risk ratios and corresponding 95% confidence intervals were computed for these topical antiviral treatment comparisons at 14 days. An adjusted risk

ratio was also estimated, when feasible, by combining the direct and indirect relative treatment effects (Song 2003; Vandermeer 2007). I^2 was used to judge the consistency between direct and adjusted indirect comparisons when estimating a combined relative effect measure.

Hazard ratio: Healing times were estimated for studies reporting outcomes at more than two time points after enrolment by extracting healing and censoring data from reported survival curves and life tables. The observed (O) and the logrank expected (E) numbers of events were used to compute logrank statistics (O-E) and the hypergeometric variance (V) with formulæ (Tierney 2007) implemented in a spreadsheet calculator. Hazard ratios were then pooled with a fixed-effect model to describe the relative therapeutic effect of interventions over time (Parmar 1998).

Healing probability: The cumulative healing probability was estimated by collating patient-level data from a large comparative antiviral treatment trial.

Subgroup analysis and investigation of heterogeneity—Two trials that restricted enrolment to patients with geographic epithelial keratitis were tabulated with other trials but also analysed separately. Other patient characteristics that were identified as possible prognostic factors of corneal epithelial healing time in post hoc analyses of individual trials were recorded.

Sensitivity analysis—Sensitivity analyses assessed the robustness of pooled relative effect measures and explored possible reasons for heterogeneity. In one sensitivity analysis, studies were selectively excluded from the meta-analysis if there was a potentially high risk of bias because of non-random sequence generation, unconcealed allocation, or lack of masking that could have influenced outcome assessment. Studies judged to have an 'unclear' risk of bias were not excluded from this sensitivity analysis. Another sensitivity analysis used only the results of studies with an explicit randomised, double-masked trial design.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

See the Characteristics of included studies and Characteristics of excluded studies tables for a summary of 203 studies that evaluated the comparative effectiveness of interventions for HSV epithelial keratitis, omitting one unpublished antiviral treatment trial (Characteristics of studies awaiting classification). Eighty-eight included studies that used a topical antiviral agent in at least one treatment arm were reviewed for antiviral safety.

Results of the search—The electronic and manual searches identified a total of 1535 clinical reports of therapeutic studies of HSV keratitis. After all reports were reviewed, 203 comparative clinical trials were identified that compared two or more interventions in the

treatment of 14,159 eyes with acute HSV epithelial keratitis (Figure 1). These trials were described in 262 primary and auxiliary published reports that were assessed for inclusion or exclusion in this systematic review. One hundred and fifty-two trials were found to be eligible for analysis, but 46 studies did not provide sufficient outcome data to compute risk ratios at seven days or 14 days. Thus, 106 trials published in 99 different primary reports and published between 1963 and 2009 were retained for data analysis (Characteristics of included studies).

An update search was done in October 2010 which yielded a further 114 reports of studies. We screened the titles and abstracts, but none of the references met the inclusion criteria for the review.

Included studies

Interventions: Trials varied in design characteristics (Table 1), and the investigators studied various pharmacological and non-pharmacological interventions. The number of included studies ranged from one to 11 studies for each of the different antiviral treatment comparisons; from one to nine studies for the interferon treatment categories; from one to 11 studies for different comparisons of débridement methods; and single trials of four adjunctive agents. Eighty-five trials compared two interventions or an intervention and a control; 16 trials compared three interventions; four trials compared four interventions; and one trial compared five interventions. The 106 studies of 130 two-way comparisons were divided into 36 treatment comparisons that were collated among four groups: 70 studies were included in 17 two-way comparisons of topical antivirals; four studies were used for two comparisons of oral antiviral treatment; 22 studies were used for seven interferon comparisons; 30 studies were used for six comparisons of corneal epithelial débridement; and four studies examined four miscellaneous drugs.

Ancillary medications: Use of a cycloplegic agent was reported in 41 trials (atropine in 19, scopolamine in six, homatropine in five, and a non-specified mydriatic or cycloplegic agent in 11). Ten trials reported using a concomitant topical antibiotic.

Sample sizes: A total of 5872 eyes with HSV epithelial keratitis were enrolled and analysed in the 106 trials included for analysis in this systematic review. The minimum number of enrolled participants in a trial was 15 and the maximum was 287. The median number of infected eyes per study was 44 (interquartile range, 32 to 64). Study sizes were positively skewed toward smaller trials: 56 trials enrolled fewer than 50 participants; 38 trials enrolled 50 to 99 participants; 11 trials enrolled 100 to 200 participants; and one trial enrolled more than 200 participants. None of the studies reported a pretrial sample size estimation based on a priori assumptions, although one trial did report a statistical computation that was used to plan enrolment based on recurrence risk rather than epithelial healing (HEDS Group 1997).

Study participants: Of 45 trials that provided data to enable estimation of the average age of enrolled participants, the median of the average patient age was 46 years (interquartile range, 41 to 48 years). Of 50 trials reporting the gender of study participants, of which 47

trials enrolled more males than females, the median male-female ratio was 1.7 (interquartile range, 1.3 to 2.2).

Setting: Seventy trials included in this review took place in Europe, 12 in North America (including one performed in the United States and the United Kingdom), 22 in Asia, one in Africa, and one in Australia. Ninety trials included in this review took place at a single centre. Multicentred trials involved between two and 60 sites and averaged significantly more enrolled patients than single-centred trials ($P = 0.0002$, t-test). The primary report for 77 trials was published in the English language.

Type of epithelial keratitis: Sixty-three trials enrolled patients with dendritic epithelial keratitis, including two trials that may have also enrolled other types of HSV epithelial keratitis (Chen 2008; Yang 2000); 38 trials enrolled participants with either dendritic or geographic epithelial keratitis (Blake 1977; Carmassi 1993; Colin 1981; Colin 1984; Colin 1997a; Colin 1997b; Colin 2007a; Colin 2007b; Coster 1976; Coster 1980; Daniel 1972; de Koning 1983; Denis 1983; Fulhorst 1972; Genée 1987; Guerra 1979; Haut 1983; Hoang-Xuan 1984; Huang 2008a; Jackson 1984; Kitano 1985; Laibson 1964; Li 2008; Markham 1977; Maychuk 1988; McCulley 1982; McGill 1974; Patterson 1967a; Pavan-Langston 1976; Pavan-Langston 1981; Serifoglu 1987; Sugar 1980; Sundmacher 1984a; Van Bijsterveld 1989; Wellings 1972; Yeakley 1981; Young 1982); two trials were restricted to patients with geographic keratitis (Collum 1985; Coster 1979); and three trials provided insufficient information to ensure that all participants had dendritic epithelial keratitis (Burns 1963; Davidson 1964; Klauber 1982). Of studies that enrolled eyes with either dendritic or geographic epithelial keratitis, 24 trials provided information on the numbers with dendritic epithelial keratitis (1469) and with geographic epithelial keratitis (326), yielding a median dendritic to geographic epithelial keratitis ratio of 5.0:1 (interquartile range, 3.5:1 to 9.5:1).

Laboratory confirmation: Viral isolation was performed in 34 included trials. Five trials enrolled only HSV culture-confirmed eyes (Colin 1983; Meurs 1985; Sundmacher 1981a; Sundmacher 1981b; Sundmacher 1984a) and did not report the total number of screened individuals. Four trials performed HSV isolation but did not report the results (Bartholomew 1977; Hoang-Xuan 1984; Luntz 1963; Van Bijsterveld 1989). Of 25 trials that reported the prevalence of 759 positive viral culture results (including one trial that reported viral culture and immunofluorescent test results) among 1148 eyes tested at trial entry, the median prevalence of study participants who had laboratory-confirmed HSV ocular infection from corneal or conjunctival samples was 68% (interquartile range, 50% to 78%). HSV-2 was rarely isolated (Vannini 1986). None determined whether diagnostic eye drops curtailed viral recovery (Roat 1987; Seitzman 2006).

Outcome evaluation: The healing outcome was judged by biomicroscopic observation in all trials. The day of healing was taken as the time to initial re-epithelialisation of the corneal surface; if a topical dye was used then the day of healing was the first day when no confluent staining was observed. Sixty-five trials used fluorescein staining to assess corneal epithelial status; eight trials used rose-Bengal staining; and 11 trials used both fluorescein

and rose-Bengal stains. Twenty-two trials assessed the outcome without specifying the method of judging epithelial healing. One trial examined different stages of corneal epithelial regeneration during re-establishment of a normal corneal surface (Norn 1973).

The median time to healing of dendritic epithelial keratitis with trifluridine, acyclovir, brivudine, or ganciclovir was seven days. The median time to healing in both trials of geographic epithelial keratitis was nine days (Collum 1985; Coster 1979). Among parametric statistical models, the healing curve of one large antiviral treatment trial (HEDS Group 1997) was suitably fitted to a log-logistic distribution (Wilhelmus 2000), and the cumulative probability of corneal epithelial healing time (t) of dendritic epithelial keratitis during antiviral chemotherapy could be estimated by $[(7/t)^4 + 1]^{-1}$. Based on 49 trials that published survival graphs, the maximum separation of healing curves for different treatments occurred at a median of six days.

Excluded studies—Ninety-seven comparative treatment trials of acute HSV epithelial keratitis were excluded from the analysis (Characteristics of excluded studies). The four reasons for excluding studies on the basis of study design were non-concurrent treatment allocation (23 trials), use of an ethnobotanical preparation (21 trials), varied eligibility criteria (four trials), and the outcome not based on epithelial healing (three trials). In addition, 46 trials were not included because of insufficient outcome data at seven and 14 days. Apart from one study that did not report the sample size (Kuyama 1979), a total of 8287 participants with HSV epithelial keratitis were enrolled in these studies. Sample sizes of excluded trials ranged from nine to 416 participants, with a median sample size of 67 (interquartile range, 39 to 114) participants.

Risk of bias in included studies

Potential biases affected several studies (Figure 2). The statistical analysis of individual studies, when reported, sought to detect a statistically significant difference in corneal epithelial healing with resolution of active epithelial keratitis, although one study provided a post hoc non-inferiority analysis (Colin 2007b).

Allocation—Among 106 included trials, 70 explicitly stated that a randomisation process was used to allocate study interventions, and 30 did not clearly describe the randomisation method. While authenticating proper randomisation was problematic for some studies (Wu 2009), six were judged to have inadequate or incomplete randomisation: three allocated study treatment to alternate patients (Daniel 1972; Luntz 1963) or to alternate groups (Srinivas 1993) and three apparently allocated treatment by availability (Abe 1987; Altinisik 1987; Kato 1979). Forty-six trials documented adequate concealment of allocation, including 39 of the 70 randomised trials. Seven trials used a non-random sequence generation procedure. Three trials that enrolled participants with bilateral keratitis apparently randomised eyes rather than participants (Laibson 1964; Liu 2009a; Luntz 1963).

Blinding—Fifty-eight trials had a double-masked study design, including two trials that used a different outcome assessor than the investigator who allocated treatment or participated in other aspects of patient care (Parlato 1985; Sundmacher 1978a). Twenty-two

trials had an unclear masking scheme, and 26 trials used an unmasked design. English-language reports were more likely to be double-masked ($P = 0.005$, χ^2 test).

Incomplete outcome data—Attrition bias was minimal since the primary endpoint occurred within two weeks of enrolment. Eighty trials adequately addressed outcome data within the first two weeks of follow up. Eleven trials had incomplete outcome data. One trial reported that patients who did not return for follow up were excluded from the analysis (Collum 1985).

Selective reporting

Excluded studies: Forty-six of 97 excluded studies were not included because data on cumulative healing proportions at one or two weeks of study treatment were not reported (Table 2). Of these 46 excluded studies, 30 studies reported mean healing times of treatment groups, 11 other studies reported a P value for comparative treatment effectiveness over a period other than seven or 14 days, and five studies provided neither outcome analysis. Despite attempts to obtain unpublished data, not including otherwise eligible trials could lead to an outcome reporting bias that affected the robustness and generalisability of the results.

Publication bias: Three antiviral treatment comparisons had enough studies to assess possible publication bias by funnel plots. No obvious publication bias was found for the idoxuridine-placebo comparison (Figure 3). Potential publication bias may have existed for the acyclovir-idoxuridine comparison at seven days, but no serious publication bias was apparent for the 14-day outcome (Figure 4). Publication bias for both the seven and 14-day outcomes was possible for the ganciclovir-acyclovir comparison (Figure 5). The asymmetric distribution suggests a bias toward publication of studies favouring ganciclovir over acyclovir.

Other potential sources of bias—Four studies were judged to have other potential sources of bias. Two trials were stopped early (Behrens-Baumann 1992; O'Day 1975). Two trials added supplemental treatment during follow up: additional débridement in one trial (Sundmacher 1978a) and a corticosteroid eye drop in another trial (Luntz 1963).

Investigation of heterogeneity: Substantial heterogeneity ($I^2 > 50\%$) was found for 10 of 42 different treatment comparisons at the seven-day outcome assessment of risk ratios, eight of 36 pooled risk ratios at the 14-day outcome assessment of risk ratios, and five of 11 pooled comparisons for hazard ratios. Three of the eight treatment comparisons having substantial heterogeneity at 14 days also showed heterogeneous findings at seven days (Table 3). Possible treatment-related reasons for inconsistency among studies were differences in antiviral or interferon dosages or formulations and varied methods used to perform corneal débridement.

Sensitivity analysis: Thirty trials had an inadequate randomisation process, unconcealed allocation, or incomplete masking. After selectively excluding these studies from direct treatment comparisons, precision declined but relative effect measures did not substantially

shift (Table 4). The pooled results of 46 randomised, double-masked trials were generally comparable to those of all included studies (Table 5).

Effects of interventions

See: Summary of findings for the main comparison Summary of findings: relative healing rate for selected antiviral agents and combination interventions; Summary of findings 2 Summary of findings: relative healing outcome with topical antiviral therapy; Summary of findings 3 Summary of findings: relative healing outcome with oral antiviral therapy; Summary of findings 4 Summary of findings: relative healing outcome with topical interferon; Summary of findings 5 Summary of findings: relative healing outcome with débridement methods.

Interventions were considered in four categories: antiviral agents, interferon, methods of corneal epithelial débridement, and adjunctive drugs. The primary treatment effect was assessed by a risk ratio at 14 days, which was adjusted by available indirect risk ratios for antiviral treatment comparisons. The relative pace of healing was examined by a risk ratio at seven days and by a hazard ratio.

Topical antiviral therapy—Seventy trials compared topical agents in 17 treatment comparison categories (Data and analyses). Fifty-two trials evaluated head-to-head comparisons of six topical nucleoside antivirals (idoxuridine, vidarabine, trifluridine, acyclovir, brivudine, or ganciclovir) or inactive control (Figure 6). Topical antivirals were also evaluated in trials of interferon and débridement methods (Figure 7).

Idoxuridine and vidarabine: Idoxuridine was not demonstrated to be significantly different than inactive control at 14 days (Analysis 1.1); however, only one randomised trial provided the healing outcome at 14 days. Idoxuridine did appear to be significantly better than placebo at seven days and in the rate of healing (Analysis 1.2). Vidarabine was significantly better than inactive control at 14 days in one trial (Analysis 1.3; Analysis 1.4). While direct comparisons of vidarabine to idoxuridine did not show a significant advantage in the healing outcome (Analysis 1.5) or healing rate (Analysis 1.6) among included studies or in an excluded study (Pavan-Langston 1972), a combined direct and adjusted indirect comparison using studies in which vidarabine and idoxuridine were compared to a mutual antiviral indicated that vidarabine had better therapeutic effectiveness than idoxuridine (Table 6). Additionally, para-fluorophenylalanine, an amino acid analogue having antiviral activity, was relatively similar in effectiveness to idoxuridine in included studies (Analysis 1.7) and in an excluded study (Pietruschka 1968).

Trifluridine, acyclovir, brivudine, and ganciclovir: Compared to idoxuridine, trifluridine (Analysis 1.8; Analysis 1.9), acyclovir (Analysis 1.10; Analysis 1.11), and brivudine (Analysis 1.12) appeared significantly better although the acyclovir-idoxuridine comparison had high heterogeneity and possible bias toward publication of trials that showed faster healing with acyclovir. Excluded studies also generally showed that trifluridine (Assetto 1981; Pavan-Langston 1977) and acyclovir (Babushkin 1993; Inocencio 1982) were better

than idoxuridine. One trial compared acyclovir to iododeoxycytidine (Analysis 1.10). An indirect comparison indicated that ganciclovir was better than idoxuridine (Table 6).

Trifluridine (Analysis 1.13; Analysis 1.14) and acyclovir (Analysis 1.15; Analysis 1.16) while not demonstrated to be significantly different than vidarabine in direct comparisons were significantly more effective than vidarabine in adjusted analyses (Table 6) and among excluded studies (McGill 1981; Mohan 1987). Eyes treated with trifluridine or acyclovir also healed faster than with vidarabine; however, pooling in these analyses was limited by heterogeneity of the trifluridine-vidarabine comparison.

Neither acyclovir (Analysis 1.17; Analysis 1.18) nor brivudine (Analysis 1.19; Analysis 1.20) was significantly different than trifluridine (Table 6). Brivudine appeared similar to acyclovir (Analysis 1.21). Healing curves suggested that trifluridine and acyclovir provided more expeditious healing than either vidarabine or idoxuridine (Figure 8).

Ganciclovir was suggested to result in a better outcome than acyclovir in some trials and in an excluded study (Wang 2009); however, pooled trials showed similar proportions for healing at seven days. Furthermore, the ganciclovir-acyclovir comparison was limited by heterogeneity among included studies (Analysis 1.22) and by a suspected publication bias for studies favouring ganciclovir (Figure 5).

Foscarnet and cidofovir: Foscarnet (phosphonoformic acid, PFA) was similar to trifluridine in one trial (Analysis 1.23). The clinical effectiveness of cidofovir (hydroxyphosphonylmethoxypropylcytosine, HPMPC) in the treatment of dendritic epithelial keratitis has not yet been reported (Anonymous 2003).

Antiviral combination: The combination of topical acyclovir and vidarabine was not significantly different at 14 days than acyclovir alone in one trial but appeared to accelerate healing (Analysis 1.24).

Formulation of topical antivirals: Few studies of topical antiviral agents compared different vehicles (Analysis 1.25) or concentrations (Analysis 1.26). Except for the non-inclusion of ganciclovir 0.05% gel, studies comparing topical nucleoside antiviral agents were pooled without consideration of different formulations or dosages.

Safety of topical antivirals: Of 88 studies that had a topical antiviral treatment arm, 40 studies reported the occurrence of any ocular adverse reactions attributable to the topical medication. Treatment-related effects that were reported in trials included in this review were stinging upon instillation, allergic blepharoconjunctivitis, toxo-allergic follicular conjunctivitis, and superficial keratopathy. The median percentage of eyes that developed superficial keratopathy or punctate epithelial erosions in these antiviral treatment trials was 10% with idoxuridine, 11% with vidarabine, 4% with trifluridine, 10% with acyclovir, none with brivudine, and 4% with ganciclovir (Table 7).

Oral antiviral therapy—The comparison of oral antiviral to topical antiviral therapy (Analysis 2.1) and the comparison of combined oral and topical antiviral to topical antiviral therapy alone (Analysis 2.2) were limited by heterogeneity among few trials (Table 3).

Interferon therapy

Interferon monotherapy: Topical interferon therapy appeared significantly better than inactive control (Analysis 3.1). Higher interferon concentrations were generally more effective than lower concentrations (below 1 million IU/ml) but a dose-response relationship for progressively increasing interferon dosages could not be clearly demonstrated in included studies (Analysis 3.2) or by an excluded study (Shiota 1988). Few included or excluded studies (Kuyama 1979; Zhang 2003) compared different interferon formulations or types. Leukocyte-derived interferon- α and fibroblast-derived interferon- β appeared relatively similar (Analysis 3.3). Recombinant interferon was not significantly different from naturally-derived interferon (Analysis 3.4).

The comparison of topical interferon to a topical nucleoside antiviral agent (Analysis 3.5) was limited by heterogeneity among included studies (Table 3) and by insufficient outcome data among excluded studies (Jin 1992; Scialdone 1986; Tamburi 1990). A topical interferon inducer did not compare favourably with a topical antiviral agent in a single included study (Analysis 3.6) but had apparent clinical activity in excluded studies (Galin 1976; Kasparov 1972; Kasparov 1974; Kasparov 1991; Lin 2009).

Interferon-antiviral combination therapy: Studies of combined interferon and antiviral agents had inconsistent results, possibly because the concentration of interferon varied among the trials. Despite heterogeneity, the combination of interferon and an antiviral agent was not significantly better than antiviral monotherapy at 14 days (Analysis 3.7) but provided earlier and significantly faster healing (Analysis 3.8) throughout treatment in included studies (Figure 9) and, except for one report (Tamburi 1990), in several excluded studies (Chen 2007; Gu 2005; Huang 2009; Liu 2003; Zhao 2001; Zhou 2008).

Débridement

Methods of corneal débridement: Few studies compared physicochemical débridement to control treatments (Analysis 4.1). Débridement trials used various methods of curettage and cauterization for corneal epithelial removal. The comparison of débridement to topical antiviral therapy was limited by heterogeneity among included studies (Analysis 4.2) and by inconsistency among excluded studies (Patterson 1967c; Tarakji 1978; Whitcher 1976). These divergent results may be due to the irregular extent of physicochemical de-epithelialisation: wiping and swabbing selectively removed loosened, infected epithelial cells along the dendrite while thermomechanical scraping, cryotherapy, and chemical abrasion often ablated a larger area of epithelium. Also, recrudescence of epithelial keratitis occurred in some débridement-treated eyes, constraining a single use of this intervention alone. One study suggested that different methods of debriding the corneal epithelium produced similar rates of subsequent re-epithelialisation (Analysis 4.3). However, when combined with idoxuridine, one included study found that corneal epithelial healing

occurred faster after cryotherapy than after carbolicization (Fulhorst 1972); and one excluded study suggested that iodination allowed faster healing than cryotherapy (Hilsdorf 1969).

Débridement and antiviral chemotherapy: The possible benefit of physicochemical débridement followed by an antiviral agent compared to débridement alone was limited by heterogeneity among included studies (Analysis 4.4) and few excluded studies (Mathur 1984). One trial comparing acyclovir with débridement to idoxuridine with débridement did not show a significant difference in the proportion of participants healed at seven or 14 days (Analysis 4.5). Combined débridement-antiviral treatment was not significantly more effective than antiviral treatment alone at 14 days (Analysis 4.6) but possibly provided faster healing than antiviral monotherapy, although pooling was restrained by inconsistent results (Analysis 4.7). Eyes receiving antiviral monotherapy in these studies healed more slowly than those reported in other antiviral trials. Among excluded studies one trial found that the combination of débridement and an antiviral healed more quickly, on average, than antiviral treatment alone (Koev 2007); but other studies found little difference in average healing time (Fellinger 1980; Guo 2003; Shimomura 1987).

Supplemental agents—The combination of epidermal growth factor with an antiviral did not significantly enhance an antiviral agent's effect on corneal epithelial healing in one trial (Analysis 5.1). Topical panthenol, a precursor to pantothenic acid which can promote epithelial wound healing, was not significantly different from para-fluorophenylalanine in one trial (Analysis 5.2). The addition of the non-steroidal anti-inflammatory agent oxyphenbutazone to idoxuridine treatment did not differ from treatment with idoxuridine alone in one trial (Analysis 5.3). Isoprinosine, an immune modulator, did not significantly affect the natural history of acute HSV epithelial keratitis in one included study (Analysis 5.4) or in an excluded study (Prost 1986).

DISCUSSION

HSV infection is a prevalent and potentially damaging eye disease that inflicts personal distress and socioeconomic costs. Appropriate treatment alleviates symptoms, enables corneal healing, and allows visual recovery.

Summary of main results

Nucleoside antiviral therapy—Based on the healing outcome at 14 days, placebo-controlled studies were either inconsistent for idoxuridine or few in number for vidarabine. However, both idoxuridine and vidarabine appeared to provide faster healing of HSV epithelial keratitis than inactive controls (Summary of findings for the main comparison). Other nucleoside analogues such as trifluridine and acyclovir were more effective than idoxuridine, significantly increasing the relative number of successfully healed eyes at 14 days.

An interconnected web of antiviral treatment trials resulted from the availability of several antiviral agents. Analysis of this network of studies indicated that trifluridine, acyclovir, and brivudine had relatively similar effectiveness in acute treatment (Summary of findings 2). Ganciclovir was at least as effective as acyclovir. Whether the addition of a second antiviral,

either topical or oral, accelerated epithelial healing is unclear. Additional data would help to adequately assess the beneficial effects of oral antiviral therapy, used either adjunctively or alone, for treating dendritic epithelial keratitis (Summary of findings 3). The evaluation of topical foscarnet also needs further study. The role of cidofovir remains to be reported.

Adverse effects of ocular allergy and toxicity were relatively infrequent. A majority of studies found superficial keratopathy in 10% or fewer of treated eyes. While differing in topical ophthalmic formulation, trifluridine, acyclovir, brivudine, and ganciclovir did not differ greatly in safety and had analogous therapeutic profiles during acute therapy.

Interferon therapy—Interferon at a sufficient concentration has antiviral activity against HSV-infected epithelial cells. Interferon, used either alone or in combination with débridement (Cantell 1995; Sundmacher 1982; Sundmacher 1984b), appears as effective as a nucleoside antiviral agent. Combined interferon-nucleoside therapy does not differ from antiviral monotherapy at two weeks of treatment, but the combination of interferon and a nucleoside antiviral agent may enable faster healing (Summary of findings 4).

Débridement—Clinical trials of corneal epithelial removal formerly involved the application of noxious solutions such as tincture of iodine (Austin 1974; Davidson 1964; Graupner 1969; Matthäus 1970; Struck 1989) or phenol (Fulhorst 1972; MacKenzie 1964; Patterson 1967a; Patterson 1967b), often in combination with mechanical scraping. Other methods of corneal débridement include cryoapplication (Fulhorst 1972; Struck 1989), photoinactivation (Bartholomew 1977; Daniel 1972; O'Day 1975), and thermocautery (Sundmacher 1976a; Sundmacher 1976b; Sundmacher 1978a; Sundmacher 1978b). The introduction of minimal wiping débridement (Whitcher 1976) offered a simpler procedure that became widely used (Altinisk 1987; Coster 1977a; Hung 1984; Jensen 1982; Kato 1979; Parlato 1985; Richter 1986; Serifoglu 1987; Uchida 1981; Wilhelmus 1981a; Yamazaki 1984a). Despite its popularity, studies of physicochemical débridement alone were relatively few and inconsistent. The effect of patching after débridement was not systematically evaluated in most trials but could have affected the epithelial healing rate (Turner 2006) or raised the normal corneal temperature, of 34° C, to hinder HSV replication (Wheeler 1959). Shortcomings of débridement are the risk of damaging Bowman's layer and potential enhancement of corneal inflammation or scarring (Coster 1977b). Moreover, HSV persists and is shed for several days after débridement (Sundmacher 1976a; Sundmacher 1976b), contributing to the occurrence of recrudescence epithelial keratitis (Coster 1977b). While an antiviral agent or interferon following débridement averts recrudescence, any healing advantage of combined débridement and antiviral treatment is uncertain because of heterogeneity among trials on relative healing rates and a lack of a significant difference at the two-week outcome (Summary of findings 5).

Adjunctive agents—Trials that evaluated the addition of a cytokine growth factor or a nonsteroidal anti-inflammatory drug to topical antiviral therapy did not provide convincing evidence of the effectiveness of either agent. The role of other immunomodulators is uncertain.

Overall completeness and applicability of evidence

This systematic review aimed to examine the treatment of acute HSV epithelial keratitis. The literature was systematically searched for all relevant comparative clinical trials using electronic databases, handsearching, and personal contact. From a total of 203 trials that enrolled approximately 14,159 eyes with HSV epithelial keratitis, 152 trials were potentially eligible for analysis based on study design. However, 46 of these studies did not provide sufficient data to extract proportions for 14-day healing. Thus, 106 studies of 5872 eyes were included for analysis in this review, with excluded studies used for corroboration.

Clinical trial publications included in this review peaked during the 1980s (Figure 10), an era of antiviral discovery and investigation (Gordon 2000). In comparison, the number of excluded studies slowly rose over time with an upsurge in the early 21st century of trials that studied new antivirals and traditional Chinese medicines (Figure 11).

Healing responses to treatment may be affected by host susceptibility, the degree of ocular inflammation, and viral resistance. Several trials addressed one or more of these subgroups by evaluating participant history, corneal severity, and viral recovery.

Participant demographics and health history

Gender and age: Men outnumbered women in most of the trials that reported the gender of study participants. Some, but not all, study reports suggested that males are more likely to be diagnosed and treated for HSV epithelial keratitis (Gundersen 1936; HEDS Group 1997; Wilhelmus 1981b). Females are under-represented in clinical trials of chemotherapy (Van Spall 2007), and women of child-bearing potential may have been selectively excluded from ophthalmic antiviral treatment trials because of an unproven concern of teratogenicity during pregnancy (Chung 2004; Itoi 1975; Pasternak 2010). Neither gender nor age influences corneal healing during antiviral therapy (de Koning 1982; de Koning 1983; Jackson 1984; McCulley 1982; Van Bijsterveld 1980; Van Bijsterveld 1989).

Immune status: Medical conditions may modulate epithelial regeneration during HSV infection. Diabetes (Kaiserman 2005), atopy (Rezende 2006), and immunosuppression are suggested to result in slower resolution. Health status was not considered in the studies included in this review.

Previous herpetic eye disease and treatment: Neither the number of previous episodes nor the duration of symptoms prior to initiating antiviral treatment affected healing rate in most studies that evaluated these preceding factors (Blake 1977; Høvdning 1989; Jensen 1982; La Lau 1982; McCulley 1982; Pavan-Langston 1981; Sugar 1980; Van Bijsterveld 1989; Yeakley 1981). The prior use of antiviral agents did not affect relative treatment response (Jensen 1982; McCulley 1982). Neither did the recent use of corticosteroids (McCulley 1982; Pavan-Langston 1981; Sugar 1980; Yeakley 1981).

Ocular severity

Size of epithelial keratitis: The area of a corneal epithelial defect affects the pace of healing (Chung 1998); larger areas of HSV epithelial keratitis re-epithelialize at a greater

rate than smaller lesions (Jackson 1984; Sugar 1980; Wellings 1972). Even so, a longer or wider HSV epithelial keratitis still takes longer to heal (Altinisik 1987; Blake 1977; Jackson 1984; Wellings 1972; Wilhelmus 1981a; Young 1982). But while geographic epithelial keratitis resolves more slowly than dendritic epithelial keratitis (Blake 1977; Coster 1976; Jackson 1984), relative treatment effectiveness between antivirals is not necessarily affected by lesion size (Colin 2007b).

Geographic epithelial keratitis is less prevalent than dendritic keratitis. In epidemiological studies geographic epithelial keratitis accounts for 5% to 15% of HSV epithelial keratitis (Labetoulle 2005; Liesegang 1989a; Pramod 1999). In trials enrolling both forms of epithelial keratitis, geographic epithelial keratitis was five times less common than dendritic epithelial keratitis. Based on two trials restricted to geographic epithelial keratitis (Collum 1985; Coster 1979), the two-week healing outcome was better with trifluridine compared to vidarabine but was not significantly different between acyclovir and vidarabine. It is unclear that trials restricted to geographic epithelial keratitis offer a more stringent test of relative antiviral effectiveness that is generalizable.

Corneal stromal inflammation: Corneal characteristics of HSV epithelial keratitis that may be associated with prolonged healing include a peripheral corneal location (Wilhelmus 1981a) and the presence of stromal inflammation (Altinisik 1987; Daniel 1972; Klauber 1982; Wilhelmus 1981a), possibly due to an inhibitory effect of inflammatory cells on corneal epithelial wound healing (Wagoner 1984). However, other studies did not demonstrate that the presence of stromal keratitis had a consistent impact on healing (Høvdning 1989; Jackson 1984). Further studies that stratify outcome information by corneal characteristics may allow meta-regression of potential prognostic factors.

Complications slowing re-epithelialisation: Corneal epithelial wound-healing follows a distribution function (Callaghan 2006) similar to the logistic healing curve of HSV epithelial keratitis. Toxicity from topically applied antiviral medications can delay epithelial regeneration (Lass 1984). Ocular disorders that slow healing of the ocular surface, such as the occurrence of secondary microbial infection during active herpetic epithelial keratitis, are rarely encountered (Boisjoly 1983; Wilhelmus 1982).

Virology and antiviral susceptibility

Viral infection: Several methods are available to detect herpes simplex virus in specimens from the ocular surface (Satpathy 2011). One third of studies included in this review undertook viral isolation, including five studies that required viral confirmation before randomisation. The sensitivity of HSV recovery from the ocular surface was 68% at trial entry. One study reported that viral culture positivity did not affect healing (McCulley 1982). Antiviral therapy usually eliminated HSV from the ocular surface within the first few days of therapy (Sundmacher 1984a; Sundmacher 1985), although HSV could sometimes be recovered up to 10 days after beginning antiviral therapy (Colin 1997a). HSV strains may differ in pathogenicity (Brandt 2005), but how virulence genes affect the clinical phenotype and outcome of herpetic epithelial keratitis remains to be determined.

Antiviral resistance: Genetic mutations of herpes simplex virus can confer resistance to antiviral agents (Duan 2008; Duan 2009). Strains of herpes simplex virus that are not readily susceptible to acyclovir and other antivirals are becoming more prevalent, particularly among immunocompromised patients and during intermittent antiviral therapy (Zhang 2007). Virological resistance is one of the reasons for therapeutic unresponsiveness in suspected herpetic keratitis, a dilemma that may lead to the selection of an alternative antiviral (Hlinomazová 2010). If resistant ocular HSV strains continue to emerge (Choong 2010; Hlinomazová 2010) the applicability of this review may need to be modified.

Quality of the evidence

This systematic review provides a critical, quantitative overview of previous clinical research. Data were extracted from journal articles and other sources to estimate relative effect measures of corneal healing for different interventions. Healing curves have been used for many years in treatment trials of HSV epithelial keratitis (Graupner 1968; Wellings 1972) as well as nonparametric statistics and survival analysis (Coster 1976; Coster 1979). The estimation of cumulative risk for a chosen time interval and the use of hazard functions when participants have variable follow up are used in clinical trials of ophthalmic interventions (Hosmer 2009; Jewell 2009). Yet, these analytical methods are not always applied, and 30% of 152 otherwise potentially eligible studies were not included in this review because of incompletely reported data or statistical shortcomings.

Active comparator trials reporting no significant difference between treatments were not designed to demonstrate equivalence between treatments (Musch 2006) and were often inconclusive because of inadequate sample size. Pooling offers an objective appraisal of therapeutic evidence, although treatment comparisons involved relatively few studies. Indirect comparisons between antiviral drugs were examined if both agents were compared to another commutual intervention, allowing multiple interventions to be evaluated across studies of antiherpetic chemotherapy (Wilhelmus 2000).

Potential biases in the review process

Methodological quality varied among the trials. Randomisation aimed to reduce selection bias but the method of treatment allocation was unclear or irregular in one third of included studies. A lack of masked outcome evaluation was the most common methodological limitation. Sensitivity analyses that excluded studies with a higher risk of bias were confined to the few trials that remained for each treatment comparison. Also, of 152 potentially eligible studies, the non-inclusion of the 46 studies that did not provide sufficient information for estimating 14-day healing rates could have resulted in an outcome reporting bias.

Heterogeneity limited interpretation of selected treatment comparisons. A lack of homogeneity was found for one quarter of the treatment comparisons reporting two-week healing outcomes and for nearly half of the treatment comparisons providing relative healing rates. The diverse treatment dosages and formulations, the various physical and chemical methods of removing corneal epithelium, and the inconsistent use of cycloplegic and other supplemental agents could affect the summary measures of relative therapeutic effect and

limit comparability. While the extrapolation of data from healing curves that did not incorporate censoring can overestimate the actual number of healed eyes and lead to artificially narrow confidence intervals, few patients were lost to follow up during the initial two weeks of observation and therapy. Finally, since only 45% of the topical antiviral treatment trials included in this review reported the incidence of allergic and toxic adverse reactions, the relative safety of antivirals may be imprecise.

Agreements and disagreements with other studies or reviews

An evidence-based review that evaluated 28 randomised, double-masked, controlled, English-language clinical trials (including two trials that were subsets of larger trials) in the acute treatment of HSV epithelial keratitis concluded that either trifluridine or acyclovir is effective for the treatment of HSV epithelial keratitis and that the combination of an antiviral with interferon might offer additional benefit (Guess 2007). Other reviewers have also reasoned that antiviral agents are effective for HSV epithelial keratitis (Barker 2008; Behrens-Baumann 2010; Wei 2008) and recommended that interferon and débridement need further study. The finding that drug-related adverse effects on the ocular surface such as toxic punctate epithelial erosions were infrequent and not serious was corroborated by ophthalmic studies in antiviral pharmacovigilance (Chen 1989; Falcon 1981; Naito 1987). While this study excluded clinical trials of ethnomedicinal products, a review of traditional Chinese medicines in the treatment of herpetic keratitis found variable study quality and inconsistent results among 29 comparative trials of botanical and herbal preparations (Ma 2006b). The role of oral acyclovir in treating herpetic eye disease is consistent with the findings of evidence-based reviews on the episodic dosing of oral antivirals for labial or genital herpes (Cernik 2008).

This review focused on corneal healing during the acute treatment of HSV epithelial keratitis and did not examine the role of antiviral agents or other interventions in the management of HSV stromal keratitis or endotheliitis (Knickerbein 2009), the prevention of inflammatory complications, or the risk of future recurrences. Whether débridement reduces consequent HSV stromal keratitis (Maudgal 1979; Wilhelmus 1981b) or enhances corneal opacification (Parlato 1985) remains uncertain. Neither a history of HSV epithelial keratitis (HEDS Group 2001) nor short-term antiviral therapy for dendritic epithelial keratitis (HEDS Group 1997; McGill 1981; Patterson 1963a; Power 1991; Wilhelmus 1981a) alters the risk of recurrent herpetic keratitis. For prevention, chronic antiviral prophylaxis (Jones 1977) and other strategies have been proposed (Kaufman 2002; Luzi 1983). Prolonged use of a topical antiviral (Wilhelmus 1983; Romano 1988) or oral antiviral (bHEDS Group 2000b; Uchoa 2003; Wu 2002; Young 2010) reduces recurrent herpetic eye disease. Though costly (Lairson 2003), suppressive antiviral therapy may be expedient for people who are at increased risk of recurrence in anticipation of a recognized triggering factor, during topical corticosteroid use (Wilhelmus 1996a), or following ocular surgery such as corneal transplantation (Bhatt 2009).

AUTHORS' CONCLUSIONS

Implications for practice

Ophthalmic formulations of trifluridine, acyclovir, and ganciclovir are effective and safe in the acute treatment of HSV epithelial keratitis. The combination of an antiviral with interferon may speed healing and could be suitable for clinically recalcitrant cases. Débridement may be an option if chemotherapeutic drugs must be avoided but is more effective when followed by an antiviral agent.

Implications for research

The design of future clinical trials of HSV epithelial keratitis should incorporate eligibility and baseline criteria, randomised allocation, and masked outcome evaluation. Since most eyes with dendritic epithelial keratitis that are treated with currently available antiviral agents heal relatively rapidly, trialists may consider estimating the sample size based on a noninferiority comparison. Trial reports should provide patient-level data and censoring information through healing curves or tables. The prognostic importance of possible host susceptibility factors on healing could be part of a supplementary analysis. Corneal re-epithelialisation is a key measure of therapeutic efficacy, but ancillary outcomes may include residual corneal opacification, visual acuity, and quality of life. Virological studies will have increasing relevance if optimal therapy is affected by the emergence of viral strains with enhanced resistance or virulence.

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APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Keratitis, Herpetic

#2 MeSH descriptor Keratitis, Dendritic

#3 (herpe* or simplex) near (cornea* or kerati* or dendr* or epithel* or endothel* or stroma* or uveiti* or ocular)

#4 (#1 OR #2 OR #3)

Appendix 2. MEDLINE search strategy used on Ovid

1. randomized controlled trial.pt.
2. (randomised or randomized).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 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).

Appendix 3. EMBASE search strategy used on Ovid

1. exp randomised 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 ocular)).tw.
35. or/33–34
36. 32 and 35

Appendix 4. LILACS search strategy

herpe\$ or simplex and cornea\$ or kerati\$ or dendr\$ or ocular

Appendix 5. ZETOC search strategy

herpe* simplex kerati* random*

herpe* simplex kerati* trial*

Appendix 6. openSIGLE search strategy

((herpe* or simplex) AND (cornea* or kerati* or dendr* or ocular))

Appendix 7. BIOSIS search strategy

Topic=(herpe* or simplex) AND Topic=(cornea* or kerati* or dendr* or ocular) AND
Topic=(random* or trial*)

Appendix 8. metaRegister of Controlled Trials search strategy

herpe* simplex AND keratitis

Appendix 9. ClinicalTrials.gov search strategy

(herpes or simplex) AND (keratitis)

Appendix 10. JICT-EPLUS search strategy

HERPE\$ or SIMPLEX in combination with CORNEA\$ or KERATI\$ or DENDR\$

Appendix 11. CNKI and COAD search strategy

herpes simplex keratitis

DATA AND ANALYSES

Comparison 1. Topical antiviral agents

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Idoxuridine <i>versus</i> inactive control: 7-day & 14-day healing	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healing at 7 days	10	392	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.71, 3.00]
1.2 Healing at 14 days	2	63	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.80, 2.15]
2 Idoxuridine <i>versus</i> inactive control: healing rate	3	95	Hazard Ratio (95% CI)	2.02 [1.16, 3.49]
3 Vidarabine <i>versus</i> inactive control: 7-day & 14-day healing	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Healing at 7 days	1	43	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [0.81, 5.87]
3.2 Healing at 14 days	1	43	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.10, 3.49]
4 Vidarabine <i>versus</i> inactive control: healing rate	1	43	Hazard Ratio (95% CI)	2.47 [1.14, 5.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Vidarabine <i>versus</i> idoxuridine: 7-day & 14-day healing	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Healing at 7 days	3	243	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.85, 1.42]
5.2 Healing at 14 days	3	243	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.18]
6 Vidarabine <i>versus</i> idoxuridine: healing rate	2	74	Hazard Ratio (95% CI)	1.36 [0.81, 2.28]
7 <i>para</i> -Fluorophenylalanine <i>versus</i> idoxuridine: 7-day & 14-day healing	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Healing at 7 days: without débridement	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.59, 1.54]
7.2 Healing at 14 days: without débridement	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.14]
7.3 Healing at 7 days: with débridement	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.87, 1.43]
7.4 Healing at 14 days: with débridement	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.18]
8 Trifluridine <i>versus</i> idoxuridine: 7-day & 14-day healing	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Healing at 7 days	4	223	Risk Ratio (M-H, Fixed, 95% CI)	2.52 [1.74, 3.63]
8.2 Healing at 14 days	5	256	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.19, 1.60]
9 Trifluridine <i>versus</i> idoxuridine: healing rate	1	78	Hazard Ratio (95% CI)	2.29 [1.37, 3.83]
10 Acyclovir <i>versus</i> idoxuridine: 7-day & 14-day healing	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Healing at 7 days: acyclovir <i>vs.</i> idoxuridine	9	468	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.64, 2.34]
10.2 Healing at 14 days: acyclovir <i>vs.</i> idoxuridine	11	606	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.14, 1.32]
10.3 Healing at 7 days: acyclovir <i>vs.</i> iododeoxycytidine	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.76, 2.63]
10.4 Healing at 14 days: acyclovir <i>vs.</i> iododeoxycytidine	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.89, 1.12]
11 Acyclovir <i>versus</i> idoxuridine: healing rate	8	355	Hazard Ratio (95% CI)	2.15 [1.70, 2.72]
12 Brivudine <i>versus</i> idoxuridine: 7-day & 14-day healing	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Healing at 7 days	2	99	Risk Ratio (M-H, Fixed, 95% CI)	7.94 [2.80, 22.53]
12.2 Healing at 14 days	2	99	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.05, 1.81]
13 Trifluridine <i>versus</i> vidarabine: 7-day & 14-day healing	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Healing at 7 days: all groups	4	288	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.91, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Healing at 14 days: all groups	3	188	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.98, 1.22]
13.3 Healing at 7 days: geographic epithelial keratitis	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.55, 3.13]
13.4 Healing at 14 days: geographic epithelial keratitis	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.16, 3.33]
14 Trifluridine <i>versus</i> vidarabine: healing rate	3	188	Hazard Ratio (95% CI)	1.31 [0.96, 1.79]
15 Acyclovir <i>versus</i> vidarabine: 7-day & 14-day healing	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Healing at 7 days: all groups	6	314	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.05, 1.44]
15.2 Healing at 14 days: all groups	7	342	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.00, 1.18]
15.3 Healing at 7 days: geographic epithelial keratitis	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.94, 2.94]
15.4 Healing at 14 days: geographic epithelial keratitis	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.63, 1.14]
16 Acyclovir <i>versus</i> vidarabine: healing rate	5	259	Hazard Ratio (95% CI)	1.13 [0.86, 1.47]
17 Acyclovir <i>versus</i> trifluridine: 7-day & 14-day healing	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Healing at 7 days	4	178	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.20]
17.2 Healing at 14 days	4	178	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.90, 1.09]
18 Acyclovir <i>versus</i> trifluridine: healing rate	3	140	Hazard Ratio (95% CI)	0.92 [0.65, 1.32]
19 Brivudine <i>versus</i> trifluridine: 7-day & 14-day healing	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Healing at 7 days	3	147	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.71, 1.21]
19.2 Healing at 14 days	3	147	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.88, 1.14]
20 Brivudine <i>versus</i> trifluridine: healing rate	1	60	Hazard Ratio (95% CI)	0.60 [0.35, 1.02]
21 Brivudine <i>versus</i> acyclovir: 7-day & 14-day healing	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Healing at 7 days	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.93, 1.51]
21.2 Healing at 14 days	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.92, 1.20]
22 Ganciclovir <i>versus</i> acyclovir: 7-day & 14-day healing	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 Healing at 7 days	5	378	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2 Healing at 14 days	10	672	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.04, 1.23]
23 Foscarnet <i>versus</i> trifluridine: 7-day & 14-day healing	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 Healing at 14 days	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.75, 1.34]
24 Acyclovir/vidarabine <i>versus</i> acyclovir: 7-day & 14-day healing	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 Healing at 7 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [1.01, 2.24]
24.2 Healing at 14 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.89, 1.12]
25 Trifluridine (aqueous) <i>versus</i> trifluridine (viscous)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 Healing at 7 days	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.58, 4.05]
25.2 Healing at 14 days	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.96, 2.41]
26 Ganciclovir 0.15% <i>versus</i> ganciclovir 0.05%	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 Healing at 7 days	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.53, 1.74]
26.2 Healing at 14 days	2	116	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.90, 1.28]

Comparison 2. Oral antiviral agents

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral antiviral <i>versus</i> topical antiviral	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healing at 7 days	2	116	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.13, 2.02]
1.2 Healing at 14 days	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.07]
2 Oral/topical antivirals <i>versus</i> topical antiviral	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Healing at 7 days	1	287	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.95, 1.33]
2.2 Healing at 14 days	2	327	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.99, 1.17]

Comparison 3. Topical interferon formulations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Interferon <i>versus</i> inactive control, without or with débridement	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Healing at 7 days	3	178	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.07, 2.06]
1.2 Healing at 14 days	2	110	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.06, 1.64]
2 Interferon dosages	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Healing at 7 days: interferon 1000 IU/ml vs. interferon 1 million IU/ml	1	68	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.81, 2.60]
2.2 Healing at 7 days: trifluridine + interferon 10 million IU/ml vs. trifluridine + interferon 30 million IU/ml	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.94, 1.17]
2.3 Healing at 7 days: trifluridine + interferon 0.3 or 1.5 million IU/ml vs. trifluridine + interferon 30 million IU/ml	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.90, 1.38]
2.4 Healing at 7 days: trifluridine + interferon 30 million IU/ml vs. trifluridine + interferon 100 million IU/ml	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.18]
3 Interferon- α with débridement <i>versus</i> interferon- β with débridement	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Healing at 7 days	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
4 Natural interferon- α with trifluridine <i>versus</i> recombinant interferon- α with trifluridine	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Healing at 7 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.89, 1.12]
5 Interferon <i>versus</i> nucleoside antiviral	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Healing at 7 days	3	85	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.28]
5.2 Healing at 14 days	3	85	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.01, 1.49]
6 Interferon inducer <i>versus</i> nucleoside antiviral	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Healing at 7 days	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.14, 3.17]
6.2 Healing at 14 days	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.08, 1.05]
7 Interferon/nucleoside antiviral <i>versus</i> nucleoside antiviral: 7-day & 14-day healing	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Healing at 7 days	8	401	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.67, 2.31]
7.2 Healing at 14 days	9	476	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.99, 1.07]
8 Interferon/nucleoside antiviral <i>versus</i> nucleoside antiviral: healing rate	5	229	Hazard Ratio (95% CI)	2.84 [2.13, 3.79]

Comparison 4. Methods of physicochemical débridement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Débridement <i>versus</i> control	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healing at 7 days	2	105	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.82, 2.11]
1.2 Healing at 14 days	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.85, 1.43]
2 Topical antiviral agent <i>versus</i> débridement	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Healing at 7 days	7	372	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
2.2 Healing at 14 days	7	317	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.13]
3 Different débridement methods, with interferon	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Healing at 7 days	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.13]
3.2 Healing at 14 days	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.91, 1.10]
4 Débridement with antiviral or interferon <i>versus</i> débridement	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Healing at 7 days	8	347	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.03, 1.28]
4.2 Healing at 14 days	3	99	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.04, 1.42]
5 Débridement with different antivirals	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Healing at 7 days	1	25	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.80, 2.02]
5.2 Healing at 14 days	1	25	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.86, 1.16]
6 Débridement with antiviral <i>versus</i> antiviral: 7-day & 14-day healing	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Healing at 7 days	7	305	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.07, 1.53]
6.2 Healing at 14 days	6	248	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.95, 1.14]
7 Débridement with antiviral <i>versus</i> antiviral: healing rate	6	248	Hazard Ratio (95% CI)	1.76 [1.32, 2.35]

Comparison 5. Adjunctive agents: growth factors, non-steroidal anti-inflammatory drugs, immunomodulators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acyclovir/epidermal growth factor <i>versus</i> acyclovir	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Healing at 7 days	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.54, 1.86]
1.2 Healing at 14 days	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.91, 1.10]
2 Panthenol <i>versus</i> para-fluorophenylalanine, with débridement	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Healing at 7 days	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.79, 1.14]
2.2 Healing at 14 days	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.88, 1.08]
3 Idoxuridine/oxyphenbutazone <i>versus</i> idoxuridine/placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Healing at 7 days	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.56, 1.11]
4 Oral isoprinosine <i>versus</i> inactive control	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Healing at 7 days	1	26	Risk Ratio (M-H, Fixed, 95% CI)	5.14 [0.72, 36.94]
4.2 Healing at 14 days	1	26	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.74, 2.75]

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 1 Idoxuridine *versus* inactive control: 7-day % 14-day healing

Analysis 1.1.

Comparison 1 Topical antiviral agents, Outcome 1 Idoxuridine versus inactive control: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 2 Idoxuridine *versus* inactive control: healing rate

Analysis 1.2.

Comparison 1 Topical antiviral agents, Outcome 2 Idoxuridine versus inactive control: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 3 Vidarabine *versus* inactive control: 7-day % 14-day healing

Analysis 1.3.

Comparison 1 Topical antiviral agents, Outcome 3 Vidarabine versus inactive control: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 4 Vidarabine *versus* inactive control: healing rate

Analysis 1.4.

Comparison 1 Topical antiviral agents, Outcome 4 Vidarabine versus inactive control: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 5 Vidarabine *versus* idoxuridine: 7-day % 14-day healing

Analysis 1.5.

Comparison 1 Topical antiviral agents, Outcome 5 Vidarabine versus idoxuridine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 6 Vidarabine *versus* idoxuridine: healing rate

Analysis 1.6.
Comparison 1 Topical antiviral agents, Outcome 6 Vidarabine versus idoxuridine: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 7 *para*-Fluorophenylalanine *versus* idoxuridine: 7-day % 14-day healing

Analysis 1.7.

Comparison 1 Topical antiviral agents, Outcome 7 *para*-Fluorophenylalanine versus idoxuridine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 8 Trifluridine *versus* idoxuridine: 7-day % 14-day healing

Analysis 1.8.

Comparison 1 Topical antiviral agents, Outcome 8 Trifluridine versus idoxuridine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 9 Trifluridine *versus* idoxuridine: healing rate

Analysis 1.9.
Comparison 1 Topical antiviral agents, Outcome 9 Trifluridine versus idoxuridine: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 10 Acyclovir *versus* idoxuridine: 7-day % 14-day healing **Analysis 1.10.**

Comparison 1 Topical antiviral agents, Outcome 10 Acyclovir versus idoxuridine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 11 Acyclovir *versus* idoxuridine: healing rate

Analysis 1.11.

Comparison 1 Topical antiviral agents, Outcome 11 Acyclovir versus idoxuridine: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 12 Brivudine *versus* idoxuridine: 7-day % 14-day healing

Analysis 1.12.

Comparison 1 Topical antiviral agents, Outcome 12 Brivudine versus idoxuridine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 13 Trifluridine *versus* vidarabine: 7-day % 14-day healing

Analysis 1.13.

Comparison 1 Topical antiviral agents, Outcome 13 Trifluridine versus vidarabine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 14 Trifluridine *versus* vidarabine: healing rate

Analysis 1.14.
Comparison 1 Topical antiviral agents, Outcome 14 Trifluridine versus vidarabine: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 15 Acyclovir *versus* vidarabine: 7-day % 14-day healing

Analysis 1.15.

Comparison 1 Topical antiviral agents, Outcome 15 Acyclovir versus vidarabine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 16 Acyclovir *versus* vidarabine: healing rate

Analysis 1.16.

Comparison 1 Topical antiviral agents, Outcome 16 Acyclovir versus vidarabine: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 17 Acyclovir *versus* trifluridine: 7-day % 14-day healing

Analysis 1.17.

Comparison 1 Topical antiviral agents, Outcome 17 Acyclovir versus trifluridine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 18 Acyclovir *versus* trifluridine: healing rate

Analysis 1.18.

Comparison 1 Topical antiviral agents, Outcome 18 Acyclovir versus trifluridine: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 19 Brivudine *versus* trifluridine: 7-day % 14-day healing

Analysis 1.19.

Comparison 1 Topical antiviral agents, Outcome 19 Brivudine versus trifluridine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 20 Brivudine *versus* trifluridine: healing rate

Analysis 1.20.

Comparison 1 Topical antiviral agents, Outcome 20 Brivudine versus trifluridine: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 21 Brivudine *versus* acyclovir: 7-day % 14-day healing

Analysis 1.21.

Comparison 1 Topical antiviral agents, Outcome 21 Brivudine versus acyclovir: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 22 Ganciclovir *versus* acyclovir: 7-day % 14-day healing

(1) Data reported for 21 days of treatment

(2) Data reported for 21 days of treatment

(3) Data reported for 21 days of treatment

Analysis 1.22.

Comparison 1 Topical antiviral agents, Outcome 22 Ganciclovir versus acyclovir: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 23 Foscarnet *versus* trifluridine: 7-day % 14-day healing

Analysis 1.23.

Comparison 1 Topical antiviral agents, Outcome 23 Foscarnet versus trifluridine: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 24 Acyclovir/vidarabine *versus* acyclovir: 7-day % 14-day healing

Analysis 1.24.

Comparison 1 Topical antiviral agents, Outcome 24 Acyclovir/vidarabine versus acyclovir: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 25 Trifluridine (aqueous) *versus* trifluridine (viscous)

Analysis 1.25.

Comparison 1 Topical antiviral agents, Outcome 25 Trifluridine (aqueous) versus trifluridine (viscous).

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 1 Topical antiviral agents

Outcome: 26 Ganciclovir 0.15% *versus* ganciclovir 0.05%

Analysis 1.26.

Comparison 1 Topical antiviral agents, Outcome 26 Ganciclovir 0.15% versus ganciclovir 0.05%.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 2 Oral antiviral agents

Outcome: 1 Oral antiviral *versus* topical antiviral

(1) Oral acyclovir *vs* topical acyclovir

(2) Oral acyclovir *vs* topical acyclovir

(3) Oral acyclovir *vs* topical acyclovir

Analysis 2.1.

Comparison 2 Oral antiviral agents, Outcome 1 Oral antiviral versus topical antiviral.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 2 Oral antiviral agents

Outcome: 2 Oral/topical antivirals *versus* topical antiviral

(1) Oral acyclovir + topical trifluridine *vs.* topical trifluridine

(2) Oral acyclovir + topical idoxuridine *vs.* topical idoxuridine

(3) Oral acyclovir + topical trifluridine *vs.* topical trifluridine

Analysis 2.2.

Comparison 2 Oral antiviral agents, Outcome 2 Oral/topical antivirals versus topical antiviral.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 3 Topical interferon formulations

Outcome: 1 Interferon *versus* inactive control, without or with débridement

(1) Interferon- β /d débridement *vs.* d débridement/albumin

(2) Interferon- α *vs.* albumin

(3) Interferon- α (low dose) *vs.* interferon- α (high dose)

(4) Interferon- α *vs.* albumin

(5) Interferon- α (low dose) *vs.* interferon- α (high dose)

Analysis 3.1.

Comparison 3 Topical interferon formulations, Outcome 1 Interferon versus inactive control, without or with débridement.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 3 Topical interferon formulations

Outcome: 2 Interferon dosages

Analysis 3.2.

Comparison 3 Topical interferon formulations, Outcome 2 Interferon dosages.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 3 Topical interferon formulations

Outcome: 3 Interferon- α with d. débridement *versus* interferon- β with d. débridement

Analysis 3.3.

Comparison 3 Topical interferon formulations, Outcome 3 Interferon- α with débridement *versus* interferon- β with débridement.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 3 Topical interferon formulations

Outcome: 4 Natural interferon- α with trifluridine *versus* recombinant interferon- α with trifluridine

Analysis 3.4.

Comparison 3 Topical interferon formulations, Outcome 4 Natural interferon- α with trifluridine *versus* recombinant interferon- α with trifluridine.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 3 Topical interferon formulations

Outcome: 5 Interferon *versus* nucleoside antiviral

(1) Idoxuridine

(2) Idoxuridine

(3) Acyclovir

(4) Idoxuridine

(5) Idoxuridine

(6) Acyclovir

Analysis 3.5.

Comparison 3 Topical interferon formulations, Outcome 5 Interferon versus nucleoside antiviral.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 3 Topical interferon formulations

Outcome: 6 Interferon inducer *versus* nucleoside antiviral

(1) Idoxuridine

(2) Idoxuridine

Analysis 3.6.
Comparison 3 Topical interferon formulations, Outcome 6 Interferon inducer versus nucleoside antiviral.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis
Comparison: 3 Topical interferon formulations
Outcome: 7 Interferon/nucleoside antiviral *versus* nucleoside antiviral: 7-day % 14-day healing

Analysis 3.7.
Comparison 3 Topical interferon formulations, Outcome 7 Interferon/nucleoside antiviral versus nucleoside antiviral: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 3 Topical interferon formulations

Outcome: 8 Interferon/nucleoside antiviral *versus* nucleoside antiviral: healing rate

- (1) Trifluridine; two interferon groups combined
- (2) Trifluridine
- (3) Acyclovir
- (4) Acyclovir
- (5) Acyclovir

Analysis 3.8.
Comparison 3 Topical interferon formulations, Outcome 8 Interferon/nucleoside antiviral versus nucleoside antiviral: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 4 Methods of physicochemical débridement

Outcome: 1 Débridement *versus* control

(1) Débridement *vs.* gamma-globulin

(2) Débridement/placebo or low-dose interferon- α *vs.* low-dose interferon- α

(3) Débridement/placebo or low-dose interferon- α *vs.* low-dose interferon- α

Analysis 4.1.

Comparison 4 Methods of physicochemical débridement, Outcome 1 Débridement versus control.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis
Comparison: 4 Methods of physicochemical débridement
Outcome: 2 Topical antiviral agent versus débridement

- (1) Idoxuridine
- (2) Idoxuridine
- (3) Idoxuridine
- (4) Idoxuridine
- (5) Idoxuridine
- (6) Trifluridine
- (7) Idoxuridine or trifluridine or brivudine
- (8) Idoxuridine
- (9) Idoxuridine
- (10) Idoxuridine
- (11) Idoxuridine
- (12) Idoxuridine
- (13) Trifluridine
- (14) Idoxuridine or trifluridine or brivudine

Analysis 4.2.
Comparison 4 Methods of physicochemical débridement, Outcome 2 Topical antiviral agent versus débridement.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 4 Methods of physicochemical débridement

Outcome: 3 Different débridement methods, with interferon

Analysis 4.3.
Comparison 4 Methods of physicochemical débridement, Outcome 3 Different débridement methods, with interferon.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis
Comparison: 4 Methods of physicochemical d ébridement
Outcome: 4 D ébridement with antiviral or interferon *versus* d ébridement

Analysis 4.4.
Comparison 4 Methods of physicochemical débridement, Outcome 4 Débridement with antiviral or interferon versus débridement.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 4 Methods of physicochemical débridement

Outcome: 5 Débridement with different antivirals

Analysis 4.5.
Comparison 4 Methods of physicochemical débridement, Outcome 5 Débridement with different antivirals.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 4 Methods of physicochemical débridement

Outcome: 6 Débridement with antiviral *versus* antiviral: 7-day & 14-day healing

- (1) Idoxuridine
- (2) Idoxuridine
- (3) Acyclovir
- (4) Acyclovir
- (5) Trifluridine
- (6) Brivudine
- (7) Acyclovir
- (8) Idoxuridine
- (9) Acyclovir
- (10) Acyclovir
- (11) Trifluridine
- (12) Brivudine
- (13) Acyclovir

Analysis 4.6.

Comparison 4 Methods of physicochemical débridement, Outcome 6 Débridement with antiviral versus antiviral: 7-day & 14-day healing.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 4 Methods of physicochemical débridement

Outcome: 7 Débridement with antiviral *versus* antiviral: healing rate

- (1) Idoxuridine
- (2) Idoxuridine
- (3) Acyclovir
- (4) Acyclovir
- (5) Trifluridine
- (6) Acyclovir

Analysis 4.7.
Comparison 4 Methods of physicochemical débridement, Outcome 7 Débridement with antiviral versus antiviral: healing rate.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 5 Adjunctive agents: growth factors, non-steroidal anti-inflammatory drugs, immunomodulators

Outcome: 1 Acyclovir/epidermal growth factor *versus* acyclovir

Analysis 5.1.

Comparison 5 Adjunctive agents: growth factors, non-steroidal anti-inflammatory drugs, immunomodulators, Outcome 1 Acyclovir/epidermal growth factor versus acyclovir.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 5 Adjunctive agents: growth factors, non-steroidal anti-inflammatory drugs, immunomodulators

Outcome: 2 Panthenol *versus para*-fluorophenylalanine, with d bridement

Analysis 5.2.

Comparison 5 Adjunctive agents: growth factors, non-steroidal anti-inflammatory drugs, immunomodulators, Outcome 2 Panthenol versus para-fluorophenylalanine, with débridement.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 5 Adjunctive agents: growth factors, non-steroidal anti-inflammatory drugs, immunomodulators

Outcome: 3 Idoxuridine/oxyphenbutazone *versus* idoxuridine/placebo

Analysis 5.3.

Comparison 5 Adjunctive agents: growth factors, non-steroidal anti-inflammatory drugs, immunomodulators, Outcome 3 Idoxuridine/oxyphenbutazone versus idoxuridine/placebo.

Review: Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis

Comparison: 5 Adjunctive agents: growth factors, non-steroidal anti-inflammatory drugs, immunomodulators

Outcome: 4 Oral isoprinosine *versus* inactive control

Analysis 5.4.

Comparison 5 Adjunctive agents: growth factors, non-steroidal anti-inflammatory drugs, immunomodulators, Outcome 4 Oral isoprinosine versus inactive control.

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Figure 1.
PRISMA flow diagram

Figure 2.

Methodological quality graph: review author's judgements about each methodological quality item presented as percentages across all included studies.

Figure 3.
Funnel plot of idoxuridine versus inactive control

Figure 4.
Funnel plot of acyclovir versus idoxuridine

Figure 5.
Funnel plot of ganciclovir versus acyclovir

Figure 6.

Network of interconnected clinical trials comparing topical antiviral agents in the treatment of HSV epithelial keratitis: The circled numerals are the number of comparative treatment trials included in this systematic review that compared relative corneal healing at 14 days of treatment. Data from these 52 trials that enrolled 1590 eyes with HSV epithelial keratitis were used for direct and adjusted indirect comparisons of topical antiviral agents. Twenty-two head-to-head antiviral treatment comparisons, in 20 reports, were excluded from this systematic review because of methodological or presentation shortcomings, including three idoxuridine-vidarabine trials, three idoxuridine-trifluridine trials, six idoxuridine-acyclovir trials, one vidarabine-trifluridine trial, three vidarabine-acyclovir trials, and six acyclovir-ganciclovir trials. Trials comparing other topical antiviral agents (e.g., foscarnet), antiviral combinations (e.g., acyclovir-vidarabine), formulations, or oral antivirals are not mapped.

Figure 7.

Network of clinical trials comparing antiviral agents, interferon, and débridement in the treatment of HSV epithelial keratitis: The circled numerals are the number of comparative treatment trials included in this systematic review that compared relative corneal healing at 14 days. Trials comparing placebo, different interferon formulations, different débridement methods, different antiviral agents, or interferon inducers are not mapped. The débridement-antiviral combination group comprises the combination of débridement with either a nucleoside antivirals or with interferon.

Figure 8.

Comparative corneal healing rates among placebo, idoxuridine, vidarabine, trifluridine, and acyclovir: overall healing curves estimated from pooled data from 24 studies (Abe 1987; Altinisik 1987; Blake 1977; Colin 1981; Collum 1980; Collum 1985; Coster 1976; Coster 1979; Coster 1980; Denis 1983; Hart 1965; Hoang-Xuan 1984; Høvdning 1989; Jackson 1984; Klauber 1982; Kumar 1987; La Lau 1982; Luntz 1963; Markham 1977; McCulley 1982; Van Bijsterveld 1980; Wellings 1972; Yeakley 1981; Young 1982) that enrolled 1168 participants to evaluate placebo control (44 eyes), idoxuridine (278 eyes), vidarabine (262 eyes), trifluridine (201 eyes), and acyclovir (383 eyes). Compared to the healing rate with idoxuridine, the hazard ratios for healing were 1.36 (95% CI 0.81–2.28) for vidarabine, 2.29 (95% CI 1.37–3.83) for trifluridine, and 2.15 (95% CI 1.70–2.72) for acyclovir among included studies.

Figure 9.

Comparative corneal healing rates between combined antiviral and interferon therapy and antiviral monotherapy: overall healing curves estimated from pooled data from seven studies (Carmassi 1993; Colin 1983; de Koning 1982; de Koning 1983; Meurs 1985; Sundmacher 1981b; Van Bijsterveld 1989) that enrolled 363 participants to evaluate antiviral monotherapy with trifluridine (48) or acyclovir (97) or brivudine (22) in comparison to trifluridine-interferon (75) or acyclovir-interferon (102) or brivudine-interferon (19). The cumulative healing curve of antiviral monotherapy (Antiviral) in these trials differs slightly from that of either acyclovir or trifluridine in other studies ().

Figure 10.
Histogram of publication year: included studies

Figure 11.
Histogram of publication year: excluded studies

Table 1

Overview of trial design and participant characteristics among included studies

Characteristics of trial design and conduct	Categories	No. (%) trials (n=106)
No. centres	One Two or more	90 (85%) 16 (15%)
No. study participants (sample size)	15 to 24 25 to 49 50 to 74 75 to 99 100 or more	11 (10%) 45 (43%) 29 (27%) 9 (9%) 12 (11%)
Average age of study participants	< 40 years 40 to 50 years > 50 years Not stated	9 (9%) 31 (29%) 5 (5%) 61 (57%)
Gender of study participants	Males exceed females Females exceed males Not stated	47 (44%) 3 (3%) 56 (53%)
Type of epithelial keratitis	Dendritic Dendritic or geographic Geographic Not specified	64 (60%) 37 (35%) 2 (2%) 3 (3%)
No. of intervention groups ¹	Two Three Four Five	85 (80%) 16 (15%) 4 (4%) 1 (1%)
Adjunctive mydriatic or cycloplegic agent	Yes None, variable, or not stated	41 (39%) 65 (61%)
Adjunctive antibacterial agent	Yes None or not stated	10 (9%) 96 (91%)
Method of generating allocation sequence	Randomisation Ambiguous method of randomisation By alternation By contingency	70 (66%) 30 (28%) 3 (3%) 3 (3%)
Masking	Double-masked design Single-masked, unmasked, or unclear	58 (55%) 48 (45%)

¹ Of 97 excluded studies, 78 had two intervention groups, eight had three groups, six excluded studies had four groups, two excluded studies had five groups, two excluded studies had six groups, and one excluded study had eight groups. The proportion of studies with more than two interventions was similar in the included and excluded studies ($P = 0.97$, χ^2 test).

Table 2

Outcomes reported in trials excluded due to insufficient healing data

Study	Treatment group (no. eyes) ¹	Mean healing time±SD, days ²
Antiviral agents and/or débridement		
Assetto 1981	Débridement (8) Idoxuridine (16) Cytarabine (16) Trifluridine (8)	3–19 10–18 13–21 6–13
Babushkin 1993	Idoxuridine (60) Acyclovir (24)	NS 5.9±1.2
Fellinger 1980	Idoxuridine (13) Trifluridine (16) Débridement/idoxuridine (13) Débridement/trifluridine (18)	8.1±2.5 5.5±2.5 13.4±9 6.8±4.2
Guo 2003	Antiviral (34) Cryotherapy/antiviral (35)	NS NS
Hilsdorf 1969	Iodination/idoxuridine (20) Cryotherapy/idoxuridine (20)	4.3 14.0
Inocencio 1982	Idoxuridine (9) Acyclovir (14)	10.4 7.0
Koev 2007	Acyclovir (25) Acyclovir/pandavir (24) Débridement/acyclovir/pandavir (26)	9.3±1.2 8.2±1.1 6.2±1.3
Leopold 1965	Idoxuridine (5) Cytarabine (5)	NS NS
Mathur 1984	Iodination (50) Cryotherapy (20) Cryotherapy/autologous serum (24) Débridement (30) Débridement/idoxuridine (30)	11 9 7 9 6
McGill 1981	Vidarabine (29) Acyclovir (28)	6.2±1.8 4.5±2.7
Mohan 1987	Vidarabine (19) Acyclovir (21)	8.3±0.9 6.5±0.6
Patterson 1967c	Débridement (9) Idoxuridine (15)	P<0.01
Pavan-Langston 1972	Idoxuridine (14) Vidarabine (15)	3.0–4.5 3.5–4.5
Pavan-Langston 1977	Idoxuridine (17) Trifluridine (23)	5.3 5.5
Pietruschka 1968	Fluorophenylalanine (30) Idoxuridine (28) Fluorophenylalanine/idoxuridine (40)	15 18 22
Shimomura 1987	Débridement/idoxuridine (16) Idoxuridine (15)	P>0.05
Tarakji 1978	Cryotherapy (21) Idoxuridine (14)	2.4 6.2
Wang 2009	Acyclovir (39) Ganciclovir (39)	P<0.05
Whitcher 1976	Débridement (20) Idoxuridine (31)	5 13
Interferon and interferon/antiviral combinations		

Study	Treatment group (no. eyes) ¹	Mean healing time±SD, days ²
Chen 2007	Acyclovir (43) Acyclovir/interferon (69)	P<0.01
Gu 2005	Acyclovir (20) Acyclovir/interferon (19)	P<0.05
Huang 2009	Acyclovir (36) Acyclovir/interferon (29)	39.6 30.4
Jin 1992	Acyclovir (41) Interferon (59)	8.2–9.6 9.9–12.4
Kuyama 1979	Interferon- α (NS) Interferon- β (NS)	NS NS
Liu 2003	Antiviral (21) Antiviral/interferon (21)	NS NS
Scialdone 1986	Idoxuridine (8) Interferon (12)	10–14 7–10
Shiota 1988	Interferon 100,000 IU/ml (14) Interferon 1 million IU/ml (46)	4.4±3.8 4.2±4.1
Tamburi 1990	Acyclovir (8) Interferon (8) Acyclovir/interferon (8)	5.2 9.0 5.0
Zhang 2003	Interferon- α -1b (29) Interferon- α -2b (17)	12.9±2.1 9.4±3.0
Zhao 2001	Acyclovir (89) Acyclovir/interferon (97)	P<0.01
Zhou 2008	Acyclovir (35) Acyclovir/interferon (66)	P<0.05
Interferon inducers		
Galin 1976	Idoxuridine (20) Poly I:C (19)	NS NS
Kasparov 1972	Idoxuridine (16) Poly A:U (43) Immunomodulators (167) Débridement/immunomodulators (33)	P<0.01
Kasparov 1974	Control (30) Idoxuridine (28) Poly A:U (27) Idoxuridine/poly A:U (15)	14.1±2.0 14.5±2.0 10.2±1.3 13.8±3.2
Kasparov 1991	Acyclovir (45) Poly A:U (65) Acyclovir/poly A:U (40)	13.8±0.8 14.6±1.2 9.5±1.1
Lin 2009	Acyclovir (27) Acyclovir/poly I:C (22)	P<0.05
Cytokines, growth factors, and immunomodulators		
Kolomiets 1986	Control (10) HSV-immunoglobulin (14)	28.6 16.8
Liu 2007	Acyclovir (50) Acyclovir/fibroblast growth factor (46)	P<0.05
Pivetti-Pezzi 1985	Placebo (13) Thymic extract (11)	23±13 23±9
Prost 1986	Cryotherapy (20) Cryotherapy/oral isoprinosine (19)	6.8±3.9 6.5±3.8
Salcedo Hernandez 2007	Autologous serum (9) Acyclovir (8)	10 7

Study	Treatment group (no. eyes) ¹	Mean healing time±SD, days ²
Sellitti 1982	Topical/oral isoprinosine (20) Oral isoprinosine (20)	13.3 25
Topciu 1992	Idoxuridine/foscarnet (120) Idoxuridine/foscarnet/immunostimulant (113)	30 3–4
Xu 2009b	Acyclovir (30) Acyclovir/interleukin-2 (32)	11±2.7–41±6.7 9±2.5–28±4.5
Zhang 1992	Acyclovir/interferon (20) Acyclovir/interferon/transfer factor (21)	P<0.05
Zhi 2001	Acyclovir (30) Acyclovir/interleukin-2 (38)	9±2.5–30±4.5 13±2.7–25±3.1

¹ Similar treatment groups were combined when possible; further details on interventions are tabulated in Characteristics of excluded studies

² A range of values indicates that mean estimates were provided for subcategories (e.g., dendritic vs. geographic epithelial keratitis) without summary estimation; *P* values comparing proportions healed in study groups at a time other than 14 days are provided for studies not reporting mean healing times NS, not stated; SD, standard deviation (when reported)

Table 3

Heterogeneity evaluation: analyses with inconsistency ($I^2 > 50\%$) at 14-day outcome

Treatment comparisons	I^2
Idoxuridine versus inactive control	66% ¹
Acyclovir versus idoxuridine	63% ^{1,2}
Trifluridine versus vidarabine	74% ¹
Ganciclovir versus acyclovir	71% ³
Oral/topical antivirals versus topical antiviral	90%
Interferon versus nucleoside antiviral	81%
Topical antiviral agent versus débridement	79% ²
Débridement with antiviral or interferon versus débridement	89% ²

¹ In addition, $I^2 > 50\%$ for pooled hazard ratio

² In addition, $I^2 > 50\%$ for pooled risk ratio at seven days

³ Possible publication bias

Table 4

Sensitivity analysis of studies that were potentially prone to bias: relative healing at 14 days after excluding trials with incomplete randomisation, concealment, or masking

Treatment comparisons ¹	Studies under investigation ²	Risk ratio (95% confidence interval) – with studies included	I ² (with studies included)	Risk ratio (95% confidence interval) – with studies excluded	I ² (with studies excluded)
Idoxuridine vs. inactive control	Luntz 1963	1.31 (0.80–2.15)	0%	1.79 (0.98–3.26)	NA
Trifluridine vs. idoxuridine	Struck 1989	1.38 (1.19–1.60)	32%	1.43 (1.23–1.67)	0%
Acyclovir vs. idoxuridine	Abe 1987, Altinisk 1987, Maychuk 1988	1.23 (1.14–1.32)	63%	1.19 (1.10–1.29)	66%
Brivudine vs. idoxuridine	Struck 1989	1.38 (1.05–1.81)	30%	1.64 (1.15–2.35)	NA
Trifluridine vs. vidarabine	Coster 1979	1.09 (0.98–1.22)	74%	1.09 (0.98–1.21)	0%
Brivudine vs. trifluridine	Struck 1989	1.00 (0.88–1.14)	0%	0.98 (0.89–1.08)	36%
Ganciclovir vs. acyclovir	Colin 1997a, Colin 1997b, Yang 2000, Colin 2007b, Chen 2008, Huang 2008a, Li 2008, Liu 2009a, Xu 2009a	1.13 (1.04–1.23)	71%	1.21 (0.95–1.54)	NA
Oral/topical antivirals vs. topical antiviral	Srinivas 1993	1.08 (0.99–1.17)	90%	1.01 (0.93–1.09)	NA
Interferon vs. nucleoside antiviral	Kitano 1983, Vannini 1986	0.33 (0.11–1.02)	43%	0.20 (0.01–3.35)	NA
Interferon/nucleoside antiviral vs. nucleoside antiviral	Maychuk 1988	1.03 (0.99–1.07)	0%	1.03 (0.99–1.07)	0%
Topical antiviral agent vs. débridement	Bartholomew 1977, Kato 1979, MacKenzie 1964, O'Day 1975, Patterson 1967a, Struck 1989	0.97 (0.84–1.13)	79%	1.23 (0.91–1.67)	87%
Débridement with antiviral or interferon vs. débridement	Sundmacher 1976a	1.04 (0.95–1.14)	89%	1.25 (1.01–1.54)	96%
Débridement with antiviral vs. antiviral	Daniel 1972, Richter 1986, Wilhelmus 1981a	1.04 (0.95–1.14)	0%	0.98 (0.79–1.21)	0%

¹Three comparisons that included a study judged to have a potentially high risk of bias were limited to a single study (Matthäus 1970, Serifoglu 1987, Sundmacher 1976a)

²Two studies judged to have a potentially high risk of bias did not provide data for the 14-day outcome (Patterson 1967a, Travers 1978)

NA: not applicable (single study available for evaluation)

Table 5

Sensitivity analysis of higher quality studies: effect on relative healing at 14 days using only randomised, double-masked trials

Treatment comparisons	Randomised, double-masked studies [/]	Risk ratio (95% confidence interval) – all studies	I ² (with all studies)	Risk ratio (95% confidence interval) – only randomised, double-masked studies	I ² (with only randomised, double-masked studies)
Idoxuridine vs. inactive control	Markham 1977	1.31 (0.80–2.15)	47%	1.79 (0.98–3.26)	NA
Vidarabine vs. idoxuridine	Markham 1977, Pavan-Langston 1976	1.04 (0.92–1.18)	0%	1.03 (0.90–1.17)	0%
Trifluridine vs. idoxuridine	Panda 1995, Sugar 1980, Wellings 1972	1.38 (1.19–1.60)	0%	1.47 (1.23–1.75)	0%
Acyclovir vs. idoxuridine	Colin 1981, Collum 1980, Coster 1980, Kitano 1985, Kumar 1987, McCulley 1982, Panda 1995	1.23 (1.14–1.32)	63%	1.17 (1.08–1.27)	69%
Brivudine vs. idoxuridine	Panda 1995	1.38 (1.05–1.81)	30%	1.64 (1.15–2.35)	NA
Trifluridine vs. vidarabine	Coster 1976	1.09 (0.98–1.22)	74%	1.07 (0.98–1.17)	NA
Acyclovir vs. vidarabine	Collum 1985, Denis 1983, Genée 1987, Pavan-Langston 1981, Yeakley 1981, Young 1982	1.08 (1.00–1.17)	0%	1.07 (0.98–1.18)	0%
Acyclovir vs. trifluridine	Høvdling 1989, La Lau 1982, Panda 1995	0.99 (0.90–1.09)	0%	1.01 (0.91–1.12)	0%
Brivudine vs. trifluridine	Panda 1995, Power 1991	1.00 (0.88–1.14)	0%	0.98 (0.89–1.08)	0%
Brivudine vs. acyclovir	Panda 1995	1.05 (0.92–1.20)	NA	NA	NA
Ganciclovir vs. acyclovir	Colin 2007a	1.13 (1.04–1.23)	71%	1.21 (0.95–1.54)	NA
Foscarnet vs. trifluridine	Behrens-Baumann 1992	1.00 (0.89–1.12)	NA	NA	NA
Acyclovir/vidarabine vs. acyclovir	Colin 1987	1.00 (0.89–1.12)	NA	NA	NA
Oral vs. topical antiviral	Collum 1986	0.92 (0.79–1.07)	NA	NA	NA
Oral/topical antivirals vs. topical antiviral	HEDS Group 1997	1.08 (0.99–1.17)	90%	1.01 (0.93–1.09)	NA
Interferon/antiviral vs. antiviral	Colin 1983, de Koning 1982, de Koning 1983, Meurs 1985, Sundmacher 1987, Van Bijsterveld 1989	1.03 (0.99–1.07)	0%	1.03 (0.99–1.08)	0%

[/]Thirteen of 46 randomised, double-masked trials are not tabulated because two-week outcome data were not provided (Burns 1963; Wang 2004) or because comparative interventions not listed in this table were studied (Cellini 1994; Colin 1984; Coster 1977a; Guerra 1979; Parlato 1985; Sundmacher 1976b; Sundmacher 1978a; Sundmacher 1984a; Sundmacher 1985; Uchida 1981; Uchida 1982)

NA: not applicable (single study available for evaluation)

Table 6
Combined direct and indirect comparisons: relative healing of HSV epithelial keratitis at 14 days between topical antiviral agents

Treatment comparisons	Type of comparison (intermediate comparator)	No. trials ^f	Risk ratio (95% CI)	I ² among direct and indirect comparisons	Combined risk ratio (95% CI) ²
Vidarabine vs. idoxuridine	Direct	3	1.04 (0.92–1.18)	0%	1.11 (1.03–1.19)
	Indirect (inactive control)	1, 2	1.21 (0.60–2.44)		
	Indirect (trifluridine)	3, 5	1.12 (0.98–1.42)		
	Indirect (acyclovir)	7, 11	1.15 (1.03–1.28)		
Trifluridine vs. idoxuridine	Direct	5	1.38 (1.19–1.60)	0%	1.31 (1.20–1.42)
	Indirect (vidarabine)	3, 3	1.29 (0.97–1.70)		
	Indirect (acyclovir)	4, 11	1.25 (1.11–1.42)		
	Indirect (brivudine)	3, 2	1.38 (1.02–1.87)		
Acyclovir vs. idoxuridine	Direct	11	1.23 (1.14–1.32)	4%	1.23 (1.16–1.31)
	Indirect (vidarabine)	7, 3	1.12 (0.97–1.30)		
	Indirect (trifluridine)	4, 5	1.37 (1.14–1.63)		
	Indirect (brivudine)	1, 2	1.31 (0.97–1.78)		
Brivudine vs. idoxuridine	Direct	2	1.38 (1.05–1.81)	0%	1.38 (1.18–1.61)
	Indirect (trifluridine)	3, 5	1.38 (1.13–1.68)		
	Indirect (acyclovir)	1, 11	1.30 (0.69–2.46)		
	Direct	0	NA		
Ganciclovir vs. idoxuridine	Indirect (acyclovir)	10, 11	1.40 (1.25–1.57)	12%	1.12 (1.04–1.21)
	Direct ³	3	1.09 (0.98–1.22)		
	Indirect (idoxuridine)	5, 3	1.33 (1.09–1.61)		
	Indirect (acyclovir)	4, 7	1.09 (0.96–1.23)		
Acyclovir vs. vidarabine	Direct	7	1.08 (1.00–1.17)	0%	1.11 (1.05–1.19)
	Indirect (idoxuridine)	11, 3	1.19 (1.03–1.38)		
	Indirect (trifluridine)	4, 3	1.16 (1.00–1.34)		
	Direct	4	0.99 (0.90–1.09)		
Acyclovir vs. trifluridine	Indirect (idoxuridine)	11, 5	0.90 (0.76–1.06)	0%	0.95 (0.89–1.02)
	Indirect (vidarabine)	7, 3	0.92 (0.81–1.06)		

Treatment comparisons	Type of comparison (intermediate comparator)	No. trials ¹	Risk ratio (95% CI)	I ² among direct and indirect comparisons	Combined risk ratio (95% CI) ²
Brivudine vs. trifluridine	Indirect (brivudine)	1, 3	0.95 (0.79–1.15)		
	Direct	3	1.00 (0.88–1.14)	0%	1.02 (0.92–1.12)
	Indirect (acyclovir)	1, 4	1.04 (0.88–1.22)		
Brivudine vs. acyclovir	Direct	1	1.05 (0.92–1.20)	0%	1.04 (0.95–1.15)
	Indirect (idoxuridine)	2, 11	1.11 (0.84–1.48)		
	Indirect (trifluridine)	4, 3	1.01 (0.86–1.19)		
Ganciclovir vs. trifluridine	Direct	0	NA	NA	1.12 (0.98–1.27)
	Indirect (acyclovir)	10, 4	1.12 (0.98–1.27)		
	Direct ³	10	1.13 (1.04–1.23)	NA	1.13 (1.04–1.23)

¹ Data derive from a network of 12 different interconnections among 46 trials that enrolled 1238 study participants (Figure 6). Comparisons are based on reported two-week outcomes among various combinations of seven topical interventions: inactive control, idoxuridine, vidarabine, trifluridine, acyclovir, brivudine, and ganciclovir. Indirect comparisons are limited to a linked network of trials having a single shared intermediate intervention; multiple intermediates were not considered for indirect adjustment

² Combination of direct and indirect comparisons estimated by the fixed-effect Mantel-Haenszel method

³ Heterogeneity of studies in direct comparison, with lack of significant difference using random-effects Mantel-Haenszel method (Table 3)

Table 7

Safety assessment among antiviral treatment studies

Topical antiviral agent	No. studies with at least one topical antiviral treatment arm	No. studies reporting corneal toxicity assessment	No. antiviral-treated participants assessed for corneal toxicity	Median prevalence of punctate epithelial erosions during antiviral use (interquartile range)
Idoxuridine	43	14 ¹	430	10% (5%–20%)
Vidarabine	14	12 ²	395	11% (4%–17%)
Trifluridine	20	9 ³	220	4% (2%–7%)
Acyclovir	42	25 ⁴	667	10% (0%–17%)
Brivudine	5	3 ⁵	72	0%
Ganciclovir	10	4 ⁶	156	4% (0%–11%)
All of above	88	40	1940	8% (0%–17%)

¹ Included idoxuridine studies: Altinisik 1987; Blake 1977; Colin 1981; Collum 1980; Kitano 1985; Klauber 1982; Laibson 1977; MacKenzie 1964; Markham 1977; McCulley 1982; Panda 1995; Pavan-Langston 1976; Vannini 1986; Wellings 1972

² Included vidarabine studies: Blake 1977; Collum 1985; Coster 1976; Coster 1979; Denis 1983; Jackson 1984; Markham 1977; Pavan-Langston 1976; Pavan-Langston 1981; Van Bijsterveld 1980; Yeakley 1981; Young 1982

³ Included trifluridine studies: Behrens-Baumann 1992; Coster 1976; Coster 1979; Hoang-Xuan 1984; Panda 1995; Parlato 1985; Power 1991; Van Bijsterveld 1980; Wellings 1972 (excluding La Lau 1982 because of imprecise assessment)

⁴ Included acyclovir studies: Altinisik 1987; Carmassi 1993; Colin 1981; Colin 1983; Colin 1984; Colin 1987; Colin 1997a; Colin 1997b; Colin 2007b; Collum 1980; Collum 1985; Collum 1986; Denis 1983; Hoang-Xuan 1984; Huang 2008a; Jackson 1984; Jensen 1982; Kitano 1985; Klauber 1982; McCulley 1982; Panda 1995; Pavan-Langston 1981; Wilhelmus 1981a; Yeakley 1981; Young 1982 (excluding La Lau 1982 because of imprecise assessment)

⁵ Included brivudine studies: Panda 1995; Power 1991; Van Bijsterveld 1989

⁶ Included ganciclovir studies: Colin 1997a; Colin 1997b; Colin 2007b; Huang 2008a

Characteristics of included studies [ordered by study ID]

Abe 1987		
Methods	Allocation method: not given Masking: none Number of centres: one	
Participants	Country: Japan Number enrolled: 27 Average age (range): 35 (2–77) Sex: 17 males, 10 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=9): idoxuridine solution Treatment two (n=18): acyclovir 3% ointment 3 to 5 times per day (one patient received intravenous acyclovir 5 mg/kg every 8 hours)	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: antibiotic solution 3 to 5 times per day Report language: Japanese Study date: not given Financial support: not given	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Unequal (1:2) treatment assignment, with allocation of treatment based on availability of the intervention and on judgement of the clinician
Allocation concealment (selection bias)	High risk	Unconcealed procedure.
Blinding (performance bias and detection bias) All outcomes	High risk	Study personnel not masked, although outcome assessment is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	The study interventions may not have occurred concurrently.
Altinisik 1987		
Methods	Allocation method: not given Masking: single Number of centres: one	
Participants	Country: Turkey Number enrolled: 27 Average age (range): 38 (4–73) Sex: 16 males, 11 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=9): idoxuridine 0.5% ointment 5 times per day Treatment two (n=10): acyclovir 3% ointment 5 times per day Treatment three (n=8): acyclovir 3% ointment 5 times per day + wiping débridement	
Outcomes	Epithelial healing (resolution of ‘punctat epitelial defektler’)	
Notes	Nonstudy interventions: atropine Report language: Turkish Study date: 1985–1986 Financial support: not given Adverse reactions: One case of punctate epithelial erosions observed in the idoxuridine group, and none in the acyclovir group	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	High risk	Allocation apparently by judgment of the clinician.
Allocation concealment (selection bias)	High risk	Unconcealed procedure.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No masking, although outcome may not have been influenced by lack of masking
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information to determine if patients were treated concurrently or sequentially during 9 months of study enrolment

Austin 1974

Methods	Allocation method: not given Masking: none Number of centres: one
Participants	Country: Great Britain Number enrolled: 41 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=16): iodination Treatment two (n=25): idoxuridine
Outcomes	'When no corneal staining remained'
Notes	Nonstudy interventions: mydriatic, antibiotic (iodination group), pad Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Treatment failures (area of corneal staining increased from one visit to the next) included 5 in idoxuridine treatment group and 2 in iodination group
Selective reporting (reporting bias)	Low risk	Insufficient information provided about the sequence generation process
Other bias	Unclear risk	Insufficient information.

Bartholomew 1977

Methods	Allocation method: randomised Masking: none Number of centres: one HSV isolation (conjunctiva and cornea): performed but results not reported
Participants	Country: Great Britain Number enrolled: 21 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis

Interventions	Treatment one (n=6): photodynamic inactivation (neutral red 1 % solution × 2 then blue light for 15 minutes) Treatment two (n=7): carbolization Treatment 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 scraping Report language: English Study date: not given Financial support: private foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	High risk	No masking was likely because of disparate interventions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data, although times to treatment failure (2 in idoxuridine group, 1 in carbolization group, and 2 in 'dye light' group) were not provided
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.

Behrens-Baumann 1992

Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva): 19 positive of 20 tested
Participants	Country: Germany Number enrolled: 20 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one: (n=10): trifluridine 1% solution 5 times per day Treatment two (n=10): foscarnet 3% solution 5 times per day
Outcomes	Fluorescein staining with 'closure of the corneal epithelium'
Notes	Nonstudy interventions: scopolamine Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "No punctate keratitis or allergic reactions were observed."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data, although times to treatment failure (1 in trifluridine group and 1 in foscarnet group) were not described

Selective reporting (reporting bias)	Unclear risk	The method of performing paired comparison that “was made prospectively and at random” is unclear
Other bias	High risk	The trial was apparently stopped early when “no significant difference between [treatment groups was found]...after 10 paired analyses.”

Blake 1977

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: Ireland Number enrolled: 30 Average age (range): 45 (7–75) Sex: 16 males, 14 females Inclusion criteria: dendritic (23) or geographic (7) epithelial keratitis
Interventions	Treatment one (n=13): idoxuridine ointment 0.5% 4 times daily Treatment two (n=17): vidarabine ointment 3% 4 times daily
Outcomes	‘Complete re-epithelialisation’
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): “Two patients in the Ara-A group developed mild punctate keratitis...in both cases the condition cleared spontaneously on discontinuing medication.”

Risk of bias

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	The drug allocation code was not “broken” unless “treatment was considered a failure.”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data within 14 days of treatment onset
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	While “patients with disciform keratitis... were excluded” the table of patient characteristics lists one patient with “stromal” keratitis. In addition, a baseline imbalance of treatment groups occurred with respect to patient age

Burns 1963

Methods	Allocation method: randomised Masking: double Number of centres: several (42 sites in entire study) Quote: “The signs and symptoms of this infection are clear cut and pathognomonic, thus no confirmatory laboratory tests will be necessary to establish the diagnosis.”
Participants	Country: United States Number enrolled: 38 Average age (range): not given Sex: not given Inclusion criteria: acute epithelial keratitis
Interventions	Control (n=15): distilled water hourly day, 2-hourly night Treatment one (n=23): idoxuridine solution hourly day, 2-hourly night
Outcomes	Fluorescein staining with ‘healing of the ulcer’
Notes	Nonstudy interventions: not given Report language: English Study date: 1962–1963 Financial support: pharmaceutical industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The bottles were numbered consecutively, and active drug and placebo were randomly distributed."
Allocation concealment (selection bias)	Low risk	Study medications were distributed from a central location and "dispensed consecutively to ophthalmologists when requested."
Blinding (performance bias and detection bias) All outcomes	Low risk	Study treatment medications "were supplied in identical brown bottles, labelled only with a code number."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition.
Selective reporting (reporting bias)	Unclear risk	The time to "healing of the ulcer" was not clearly described
Other bias	Unclear risk	Quote: "The physician was instructed that, if after a week of therapy, he was dissatisfied with the patient's results, he could telephone this report, and the code would be broken."

Carmassi 1993

Methods	Allocation method: not given Masking: none Number of centres: one HSV isolation (cornea): 10 positive of 15 tested
Participants	Country: Italy Number enrolled: 15 Average age (range): 44 (25–71) Sex: 7 males, 8 females Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=5): acyclovir 3% ointment 5 times per day Treatment 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' ('riepitelizzazione corneale e negativizzazione del test alla fluoresceina')
Notes	Nonstudy interventions: none Report language: Italian Study date: not given Financial support: not given Adverse reactions: Two cases of "cheratite puntata" occurred in the acyclovir group, and one case occurred in the acyclovir-interferon group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Cellini 1994

Methods	Allocation method: randomised
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	Masking: double Number of centres: one
Participants	Country: Italy Number enrolled: 40 Average age (range): 43 (19–70) Sex: 24 males, 16 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=20): acyclovir 3% ointment 4 times per day Treatment 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: none Report language: English Study date: not given Financial support: pharmaceutical industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.

Chen 2008

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 40 Average age (range): 44 Sex: 23 males, 17 females Inclusion criteria: dendritic (9) epithelial keratitis
Interventions	Treatment one (n=20): acyclovir 0.1% solution 4 times per day Treatment two (n=20): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: not given Report language: Chinese Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	High risk	No masking was undertaken, and outcome assessment could have been influenced by the lack of a masked assessor

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.
Colin 1981		
Methods	Allocation method: randomised Masking: double Number of centres: one	
Participants	Country: France Number enrolled: 52 Average age (range): 49 (8–84) Sex: 31 males, 21 females Inclusion criteria: dendritic or geographic epithelial keratitis	
Interventions	Treatment one (n=27): idoxuridine 0.5% ointment 5 times per day Treatment two (n=25): acyclovir 3% ointment 5 times per day	
Outcomes	‘The absence of epithelial ulceration after instillation of fluorescein (‘l’absence d’ulcération épithéliale après instillation de fluorescéine’)	
Notes	Nonstudy interventions: atropine Report language: French Study date: not given Financial support: pharmaceutical industry Adverse reactions: Two cases of “kératite ponctuelle” occurred in the idoxuridine group, and one case in the acyclovir group [Presumed typographical error in publication’s table of 11 males, instead of 17 males, randomised to idoxuridine]	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked (“en double insu”) trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data, although results of treatment failure (“échecs”) not described
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.’
Other bias	Low risk	The study appears to be free of other sources of bias.
Colin 1983		
Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva and cornea): inclusion criterion	
Participants	Country: France Number enrolled: 45 Average age (range): not given Sex: 36 males, 9 females Inclusion criteria: dendritic epithelial keratitis (culture-confirmed)	
Interventions	Treatment one (n=21): acyclovir 3% ointment 5 times per day and albumin once per day Treatment 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: none Report language: English Study date: not given Financial support: not given Adverse reactions: "Diffuse superficial punctate epitheliopathy was noted in five patients" including three in the acyclovir-placebo group and two in the acyclovir-interferon group
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked ("en double insu") trial design described in the preliminary report
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported. The trial was limited to "virologically identified dendritic keratitis.
Other bias	Low risk	The study appears to be free of other sources of bias.

Colin 1984

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: France Number enrolled: 32 Average age (range): 48 (7–79) Sex: 20 males, 12 females Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=17): iododeoxycytidine 1% ointment 5 times per day Treatment two (n=15): acyclovir 3% ointment 5 times per day
Outcomes	'The absence of epithelial ulceration after the instillation of fluorescein, using the biomicroscope' ('l'absence d'ulcération après instillation de fluorescéine')
Notes	Nonstudy interventions: atropine Report language: French Study date: not given Financial support: not given Adverse reactions: One case of kératite ponctuelle was observed in the iododeoxycytidine group and one case in the acyclovir group. Another case of "allergie oculo-palpébrale" occurred in the acyclovir group [Day 15 healing data of iododeoxycytidine group used for day 14 data table in this systematic review]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked ("en double insu") trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Colin 1987

Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva): 24 positive of 32 tested
Participants	Country: France Number enrolled: 32 Average age (range): 49 (8–77) Sex: 19 males, 23 females Inclusion criteria: dendritic 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: none Report language: English Study date: not given Financial support: governmental agency Adverse reactions (Quote): "Diffuse superficial punctate epitheliopathy was noted in four patients (two in each group)...and resolved after the treatment was discontinued."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "The coded treatment were randomly allocated by the pharmacist."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All patients were examined by one ophthalmologist (JC), who did not know whether the patient was receiving vidarabine or placebo."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Colin 1997a

Methods	Allocation method: randomised Masking: none Number of centres: three HSV isolation (conjunctiva): 35 positive of 59 tested
Participants	Country: Mali and Tunisia Number enrolled: 67 Average age (range): 41 Sex: 37 males, 30 females Inclusion criteria: dendritic (51) or geographic (16) epithelial keratitis
Interventions	Treatment one (n=22): acyclovir 3% ointment 5 times per day Treatment two (n=23): ganciclovir 0.15% gel 5 times per day Treatment three (n=22): ganciclovir 0.05% gel 5 times per day
Outcomes	'Absence of fluorescein staining at ulcer site'
Notes	Nonstudy interventions: none Report language: English Study date: 1990–1992 Financial support: pharmaceutical industry Adverse reactions (from Colin, 2007, Table 3): "Toxic superficial punctate keratitis related to treatment at Day 14" was observed in two cases in the acyclovir group, three cases in the ganciclovir 0.15% group, and no cases in the ganciclovir 0.05% group

Risk of bias

Bias	Authors' judgement	Support for judgement
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Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly allocated to the various treatment groups."
Allocation concealment (selection bias)	Low risk	There is no evidence that treatment assignments was not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "Double-blind conditions were not possible because of the obviously different formulations of the two antiviral agents."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Eight case-report forms from seven of the 67 patients included were found to be faulty during on-site audits and were excluded from the efficacy analysis. Therefore, only 59 patients were assessed from the efficacy (per protocol analysis)."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.

Colin 1997b

Methods	Allocation method: randomised Masking: none Number of centres: four HSV isolation (conjunctiva): 7 positive of 35 tested (Quote: "Because of problems of refrigeration during transportation, percentages of positive conjunctival swabs were very low")
Participants	Country: France, Switzerland, and Great Britain Number enrolled: 37 Average age (range): 48 Sex: 26 males, 11 females Inclusion criteria: dendritic (36) or geographic (1) epithelial keratitis
Interventions	Treatment one (n=18): acyclovir 3% ointment 5 times per day Treatment two (n=19): ganciclovir 0.15% gel 5 times per day
Outcomes	'Absence of fluorescein staining at ulcer site'
Notes	Nonstudy interventions: none Report language: English Study date: 1990–1992 Financial support: pharmaceutical industry Adverse reactions (Quote from Colin, 2007, Study B): "There were no cases of superficial punctate keratitis that were found to be toxic."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	There is no evidence that treatment assignments were not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	No masking performed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Two patients were found to have been misdiagnosed (one in each treatment group): they were excluded from efficacy analysis."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcomes was adequately reported.
Other bias	Unclear risk	Quote: "There was a longer duration of disease before presentation" in the acyclovir group compared to the ganciclovir group that "occurred entirely by accident despite the randomization procedure."

Colin 2007a

Methods	Allocation method: randomised Masking: none Number of centres: multiple
Participants	Country: Pakistan Number enrolled: 109

	Average age (range): not given Sex: not given Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=38): acyclovir 3% ointment 5 times per day Treatment two (n=36): ganciclovir 0.15% gel 5 times per day Treatment three (n=35): ganciclovir 0.05% gel 5 times per day
Outcomes	'Lack of fluorescein staining'
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: pharmaceutical industry Adverse reactions (Quote): "The number of superficial punctate keratitis cases that appeared or were exacerbated while receiving treatment was similar across the treatment groups."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process ("étude clinique comparative randomisée")
Allocation concealment (selection bias)	Low risk	Centralized distribution process.
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-blind ("en simple insu") trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	Outcome data are provided for both the intention-to-treat analysis and the per-protocol analysis
Other bias	Low risk	The study appears to be free of other sources of bias.

Colin 2007b

Methods	Allocation method: randomised Masking: none Number of centres: 28
Participants	Country: 28 European centres Number enrolled: 164 Average age (range): 45 Sex: not given Inclusion 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: none Report language: English Study date: 1992-1994 Financial support: not given Adverse reactions (Quote): "The frequency of toxic superficial punctate keratitis was reduced by half in the GCV0.15% group compared with the ACV group."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Centralized distribution scheme.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The trial could not be made double masked owing to the obvious difference in the appearance between the gel and ointment formulations of the two drugs."

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Collum 1980		
Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva): 19 positive of 54 tested	
Participants	Country: Ireland Number enrolled: 60, including 8 idoxuridine-treated censored patients (7 who were not improved or worse at day 4 and one who defaulted) Average age (range): 41 (4–79) Sex: 44 males, 16 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=30): idoxuridine 0.5% ointment 5 times per day Treatment two (n=30): acyclovir 3% ointment 5 times per day	
Outcomes	‘No fluorescein uptake’	
Notes	Nonstudy interventions: homatropine, pad Report language: English Study date: not given Financial support: pharmaceutical industry Adverse reactions: Six cases of “superficial punctate keratopathy” were observed in the idoxuridine group, and no cases in the acyclovir group	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: “The ointments were of similar appearance and packed in identical tubes.”
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seven patients treated with idoxuridine were “withdrawn” and 1 “defaulted.”
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Collum 1985		
Methods	Allocation method: randomised Masking: double Number of centres: two	
Participants	Country: Ireland and UK Number enrolled: 51 Average age (range): 55 (range not given) Sex: 29 males, 22 females Inclusion criteria: geographic epithelial keratitis	
Interventions	Treatment one (n=26): vidarabine 3% ointment 5 times per day Treatment 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: English Study date: not given Financial support: pharmaceutical industry	

Adverse reactions (Quote): "The only adverse reaction noted was superficial punctate epitheliopathy in two patients receiving acyclovir and five patients receiving Ara-A."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Both drugs were identically packaged and coded."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three patients were withdrawn from the study owing to failure of treatment."
Selective reporting (reporting bias)	High risk	Quote: "Three patients randomly allocated to acyclovir treatment failed to return after their initial assessment and were excluded from the analysis."
Other bias	Low risk	The study appears to be free of other sources of bias.

Collum 1986

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: Ireland Number enrolled: 56 Average age (range): 47 (range not given) Sex: 45 males, 11 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=29): acyclovir 3% ointment 5 times per day and oral placebo 5 times per day Treatment 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: none Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "In four patients receiving acyclovir ointment large punctate epithelial defects were noted...one other patient receiving acyclovir ointment had a minor degree of superficial punctate epitheliopathy"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "On a random basis patients were allocated either 3% acyclovir ophthalmic ointment and placebo tablets, or placebo ointment and acyclovir tablets."
Allocation concealment (selection bias)	Low risk	There is no evidence that participants or investigators could foresee treatment assignment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 60 patients who entered the study three receiving the oral medication failed to come for follow-up, and one was lost from the local therapy group."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Coster 1976

Methods	Allocation method: randomised Masking: none
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	Number of centres: one
Participants	Country: Great Britain Number enrolled: 102 Average age (range): not given Sex: not given Inclusion criteria: dendritic (87) or geographic (15) epithelial keratitis
Interventions	Treatment one (n=48): vidarabine 3.3% ointment 5 times per day Treatment two (n=54): trifluridine 1% solution 5 times per day
Outcomes	'Absence of staining with fluorescein'
Notes	Nonstudy interventions: atropine Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "The only indication of toxicity observed was punctate epithelial staining with Bengal rose. This effect was considered to be due to drug toxicity if it affected areas of the cornea remote from the original lesion. Such a staining pattern was seen in nine patients, of whom eight had been treated with ara-A and one with F ₃ T

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Each patient received coded treatment, randomly allocated by the pharmacist, who followed a stratification table."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 107 patients "who consented to the study...five patients were subsequently withdraw-four because of failure to attend the clinic for assessment and one because of an error dispensing."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Coster 1977a

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: Great Britain Number enrolled: 78 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=22): minimal wiping débridement and placebo solution once per day Treatment one (n=26): minimal wiping débridement and human leukocyte interferon 11 million units/ml once per day Treatment two (n=30): minimal wiping débridement and human leukocyte interferon 33 million units/ml once per day
Outcomes	Not given
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A preliminary communication (Jones et al, 1976) described treatment allocation in a "randomised manner."

Allocation concealment (selection bias)	Low risk	According to a preliminary report (Jones et al, 1976), "the coded, randomized allocation of treatment was stratified for size of the ulcer."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design implied. (Note: Another systematic review judged this trial as not double-blind (Guess 2007).)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All the ulcers healed within 48 hours."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Coster 1979

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: Great Britain Number enrolled: 30 Average age (range): not given Sex: not given Inclusion criteria: geographic epithelial keratitis
Interventions	Treatment one (n=17): vidarabine 3.3% ointment 5 times per day Treatment two (n=13): trifluridine 1% solution 5 times per day
Outcomes	'The absence of staining with fluorescein'
Notes	Nonstudy interventions: atropine Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "The only manifestation of antiviral toxicity observed was punctate staining of the corneal epithelium with Bengal rose. This occurred in 3 patients treated with Ara-A and 4 treated with F ₃ T."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "The coded treatments were randomly allocated by the pharmacist within closely matched strata."
Blinding (performance bias and detection bias) All outcomes	High risk	The different treatment formulations (ointment <i>versus</i> drops) indicate probable lack of masking.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In 6 patients the ulcers failed to heal."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Coster 1980

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: Great Britain Number enrolled: 59 Average age (range): not given Sex: not given Inclusion criteria: dendritic (54) or geographic (5) epithelial keratitis
Interventions	Treatment one (n=30): idoxuridine 1% ointment 5 times per day Treatment 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: atropine Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "There were no untoward reactions that necessitated withdrawal of therapy."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Patients were allocated to strata on the basis of clinical features likely to be significant in prognosis.... Within these strata patients were randomly allocated to 1 of 2 treatment groups."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Neither the patient nor the ophthalmologist knew which treatment was being used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient treated with acyclovir failed to present regularly for follow-up [and]... is not included in the analysis."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Daniel 1972

Methods	Allocation method: alternate patients Masking: none Number of centres: one
Participants	Country: Great Britain Number enrolled: 54 Average age (range): not given Sex: not given Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=25): idoxuridine ointment 5 times per day Treatment two (n=29): idoxuridine ointment 5 times per day and ultraviolet (2536 Å) light for 2–4 minutes once or twice
Outcomes	Fluorescein and rose-Bengal staining
Notes	Nonstudy interventions: mydriatic, pad Report language: English Study date: 1970–1971 Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The investigators describe a non-random component in the sequence generation process
Allocation concealment (selection bias)	High risk	Quote: "The first four patients who presented were treated with the combined therapy...; thereafter alternate patients were treated" with combined idoxuridine and ultraviolet therapy or with idoxuridine alone
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "A double-blind controlled trial was not possible as it was obvious to any observer which patients had received ultraviolet therapy."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three censored patients underwent débridement.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	This study appears to be free of other sources of bias.

Davidson 1964

Methods	Allocation method: randomised with table Masking: none Number of centres: one HSV isolation (cornea): 51 positive of 75 tested
Participants	Country: Great Britain Number enrolled: 75 Average age (range): not given Sex: not given Inclusion criteria: not given
Interventions	Control (n=25): gamma-globulin 1% solution hourly during day, 2-hourly during night Treatment one (n=25): débridement (with orange stick) and iodination (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 (débridement group), chloramphenicol ointment (débridement group) Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "There were no allergic reactions to the drops, nor were there any complaints of burning or irritation. Some areas of punctate stain were noted after healing with IDU or gamma globulin drops, but there were no more frequent than after iodization."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "The patients admitted to the trial were allocated to one of the three groups using randomized sample tables, with which the pharmacist was provided."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "The usual precautions of a double-blind clinical trial were followed, e.g. the observer was unaware of the type of drop being administered." While the nature of the interventions (chemical débridement and topical antiviral agent) would not permit a double-masked design, it is unclear whether lack of masking could have influenced outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcomes were reported only for virologically confirmed cases
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

de Koning 1982

Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (cornea): 58 positive of 61 tested
Participants	Country: Netherlands Number enrolled: 53 Average age (range): not given Sex: 33 males, 20 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=28): trifluridine 1% solution 5 times per day and albumin solution Treatment 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: none Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe "a randomised arrangement" of the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Eight patients were excluded from the study"-two for failure to comply with the examination protocol, 3 for negative herpes simplex virus isolation, 2 for stromal keratitis, and 1 for metaherpes
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

de Koning 1983

Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (cornea): 55 positive of 59 tested
Participants	Country: Netherlands Number enrolled: 51 Average age (range): not given Sex: 30 males, 21 females Inclusion criteria: dendritic (42) or geographic (9) epithelial keratitis
Interventions	Treatment one (n=26): acyclovir 3% ointment 5 times per day and albumin solution every morning Treatment 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: none Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment with either interferon or placebo was assigned randomly to patients."
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Eight patients were excluded from the trial"-2 for compliance problems, 4 for negative herpes simplex virus isolation, and 2 for worsening into geographic epithelial keratitis
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Denis 1983

Methods	Allocation method: randomised Masking: single Number of centres: one
Participants	Country: France Number enrolled: 23 Average age (range): not given

	Sex: not given Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=9): vidarabine 3% ointment 5 times per day Treatment two (n=14): acyclovir 3% ointment 5 times per day
Outcomes	Ulcer healing ('cicatrisation de l'ulcère')
Notes	Nonstudy interventions: mydriatic, antibiotic (rarely) Report language: French Study date: 1980–1981 Financial support: not given Adverse reactions (Quote): "La tolérance locale à l'acyclovir et à l'Ara A est bonne, identique pour les deux substances. Chacune d'elle a occasionné dans cette étude: 5 kératites ponctuées superficielles qui n'ont pas empêché la poursuite du traitement et one disparu spontanément dès l'arrêt; et, chez 3 malades, une douleur modérée à chaque application de pommade."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked ("en double insu") trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Fulhorst 1972

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: Great Britain Number enrolled: 90 Average age (range): not given Sex: not given Inclusion criteria: dendritic (74) or geographic (16) epithelial keratitis
Interventions	Treatment one (n=26): idoxuridine ointment 5 times per day Treatment two (n=18): cryotherapy (multiple applications at -70° to -80° C) and idoxuridine ointment 5 times per day Treatment three (n=18): cryotherapy (multiple applications at -70° to -80° C) and idoxuridine ointment 5 times per day and placebo 5 times per day Treatment four (n=13): carbolicization (débridement with orange stick followed by touching epithelial edge with phenol) and idoxuridine ointment 5 times per day Treatment five (n=15): carbolicization (débridement 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 hours Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patient's treatment was determined by stratified randomization."
Allocation concealment (selection bias)	Unclear risk	Insufficient information.

Blinding (performance bias and detection bias) All outcomes	Unclear risk	While the trial is described as “double-blind,” the trial design is unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Genée 1987

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: Germany Number enrolled: 28 Average age (range): not given Sex: 21 males, 7 females Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=14): acyclovir 3% ointment 5 times per day Treatment two (n=14): vidarabine 3% ointment 5 times per day
Outcomes	Epithelial healing
Notes	Nonstudy interventions: none Report language: German Study date: 1981–1984 Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design (“Doppel-blindstudie”) described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 30 enrolled patients, 2 were excluded-1 for incorrect enrolment (recent vidarabine treatment) and 1 for non-compliance. Note that there is an apparent typographical error in the table (13 instead of 14 patients in one treatment arm)
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Graupner 1966

Methods	Allocation method: not given Masking: double (partial) Number of centres: one
Participants	Country: Germany Number enrolled: 32 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=12): idoxuridine 0.1% solution every 2 hours Treatment two (n=20): para-fluorophenylalanine 0.1% solution every 2 hours
Outcomes	Epithelial healing (‘Anfärbarkeit der Cornea beurteilt’)
Notes	Nonstudy interventions: atropine Report language: German Study date: not given

Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Graupner 1968

Methods	Allocation method: not given Masking: single Number of centres: one
Participants	Country: Germany Number enrolled: 53 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=27): idoxuridine 0.1% ointment 5 times per day Treatment two (n=26): para-fluorophenylalanine 0.1% ointment 5 times per day
Outcomes	Epithelial healing ('vollständige Epithelisation der Hornhaut')
Notes	Nonstudy interventions: atropine Report language: German Study date: not given Financial support: pharmaceutical industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Graupner 1969

Methods	Allocation methods: not given Masking: single Number of centres: one
Participants	Country: Germany Number enrolled: 33 Average age (range): not given

	Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=18): iodination /débridement plus idoxuridine 0.1% ointment every 4 hours Treatment two (n=15): iodination /débridement plus <i>para</i> -fluorophenylalanine 0.1% ointment every 4 hours
Outcomes	Epithelial healing ('Anfärbbarkeit der Hornhaut beurteilt')
Notes	Nonstudy interventions: atropine Report language: German Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Guerra 1979

Methods	Allocation method: randomised by table Masking: single Number of centres: one HSV isolation (cornea): 11 positive of 20 tested
Participants	Country: Italy Number enrolled: 20 Average age (range): 46 (9–76) Sex: 13 males, 7 females Inclusion criteria: dendritic (18) or geographic (2) epithelial keratitis
Interventions	Treatment one (n=10): polyinosinic-polycytidylic 1000 µg/ml hourly Treatment two (n=10): idoxuridine 0.2% solution hourly
Outcomes	Healing ('cicatrizzato')
Notes	Nonstudy interventions: atropine Report language: Italian Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote from preliminary report (Guerra et al, 1970): "Plastic dispensing bottles...were the same for both [study] medications."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked study design described in a preliminary report (Guerra et al, 1970)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.

Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Hart 1965		
Methods	Allocation method: randomised by table Masking: double Number of centres: one HSV isolation (cornea): 25 positive of 32 tested	
Participants	Country: Australia Number enrolled: 32 Average 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 night Treatment 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, pad Report language: English Study date: not given Financial support: pharmaceutical industry	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: Study medications “were supplied by [the manufacturer] in plastic dispensing bottles of identical appearance...[that were] then arranged...in random order.”
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: “The investigators were unaware of the nature of the drops being used to treat a particular patient until after assessment of the results had been made on the seventh day of treatment.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two patients “were admitted to the trial but were subsequently discarded”-1 for loss to follow up and 1 for worsened corneal disease
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Haut 1983		
Methods	Allocation method: not given Masking: double Number of centres: one	
Participants	Country: France Number enrolled: 26 Average age (range): not given Sex: not given Inclusion criteria: dendritic (15) or geographic (11) epithelial keratitis	
Interventions	Control (n=12): oral placebo Treatment one (n=14): oral isoprinosine 500 mg 6 times per day	
Outcomes	Healing (‘amélioration’)	
Notes	Nonstudy interventions: atropine, antibiotic Report language: French Study date: not given Financial support: not given	
Risk of bias		
Bias	Authors’ judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked ("en double-insu") trial design described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information. The time to healing was not adequately provided
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.

HEDS Group 1997

Methods	Allocation method: randomised by permuted blocks Masking: double Number of centres: 60
Participants	Country: USA Number enrolled: 287 Average age (range): 48 (range not given) Sex: 179 males, 108 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=134): trifluridine 1% solution 8 times per day and oral placebo 5 times per day Treatment 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: none Report language: English Study date: 1992–1995 Financial support: governmental agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe the use of "a computer-generated list of random numbers" in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Each patient was randomly assigned to receive either oral acyclovir...or oral placebo...identical in appearance and taste."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Patients and clinic personnel were masked to the oral medication treatment assignments; the data analysts and the data and safety monitoring committee were not."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Hoang-Xuan 1984

Methods	Allocation method: arbitrary Masking: none Number of centres: one HSV isolation (cornea and conjunctiva): results not reported
Participants	Country: France Number enrolled: 29 Average age (range): not given Sex: only given for total group with herpetic keratitis (28 males, 9 females) Inclusion criteria: dendritic or geographic epithelial keratitis (n=29), or keratouveitis (n=8)
Interventions	Treatment one (n=11): trifluridine 1% solution 6 times per day

	Treatment two (n=18): acyclovir 3% ointment 5 times per day
Outcomes	No fluorescein staining ('lorsque la coloration épithéliale par la fluorescéine à l'examen biomicroscopique de la cornée a disparu')
Notes	Nonstudy interventions: cycloplegic, antibiotic, timolol Report language: French Study date: 1980–1982 Financial support: not given Adverse reactions (Quote): "Effets secondaires...sont limités à de simples kératites ponctuées superficielles: 8 dans le groupe ACV et 3 dans le groupe TFT, et à une conjonctivite folliculaire dans le groupe ACV."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to determine if trial used a randomised sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation method based on availability of the drug at the time of treatment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment of whether lack of masking influenced outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Huang 2008a

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 45 Average age (range): 32 Sex: 31 males, 14 females Inclusion criteria: dendritic (29) or geographic (16) epithelial keratitis
Interventions	Treatment one (n=15): acyclovir 0.1% solution 4 times per day Treatment two (n=16): ganciclovir 0.15% gel 4 times per day Treatment three (n=14): ganciclovir 0.1% solution 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: not given Report language: Chinese Study date: not given Financial support: not given Adverse reactions (Quote): "No obviously adverse drug reaction was found in all of three agents."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The investigators describe a double-masked design, but different formulations (ointment, gel, and solution) of study medications were used
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.

Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.
Hung 1984		
Methods	Allocation method: randomised Masking: double Number of centres: one	
Participants	Country: Great Britain Number enrolled: 29 Average age (range): 56 (range not given) Sex: 23 males, 6 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=14): minimal wiping débridement and oral placebo 5 times per day Treatment two (n=15): minimal wiping débridement and oral acyclovir 400 mg 5 times per day	
Outcomes	'Ulcer stained with rose-Bengal to assess healing'	
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: pharmaceutical industry Adverse reactions (Quote): "No adverse reaction was found in the acyclovir treated group."	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two patients were excluded from the analysis because no clinical assessment was made on day 6,7, or 8."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.

Høvding 1989

Methods	Allocation method: randomised Masking: double Number of centres: one	
Participants	Country: Norway Number enrolled: 50 Average age (range): 46 (range not given) Sex: 27 males, 23 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=25): trifluridine 2% ointment 5 times per day Treatment two (n=25): acyclovir 3% ointment 5 times per day	
Outcomes	'Disappearance of epithelial ulceration(s) staining with fluorescein'	
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "Apart from a slight epithelial punctate keratopathy in a few patients in both treatment groups, no drug adverse effects were observed."	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Random sequence generation (selection bias)	Low risk	The investigator describes a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Each patient received 2 identical, masked tubes containing either 3% acyclovir or 2% [trifluridine] ophthalmic ointment."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data during 14 days of follow up.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately assessed.
Other bias	Low risk	The study appears to be free of other sources of bias.

Jackson 1984

Methods	Allocation method: randomised Masking: double Number of centres: three HSV isolation (conjunctiva): 14 positive of 29 tested
Participants	Country: Canada Number enrolled: 66 Average age (range): 45 (12–80) Sex: 39 males, 27 females Inclusion criteria: dendritic (59) or geographic (7) epithelial keratitis
Interventions	Treatment one (n=34): vidarabine 3% ointment 5 times per day Treatment two (n=32): acyclovir 3% ointment 5 times per day
Outcomes	Not given
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: pharmaceutical industry Adverse reactions (Quote): "Lid swelling with burning were each reported by one patient treated with vidarabine. Four patients treated with acyclovir and two treated with vidarabine were thought to exhibit drug-related punctate epithelial keratitis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Low risk	Quote: "Each patient [received] a numbered tube of ointment containing either 3% acyclovir or 3% vidarabine."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Jensen 1982

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: Denmark Number enrolled: 43 Average age (range): not given Sex: not given

	Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=20): acyclovir 3% ointment 6 times per day Treatment two (n=23): acyclovir 3% ointment 6 times per day and wiping débridement
Outcomes	'No epithelial defect was demonstrated after staining'
Notes	Nonstudy interventions: cycloplegic, chloramphenicol ointment Report language: English Study date: not given Financial support: pharmaceutical industry Adverse reactions: "Superficial punctate keratitis" was observed in four cases in the acyclovir group and in three cases in the acyclovir-débridement group. Six patients "complained of stinging after application of acyclovir ointment." "No other side effects were observed, and no patients were withdrawn due to side effects."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Whether the lack of masking influenced outcome assessment could not be determined
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Jepson 1964

Methods	Allocation method: not given Masking: double Number of centres: one Quote: "No viral identification studies were done. We considered the acute initial or recurrent dendritic figure to be definitely of herpetic etiology."
Participants	Country: United States Number enrolled: 24 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=12): distilled water with thimerosal hourly day, 2-hourly night Treatment one (n=12): idoxuridine 0.1% solution hourly day, 2-hourly night
Outcomes	'Absence of fluorescein staining pattern'
Notes	Nonstudy interventions: scopolamine Report language: English Study date: 1962–1963 Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Low risk	Quote: "The hospital pharmacy coded the two groups" of study medications
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Neither the physician nor the patient knew whether the active substance or placebo was being used."

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately assessed.
Other bias	Unclear risk	Insufficient information.
Kato 1979		
Methods	Allocation method: not given Masking: none Number of centres: one	
Participants	Country: Japan Number enrolled: 27 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=10): minimal wiping débridement Treatment two (n=17): idoxuridine	
Outcomes	‘Fluorescein staining’	
Notes	Nonstudy interventions: pad (débridement group) Report language: Japanese Study date: not given Financial support: not given	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The investigators describe a non-random component in the sequence generation process
Allocation concealment (selection bias)	High risk	Unconcealed allocation procedure.
Blinding (performance bias and detection bias) All outcomes	High risk	No masking was undertaken, and outcome assessment could have been influenced by the lack of a masked assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.
Kitano 1983		
Methods	Allocation method: randomised Masking: single (partial) Number of centres: 21	
Participants	Country: Japan Number enrolled: 55 Average age (range): not given Sex: 34 males, 21 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=25): idoxuridine every 1 or 2 hours Treatment two (n=30): interferon-β 20,000 IU/ml 4 times per day	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: none Report language: Japanese Study date: not given Financial support: not given	
Risk of bias		

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	High risk	Incomplete masking.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Kitano 1985

Methods	Allocation method: randomised Masking: double Number of centres: several
Participants	Country: Japan Number enrolled: 109 (excluding 5 withdrawals) Average age (range): not given Sex: not given Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=55, excluding 3 drop outs): idoxuridine 0.25% ointment 5 times per day Treatment two: (n=54, excluding 2 drop outs): acyclovir 3% ointment 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: none Report language: Japanese Study date: August 1981 – May 1982 Financial support: not given Adverse reactions: "Multiple erosion" (Table 6) occurred in seven of 56 eyes treated with idoxuridine and in 12 of 54 eyes treated with acyclovir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component of the sequence generation process
Allocation concealment (selection bias)	Low risk	Centralized allocation scheme.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Klauber 1982

Methods	Allocation method: not given Masking: double Number of centres: one
Participants	Country: Denmark Number enrolled: 38 Average age (range): 51 (range not given) Sex: 25 males, 13 females

	Inclusion criteria: epithelial keratitis without or with stromal keratitis
Interventions	Treatment one (n=20): idoxuridine 0.5% ointment 5 times per day Treatment two (n=18): acyclovir 3% ointment 5 times per day
Outcomes	'Fluorescein and rose-Bengal staining'
Notes	Nonstudy interventions: scopolamine Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "Punctate staining with Rose-Bengal was the only adverse reaction in 6 patients. A transient staining was localised at the inferior cornea and adjacent conjunctiva in 1 patient treated with ACV, corresponding to the application of the ointment. In the other 5 patients (1 treated with ACV and 4 with IDU) the staining was temporarily localised around the previous ulcer and disappeared with the discontinuation of the ointment."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Low risk	Quote: "The Burroughs Wellcome Foundation, Copenhagen supplied the coded 3% acyclovir eye ointment and the coded 0.5% idoxuridine eye ointment."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Kumar 1987

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: India Number enrolled: 36 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=17): idoxuridine 0.5% ointment 5 times per day Treatment two (n=19): acyclovir 3% ointment 5 times per day
Outcomes	'Fluorescein staining'
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The authors describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "[Idoxuridine] and acyclovir were in form of ointments, these were wrapped in similar paper and were labelled with different numbers randomly distributed. The master list was kept with the person who was dispensing the drug and was not connected with the study."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
La Lau 1982		
Methods	Allocation method: randomised Masking: double Number of centres: four	
Participants	Country: Netherlands Number enrolled: 59 Average age (range): not given Sex: 34 males, 25 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=28): trifluridine 2% ointment 5 times per day Treatment two (n=31): acyclovir 3% ointment 5 times per day	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "The most frequently observed side effect was superficial punctate keratopathy, showing fluorescein staining outside the area of the herpetic lesions. This occurred in about 70& of patients in both groups...In both groups a few patients complained of a stinging sensation after application of the ointment, but extensive conjunctival hyperaemia was seen in only 3 patients receiving TFT."	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "We used 3% acyclovir and 2% trifluorothymidine ointment, both specially prepared for this trial and packed in identical tubes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Laibson 1964		
Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (cornea): 18 positive of 21 tested	
Participants	Country: United States Number enrolled: 100 Average age (range): 45 (range not given) Sex: 72 males, 28 females Inclusion criteria: dendritic or geographic epithelial keratitis, without or with stromal keratitis	
Interventions	Control one (n=53): distilled water with thimerosal 0.002% hourly day, 2-hourly night Treatment one (n=47): idoxuridine 0.1% solution hourly day, 2-hourly night	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: none Report language: English	

Study date: 1962–1963
Financial support: governmental agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Low risk	Quote: "All patients...were given a plain brown bottle sealed at the neck with a label on it bearing code numbers. The sealed code was held by the supplier (SKF) and was not known to the investigators. The bottles...were used in sequence."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Cautery was necessary in 5 cases because of failure to respond."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Laibson 1977

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: United States Number enrolled: 33 Average age (range): not given Sex: 25 males, 8 females Inclusion criteria: dendritic (30) or geographic (3) epithelial keratitis
Interventions	Treatment one (n=17): idoxuridine solution hourly day, 2-hourly night Treatment two (n=16): trifluridine solution hourly day, 2-hourly night
Outcomes	Epithelial healing
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given Adverse reactions: One patient in the idoxuridine group "developed a drug toxicity."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Quote: "Patients who developed signs of toxicity to the drug were also construed as treatment failures." Thus, the investigators did not distinguish between effectiveness outcomes and withdrawals for other reasons
Other bias	Low risk	The study appears to be free of other sources of bias.

Li 2008

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 58 Average age (range): 38 (10–65) Sex: 22 males, 36 females Inclusion criteria: dendritic (48) or geographic (10) epithelial keratitis
Interventions	Treatment one (n=28): acyclovir 0.1% solution 6 times per day Treatment two (n=30): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: not given Report language: Chinese Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	High risk	No masking was undertaken, and outcome assessment could have been influenced by the lack of a masked assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Liu 2009a

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 36 eyes (29 patients) Average age (range): 40 Sex: 17 males, 12 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=13 eyes, 11 patients): acyclovir 0.3% solution 6 times per day Treatment two (n=23 eyes, 18 patients): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: not given Report language: Chinese Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	High risk	No masking was undertaken, and outcome assessment could have been influenced by the lack of a masked assessor

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.
Luntz 1963		
Methods	Allocation method: alternate patients Masking: none Number of centres: one HSV isolation (cornea): results not reported	
Participants	Country: Great Britain Number enrolled: 22 Average age (range): 49 (20–83) Sex: 15 males, 7 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Control (n=11): neomycin 1% ointment 2 times daily Treatment one (n=11): idoxuridine 0.1% solution hourly	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: atropine, pad, small scraping Report language: English Study date: 1962 Financial support: not given	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Alternate patients were put into 'treated' (with I.D.U.) and 'control' (without I.D.U.) groups."
Allocation concealment (selection bias)	High risk	Allocation based on non-random alternation.
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	High risk	Quote: "Three 'treated' cases were given topical cortisone drops."
MacKenzie 1964		
Methods	Allocation method: not given Masking: none Number of centres: one	
Participants	Country: Great Britain Number enrolled: 80 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=27): carbolization "followed by local chemotherapy" Treatment two (n=25): idoxuridine 0.1% solution hourly day, 2-hourly night Treatment three (n=28): idoxuridine 0.5% ointment 4 times per day	
Outcomes	"The disappearance of staining with 2 per cent fluorescein"	
Notes	Nonstudy interventions: mydriatic Report language: English Study date: not given Financial support: not given Adverse reactions: One case of "S.P.K." was observed in the idoxuridine 0.1% solution	

group, four cases in the idoxuridine 0.5% ointment group, and three in the carbolization group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	High risk	Apparent open allocation scheme.
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking may have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.

Markham 1977

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: Great Britain Number enrolled: 64 Average age (range): 51 (18–87) Sex: 44 males, 20 females Inclusion criteria: dendritic (60) or geographic (4) epithelial keratitis
Interventions	Control (n=20): placebo ointment 4 times per day Treatment one (n=21): idoxuridine 0.5% ointment 4 times per day Treatment two (n=23): vidarabine 3% ointment 4 times per day
Outcomes	Rose-Bengal staining
Notes	Nonstudy interventions: homatropine Report language: English Study date: not given Financial support: governmental agency Adverse reactions (Quote): "No patient had to be removed from the trial because of drug toxicity. In the group receiving Ara-A, two patients developed punctate epithelial keratitis over the lower cornea and away from the ulcer area; two others developed a mild follicular reaction chiefly on the lower tarsal plate and fornix; a further patient developed an allergic skin rash, but this might equally have been due to homatropine. In the group receiving IDU, one patient developed a punctate epithelial keratitis, and three others a mild follicular reaction. ...All reactions were short-lived."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "The drugs were issued according to a fully randomized code, so that neither the patient nor the observer was at any time aware of which therapy had been allocated."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the original 69 patients four failed to attend for sufficient follow-up examinations, and one received incorrect treatment, leaving 64 patients in the trial."
Selective reporting (reporting bias)	Low risk	Quote: "No patient had to be removed from the trial because of drug toxicity."
Other bias	Low risk	The study appears to be free of other sources of bias.

Matthäus 1970

Methods	Allocation method: not given Masking: none Number of centres: one
Participants	Country: Germany Number enrolled: 120 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=33): iodisation plus panthenol ointment Treatment two (n=27): iodisation plus <i>para</i> -fluorophenylalanine 0.1% ointment Treatment three (n=26): cryotherapy plus panthenol ointment Treatment four (n=34): cryotherapy plus <i>para</i> -fluorophenylalanine 0.1% ointment
Outcomes	Fluorescein staining ('Anfärbbarkeit der Hornhaut mit Fluoreszein beurteilt')
Notes	Nonstudy interventions: atropine Report language: German Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Alle Patienten, bei denen die Diagnose einer Keratitis dendritica... wurden zufällig eine der folgenden 4 Therapiegruppen."
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.

Maychuk 1988

Methods	Allocation method: not given Masking: none Number of centres: one
Participants	Country: Russia Number enrolled: 138 Average age (range): not given Sex: not given Inclusion criteria: dendritic (76) or geographic (62) epithelial keratitis
Interventions	Treatment one (n=63): idoxuridine 0.1% solution Treatment two (n=39): acyclovir 3% ointment Treatment three (n=36): acyclovir 3% ointment and leukocyte interferon 10,000 units/ml
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: variable, including corticosteroid Report language: Russian Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.

Allocation concealment (selection bias)	High risk	Open allocation schedule.
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

McCulley 1982

Methods	Allocation method: randomised by table Masking: double Number of centres: five
Participants	Country: United States Number enrolled: 64 Average age (range): 46 (15–80) Sex: 43 males, 21 females Inclusion criteria: dendritic (52) or geographic (12) epithelial keratitis
Interventions	Treatment one (n=34): idoxuridine 0.5% ointment 5 times per day Treatment two (n=30): acyclovir 3% ointment 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "Few adverse reactions were encountered in either treatment group.... The most frequently encountered adverse reaction was superficial punctate keratopathy, which was found in 11% (<i>sic</i>) of patients receiving ACV and 42.4% (<i>sic</i>) of those receiving IDU...and was mild to moderate, not severe."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component to the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Acyclovir ophthalmic ointment, 3%, and IDU ophthalmic ointment, 0.5%, were assigned to patients by a predesignated random code test."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

McGill 1974

Methods	Allocation method: randomised Masking: single Number of centres: one
Participants	Country: Great Britain Number enrolled: 20 Average age (range): 48 (21–79) Sex: not given Inclusion criteria: dendritic (15) or geographic (5) epithelial keratitis
Interventions	Treatment one (n=9): trifluridine 1% aqueous solution 5 times per day Treatment two (n=11): trifluridine 1% viscous solution 5 times per day

Outcomes	Not given
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Meurs 1985

Methods	Allocation method: not given Masking: double Number of centres: one HSV isolation (cornea and conjunctiva): eligibility criterion
Participants	Country: Netherlands Number enrolled: 93 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis (culture-confirmed)
Interventions	Treatment one (n=45): acyclovir ointment 5 times per day and albumin solution every morning Treatment two (n=24): acyclovir ointment 5 times per day and recombinant human interferon- α -2 30 million units/ml every morning Treatment three (n=24): acyclovir ointment 5 times per day and recombinant human interferon- α -2 rod every morning
Outcomes	Partial healing (closure of epithelial wound) and complete healing (no edematous or cystic changes in epithelium)
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.

Other bias	Unclear risk	Study limited to virologically confirmed participants.
Norn 1973		
Methods	Allocation method: randomised Masking: double Number of centres: one Quote: "Virus culture was not performed."	
Participants	Country: Denmark Number enrolled: 29 Average age (range): not given Sex: not given Inclusion 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 day Treatment 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: none Report language: English Study date: 1990–1993 Financial support: not given	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Low risk	Quote: "Each tube was provided with a code number (1–30). The code was broken after the recording of the results."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

O'Day 1975

Methods	Allocation method: not given Masking: none Number of centres: one Quote: "Viral isolation was not attempted routinely."	
Participants	Country: Great Britain Number enrolled: 17 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=9): idoxuridine 0.5% ointment 5 times per day Treatment 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: none Report language: English Study date: not given Financial support: not given	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Random sequence generation (selection bias)	Unclear risk	The investigators describe an allocation sequence process that aimed “to evaluate photoinactivation in comparison with IDU by random selection.” However, it is unclear how “these eight eyes were matched to nine randomly selected eyes that received IDU therapy for dendritic ulcers.”
Allocation concealment (selection bias)	High risk	The investigators apparently used an open allocation schedule
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Idoxuridine-treated eyes “healed in approximately seven days,” but “one of the nine eyes was a failure.”
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	High risk	The investigators “suspended the study because several of the patients [treated with proflavine photoinactivation] ...had mild adverse reactions.”

Panda 1995

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: India Number enrolled: 80 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis (first episode)
Interventions	Treatment one (n=20): idoxuridine 1% ointment 5 times per day Treatment two (n=20): trifluridine 2% ointment 5 times per day Treatment three (n=20): acyclovir 3% ointment 5 times per day Treatment four (n=20): brivudine 1% ointment 5 times per day
Outcomes	“Fluorescein staining and reduced corneal sensitivity“
Notes	Nonstudy interventions: none Report language: English Study date: 1988–1993 Financial support: not given Adverse reactions: Follicular conjunctivitis occurred in one case in the idoxuridine group. Epithelial keratopathy was observed in four cases: three in the idoxuridine group and one in the trifluridine group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data. Thirteen patients were classified as “treatment failures“ by the prespecified definition of being “not healed after 14 days of therapy
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Parlato 1985

Methods	Allocation method: randomised by table Masking: single (partial) Number of centres: one HSV isolation (cornea or conjunctiva): 11 positive of 22 tested, including 10 of 13
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	corneal specimens and 1 of 9 conjunctival specimens
Participants	Country: United States Number enrolled: 34 Average age (range): 46 (15–80) Sex: 25 males, 9 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=8): minimal wiping débridement Treatment two (n=14): trifluridine 1% solution 9 times per day Treatment three (n=12): minimal wiping débridement 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 (débridement group) Report language: English Study date: 1981–1984 Financial support: pharmaceutical industry Adverse reactions (Quote): “Adverse reactions to treatment were minimal. One patient developed superficial punctate keratitis that resolved when treatment was stopped. Mechanical débridement was not associated with notable discomfort in any patients.”

Risk of bias

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: “Patients were placed by random number selections in three treatment categories.”
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: “Healing was determined in a masked fashion by one of two investigators (E.J.C. and P.R.L.) who did not participate in other aspects of patient care in the study...including débridement, patching, and dispensing of medication.” (Note: Another systematic review judged this trial as not double-blind (Guess 2007). While participants were aware of the choice of intervention, this review classifies the study’s blinding status as adequate.)
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: “Thirty-nine patients with a clinical diagnosis of herpes simplex dendritic keratitis were enrolled in the study...[and]...thirty-four (87%) completed the study.” Patients assigned to the minimal-wiping débridement group were considered a treatment failure and received trifluridine “if new dendrites were noted at any follow-up before healing occurred.”
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Patterson 1963a

Methods	Allocation method: not given Masking: double Number of centres: one
Participants	Country: Great Britain Number enrolled: 23 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=13): 199 tissue-culture medium hourly day, 2-hourly night Treatment one (n=10): idoxuridine 0.1% solution hourly day, 2-hourly night
Outcomes	Fluorescein and rose-Bengal staining
Notes	Nonstudy interventions: atropine, pad Report language: English Study date: 1962 Financial support: not given

Risk of bias

Bias	Authors’ judgement	Support for judgement
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Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Patterson 1963b

Methods	Allocation method: not given Masking: double Number of centres: one
Participants	Country: Great Britain Number enrolled: 32 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=15): phenyl mercuric nitrate 0.004% hourly day, 2-hourly night Treatment one (n=17): idoxuridine 0.1% solution hourly day, 2-hourly night
Outcomes	Fluorescein and rose-Bengal staining
Notes	Nonstudy interventions: atropine, pad Report language: English Study date: 1962 Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Patterson 1963c

Methods	Allocation method: not given Masking: double Number of centres: one
Participants	Country: Great Britain Number enrolled: 30 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Control (n=14): placebo hourly day, 2-hourly night Treatment one (n=16): idoxuridine 0.1% solution hourly day, 2-hourly night

Outcomes	Fluorescein and rose-Bengal staining	
Notes	Nonstudy interventions: atropine, pad Report language: English Study date: 1962 Financial support: not given	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.
Patterson 1967a		
Methods	Allocation method: not given Masking: none Number of centres: one	
Participants	Country: Great Britain Number enrolled: 77 Average age (range): 33 (1–66) Sex: 54 males, 23 females Inclusion criteria: dendritic (74) or geographic (3) epithelial keratitis	
Interventions	Control (n=39): carbolization Treatment one (n=38): idoxuridine ointment 5 times per day	
Outcomes	Rose-Bengal staining	
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	High risk	Quote: “Those cases treated with IDU which did not show progression to healing at 5 days were classed as failures and cauterized; ulcers treated initially with cauterization which showed dendritic figures in the next few days were classed as failures and either cauterized again or treated with IDU.”
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.
Patterson 1967b		

Methods	Allocation method: not given Masking: none Number of centres: one
Participants	Country: Great Britain Number enrolled: 28 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis with disciform keratitis
Interventions	Control (n=11): carbolization Treatment one (n=17): idoxuridine ointment 5 times per day
Outcomes	Rose-Bengal staining
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Pavan-Langston 1976

Methods	Allocation method: randomised Masking: double Number of centres: several
Participants	Country: United States Number enrolled: 169 Average age (range): 47 (2–85) Sex: 115 males, 54 females Inclusion criteria: dendritic (133) or geographic (36) epithelial keratitis
Interventions	Treatment one (n=82): idoxuridine ointment 5 times per day Treatment two (n=87): vidarabine ointment 5 times per day
Outcomes	Epithelial healing
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: pharmaceutical industry Adverse reactions: There were six cases of “drug-related adverse experiences” but no case of superficial keratopathy in the idoxuridine group. There were ten cases of “drug-related adverse experiences” including one case of “marked superficial punctate keratitis” in the vidarabine group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: “Drugs were identified for patient and investigator by number only; the code was not broken until the end of the study, or until a patient was removed.”

Blinking (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Pavan-Langston 1981

Methods	Allocation method: randomised Masking: double Number of centres: two HSV isolation (conjunctiva): 3 positive of 81 tested before treatment
Participants	Country: United States Number enrolled: 41 Average age (range): not given (16–82) Sex: 23 males, 18 females Inclusion criteria: dendritic (36) or geographic (5) epithelial keratitis
Interventions	Treatment one (n=21): vidarabine 3% ointment 5 times per day Treatment two (n=20): acyclovir 3% ointment 5 times per day
Outcomes	Epithelial healing
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: pharmaceutical industry and governmental agency Adverse reactions (Quote): “Adverse reactions for vidarabine included two instances of superficial punctate keratitis and one instance of severe pain (possibly related but lasting only one day). In the acyclovir-treated group, one patient reported itching and discontinued the drug within one week of entering the study...[but] there was no objective sign of allergic reaction. Approximately 25% of patients in both groups had superficial punctate keratitis...not believed to be drug-related.”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: “Drugs were packaged in a sequential order by random code number designation and were also dispensed sequentially” according to an ancillary, subsequent report (Laibson et al, 1982)
Blinking (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Power 1991

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: Ireland Number enrolled: 60 Average age (range): 45 (9–72) Sex: 43 males, 17 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=30): trifluridine 1% solution 5 times per day

	Treatment two (n=30): brivudine 0.1% solution 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "Side effects were seen infrequently. Stinging on initial application of the drops was noted by three patients in the BVDU group and in five who were treated with TFT...One patient in the TFT group developed a punctate epitheliopathy...There was no evidence of epithelial toxicity in any of the patients treated with BVDU."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Treatment consisted of either BVDU 0.1% or TFT 1.0% ophthalmic drops, which were packaged in identical bottles and prescribed five times daily."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient in the BVDU group was lost to follow-up and was not included in the analysis."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Richter 1986

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: Germany Number enrolled: 57 Average age (range): not given (11–71) Sex: 34 males, 23 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=32): brivudine solution Treatment two (n=25): brivudine solution and epithelial abrasion
Outcomes	Fluorescein staining ('den fluoreszeinnegativen Schluß der Dendriticafigur')
Notes	Nonstudy interventions: cycloplegic, antibiotic Report language: German Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	High risk	The investigators apparently used an open allocation schedule
Blinding (performance bias and detection bias) All outcomes	High risk	Unmasked study design could have influenced outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.

Other bias	Unclear risk	Insufficient information.
Serifoglu 1987		
Methods	Allocation method: randomised Masking: single Number of centres: one	
Participants	Country: Turkey Number enrolled: 25 Average age (range): 36 (4–78) Sex: 17 males, 8 females Inclusion criteria: dendritic (21) or geographic (4) epithelial keratitis	
Interventions	Treatment one (n=12): minimal wiping débridement and idoxuridine 0.5% ointment 5 times per day Treatment two (n=13): minimal wiping débridement and acyclovir 3% ointment 5 times per day	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: none Report language: Turkish Study date: 1985–1986 Financial support: not given	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of apparent masking could have influenced outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.

Srinivas 1993

Methods	Allocation method: non-random Masking: none Number of centres: one	
Participants	Country: India Number enrolled: 40 Average age (range): not given Sex: 18 males, 14 females, 8 children Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=20): idoxuridine solution 5 times per day Treatment two (n=20): idoxuridine solution 5 times per day and oral acyclovir 200 mg 3 times per day	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: cycloplegic Report language: English Study date: not given Financial support: not given	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The investigators describe a non-random component in the sequence generation process
Allocation concealment (selection bias)	High risk	Quote: "The first twenty cases were treated with Acyclovir...along with IDU drops.... The second 20 cases received the IDU eye drops."

Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition or delayed healing.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Struck 1989

Methods	Allocation method: not given Masking: none Number of centres: one
Participants	Country: Germany Number enrolled: 109 Average age (range): not given (1–89) Inclusion criteria: dendritic epithelial keratitis without or with stromal keratitis
Interventions	Control (n=34): débridement, débridement with iodination, cryoapplication, or other Treatment one (n=28): idoxuridine 0.1% solution 5 times per day Treatment two (n=16): trifluridine 1% solution 5 times per day Treatment three (n=31): brivudine 0.1% solution
Outcomes	Fluorescein and rose-Bengal straining
Notes	Nonstudy interventions: none Report language: German Study date: 1981–1985 Financial support: not given Adverse reactions (superficial keratopathy): none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	High risk	Investigators enrolling participants could possibly have foreseen treatment assignment
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of apparent masking could have influenced outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data within first 14 days of treatment and follow up
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Sugar 1980

Methods	Allocation method: randomised Masking: double Number of centres: six
Participants	Country: United States Number enrolled: 61 Average age (range): 46 (range not given) Sex: 43 males, 18 females Inclusion criteria: dendritic (44) or geographic (17) epithelial keratitis
Interventions	Treatment one (n=27): idoxuridine 0.1% solution 19 times per day Treatment two (n=34): trifluridine 1% solution 9 times per day
Outcomes	Not given
Notes	Nonstudy interventions: none

Report language: English
 Study date: not given
 Financial support: pharmaceutical industry
 Adverse reactions: "One patient taking IDU developed follicular conjunctivitis." "No patients developed allergic reactions to F₃T"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "An administrative assistant dispensed medication in the double-masked protocol on a random basis."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "During the double-masked study the ophthalmologist who examined the patient was not aware of the drug or dosage schedules being used." [Note: Another systematic review judged this trial as not double-blind (Guess 2007).]
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Sundmacher 1976a

Methods	Allocation method: randomised Masking: single (partial) Number of centres: one HSV isolation (cornea and conjunctiva): 55 positive of 73 tested
Participants	Country: Germany Number enrolled: 55 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=17): thermomechanical débridement and placebo solution 3 times per day Treatment two (n=22): thermomechanical débridement and human leukocyte interferon 62,500 units/ml 3 times per day Treatment 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 micropunctations'
Notes	Nonstudy interventions: scopolamine, lubricating ointment, pad Report language: English Study date: not given Financial support: governmental agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a non-random component in the sequence generation process
Allocation concealment (selection bias)	High risk	"Group 1 received uncoded interferon, and groups 2 and 3 were treated with coded interferon or mock interferon, respectively, using sequentially numbered drug containers of similar appearance. However, the same investigators who performed débridement performed the outcome assessment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Group 1 was treated with human leukocyte interferon...while] groups 2 and 2 were studied on a double-blind basis."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Fifty-five (75%) of 73 patients in the study yielded isolated herpes simplex virus before treatment, and further discussion will be confined to the results in these patients."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.

Other bias	Low risk	The study appears to be free of other sources of bias.
Sundmacher 1976b		
Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (cornea): 40 positive of 51 tested	
Participants	Country: Germany Number enrolled: 40 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=18): thermomechanical débridement and human albumin 2 times per day Treatment two (n=22): thermomechanical débridement and human leukocyte interferon 3 million units/ml 2 times per day	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: homatropine, lubricating ointment, pad Report language: English Study date: not given Financial support: governmental agency	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Centralized allocation of coded vials, but "one vial could be used for more than one patient."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Only those 40 cases...in which the diagnosis was virologically confirmed and the virologic follow-up was without technical failures were accepted for final evaluation."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Sundmacher 1978a

Methods	Allocation method: randomised Masking: none Number of centres: one HSV isolation (cornea): 42 positive of 42 tested	
Participants	Country: Germany Number enrolled: 42 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=18): thermomechanical débridement plus human leukocyte interferon 6 million units/ml once per day Treatment two (n=24): minimal wiping débridement plus human leukocyte interferon 6 million units/ml once per day	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: homatropine Report language: English Study date: not given Financial support: governmental agency	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	The outcome assessor differed from the treating investigator
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	High risk	Fifteen of 42 patients underwent additional débridement.

Sundmacher 1978b

Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (cornea): 38 positive of 53 tested
Participants	Country: Germany Number enrolled: 38 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=18): thermomechanical débridement plus human leukocyte interferon 1 million units/ml once per day Treatment two (n=20): thermomechanical débridement plus human fibroblast interferon 1 million units/ml once per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: homatropine Report language: English Study date: not given Financial support: governmental agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 53 enrolled patients, "these were reduced to 38 persons with virologically proven herpes simplex virus disease" for analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Sundmacher 1981a

Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva): eligibility criterion
Participants	Country: Germany Number enrolled: 51 Average age (range): not given Sex: not given

	Inclusion criteria: dendritic epithelial keratitis (culture-confirmed)
Interventions	Treatment one (n=24): trifluridine 1% solution 5 times per day plus human leukocyte interferon 10 million units/ml once per day Treatment 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: none Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Use of coded eyedropper vials.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only "virologically proven dendritic keratitis" cases were reported and analysed
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Study limited to virologically confirmed participants.

Sundmacher 1981b

Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva): eligibility criterion
Participants	Country: Germany Number enrolled: 70 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis (culture-confirmed)
Interventions	Treatment one (n=20): trifluridine 1% solution 5 times per day and albumin solution once per day Treatment two (n=24): trifluridine 1% solution 5 times per day and human leukocyte interferon 1 million units/ml once per day Treatment 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: none Report language: English Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Low risk	Use of coded eyedropper vials.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias)	High risk	Quote: "For final evaluation, only the results of those patients were used who had delivered positive virus cultures before initiation of therapy."

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Study limited to virologically confirmed participants.
Sundmacher 1984a		
Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva): eligibility criterion	
Participants	Country: Germany Number enrolled: 36 Average age (range): not given Sex: not given Inclusion criteria: dendritic (29) or geographic (7) epithelial keratitis (culture-confirmed)	
Interventions	Treatment one (n=17): trifluridine 1% solution 5 times per day plus human leukocyte interferon 30 million units/ml once per day Treatment 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: none Report language: English Study date: not given Financial support: not given	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "α-interferon was prepared and bottled in identical calibrated dispensing systems and then coded" by a central facility
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The only patients accepted for final evaluation were those in whom a virus culture from the cul-de-sac before the initiation of therapy had yielded herpes simplex virus."
Selective reporting (reporting bias)	Unclear risk	"Thirty-eight patients...were selected for the study," but the report gives results for 36, in one treatment group and 17 in the other treatment group
Other bias	Unclear risk	Study limited to virologically confirmed participants.
Sundmacher 1985		
Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva): 32 positive of 42 tested	
Participants	Country: Germany Number enrolled: 32 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=17): trifluridine 1% solution 5 times per day plus human interferon-α 30 million units/ml once per day Treatment two (n=15): trifluridine 1% solution 5 times per day plus recombinant inter-feron-α-2 23 million units/ml once per day	
Outcomes	Fluorescein staining 'except for minor punctate stainings'	

Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Centralized allocation facility.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only virologically confirmed participants were analysed.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.
Sundmacher 1987		
Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva): 45 positive of 75 tested	
Participants	Country: Germany Number enrolled: 45 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=16): trifluridine 1% solution 5 times per day plus recombinant interferon- α 30 million units/ml once per day Treatment two (n=14): trifluridine 1% solution 5 times per day plus recombinant interferon- γ 30 million units/ml once per day Treatment three (n=8): trifluridine 1% solution 5 times per day plus recombinant interferon- α 0.3 million units/ml once per day and interferon- γ 0.3 million units/ml once per day Treatment four (n=7): trifluridine 1% solution 5 times per day plus recombinant interferon- α 1.5 million units/ml once per day and interferon- γ 1.5 million units/ml once per day	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Coded eyedropper vials dispensed from centralized facility.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of 75 patients who entered the study 30 had to be excluded because all virus cultures turned out negative or because of noncompliance."
Selective reporting (reporting bias)	Unclear risk	Insufficient information.

Other bias	Unclear risk	Insufficient information.
Travers 1978		
Methods	Allocation method: not given Masking: none Number of centres: one	
Participants	Country: Great Britain Number enrolled: 100 Average age (range): 50 (range not given) Sex: 52 males, 48 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=50): vidarabine ointment 5 times per day Treatment two (n=50): trifluridine solution 5 times per day	
Outcomes	Rose-Bengal staining	
Notes	Nonstudy interventions: mydriatic, antiglaucoma agents ("as necessary") Report language: English Study date: not given Financial support: not given	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Uchida 1981

Methods	Allocation method: randomised by code Masking: double Number of centres: eight	
Participants	Country: Japan Number enrolled: 54 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Control (n=17): minimal wiping débridement and human albumin 4 times per day Treatment one (n=17): minimal wiping débridement and idoxuridine solution hourly day, 2-hourly night Treatment two (n=20): minimal wiping débridement and fibroblast interferon 1 million units/ml 4 times per day	
Outcomes	'Disappearance of gross staining areas with fluorescein'	
Notes	Nonstudy interventions: gentamicin solution Report language: English Study date: not given Financial support: not given	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process

Allocation concealment (selection bias)	Low risk	Quote: "the code was kept by National Institute of Health, Tokyo, and was broken after the results had been evaluated."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Uchida 1982

Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (cornea): 41 positive (by culture or immunofluorescent antigen) of 44 tested
Participants	Country: Japan Number enrolled: 68 (5 others disqualified) Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=32): human fibroblast interferon 1000 units/ml 4 times per day Treatment two (n=36): human fibroblast interferon 1 million units/ml 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: none Report language: Japanese Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigator describes a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Samples to be tested were coded.... The code was kept by National Institute of Health Tokyo, and broken after the result had been evaluated."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Out of 73 patients subjected to the double blind test, 5 were excluded from the final evaluation; three patients did not follow the medication schedule, and two were considered to have dendrites with coexisting metaherpetic alteration before treatment."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Van Bijsterveld 1980

Methods	Allocation method: randomised Masking: double Number of centres: one
Participants	Country: Netherlands Number enrolled: 56 Average age (range): 46 (range not given) Sex: 36 males, 28 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=28): vidarabine 3% ointment 5 times per day Treatment 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: scopolamine Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "In 5 out of 17 patients that received the virostatic treatment longer than 14 days a very mild diffuse epithelial staining was observed with Bengal rose. Four of these patients received ara-A and 1 received treatment with TFT."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information. The investigators did not describe how the sequence generation process was developed
Allocation concealment (selection bias)	Low risk	Quote: "Each patient received a coded treatment sequentially allocated by the central dispensing unit.... The ointment tubes were identical in design."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Seven out of 63 treated ulcers failed to heal within 23 days, which was our arbitrary limit. These cases were excluded from the analysis."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Van Bijsterveld 1989

Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (cornea): results not reported
Participants	Country: Netherlands Number enrolled: 41 Average age (range): 39 (7–81) Sex: 22 males, 19 females Inclusion criteria: dendritic (33) or geographic (8) epithelial keratitis
Interventions	Treatment one (n=22): brivudine 1% ointment 5 times per day and albumin rod daily Treatment two (n=19): brivudine 1% ointment 5 times per day and recombinant inter-feron- α -2 rod (1.5 million units) daily
Outcomes	'Wound closure'
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "In the present investigation no toxic effects, including drug allergy, were observed."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.

Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Vannini 1986		
Methods	Allocation method: randomised Masking: single Number of centres: one HSV isolation (conjunctiva): 13 positive of 20 tested, including 11 HSV-1 and 2 HSV-2	
Participants	Country: Italy Number enrolled: 20 Average age (range): 41 (18–76) Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=10): idoxuridine solution 7 times per day Treatment two (n=10): interferon- β 1 million units/ml 7 times per day	
Outcomes	Fluorescein staining	
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: pharmaceutical industry Adverse reactions: Seven cases in the idoxuridine group developed “superficial punctate keratitis [that] was evident in the days subsequent to the disappearance of dendritis (<i>sic</i>), which must be interpreted as a toxic effect of IDU on the corneal epithelium.”	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	High risk	Investigators enrolling participants could possibly have foreseen open treatment assignments
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Wang 2004		
Methods	Allocation method: randomised Masking: single Number of centres: one	
Participants	Country: China Number enrolled: 60 Average age (range): 36 (7–65) Sex: 32 males, 28 females Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=30): topical acyclovir 0.1% solution 5 to 8 times per day Treatment two (n=30): oral acyclovir 200 mg 5 times per day	
Outcomes	Epithelial healing	
Notes	Nonstudy interventions: none Report language: Chinese Study date: not given Financial support: not given	
Risk of bias		

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Wellings 1972

Methods	Allocation method: randomised by table Masking: double Number of centres: two
Participants	Country: Great Britain and United States Number enrolled: 78 Average age (range): not given Sex: not given Inclusion criteria: dendritic (69) or geographic (9) epithelial keratitis
Interventions	Treatment one (n=38): idoxuridine 0.1% solution 5 times per day Treatment two (n=40): trifluridine 1% solution 5 times per day
Outcomes	Fluorescein and rose-Bengal staining
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: governmental agency Adverse reactions: "No symptoms or signs were observed in either center during the two-week period of administration of either drug that could be ascribed to side effect of toxicity from, or allergy to either preparation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Each patient received randomly allocated coded treatment by the pharmacist, according to prearranged tables held in the pharmacy.... The two preparations were indistinguishable other than by the code."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "In no case during the trial was any observer, or any patient, aware of the identity of the antiviral drug being used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Patients whose ulcers failed to heal were taken out of the trial and treated by debridement or if slow healing had been taking place under the coded antiviral therapy, this was continued for a further short period."
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Wilhelmus 1981a

Methods	Allocation method: randomised by table Masking: none Number of centres: one
Participants	Country: Great Britain Number enrolled: 50

	Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=25): minimal wiping débridement and acyclovir 3% ointment 5 times per day Treatment 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: atropine Report language: English Study date: not given Financial support: private foundation Adverse reactions (Quote): "Whether debridement was performed or not, the only adverse symptom related to topical acyclovir was a mild transient stinging sensation immediately after application of the antiviral ointment in nine (18%) patients. We found mild punctate epithelial staining with Bengal rose of the inferior bulbar conjunctiva and corneoscleral limbus remote from the original lesion in eight (16%) patients...[that] disappeared within three days after discontinuation of the antiviral medication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Central allocation of treatment assignment to consecutive patients
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Xu 2009a

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 36 Average age (range): 45 (10–68) Sex: 19 males, 17 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=18): acyclovir 0.1% solution 4 times per day Treatment two (n=18): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: none Report language: Chinese Study date: not given Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	High risk	Lack of masking could have influenced outcome assessment.

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Unclear risk	Insufficient information.
Yamazaki 1984a		
Methods	Allocation method: not given Masking: single Number of centres: one	
Participants	Country: Japan Number enrolled: 40 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=21): minimal wiping débridement and idoxuridine 0.1% solution Treatment two (n=19): minimal wiping débridement and fibroblast interferon 20,000 units/ml	
Outcomes	Not given	
Notes	Nonstudy interventions: not given Report language: English Study date: not given Financial support: not given	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.
Yamazaki 1984b		
Methods	Allocation method: not given Masking: single Number of centres: one	
Participants	Country: Japan Number enrolled: 74 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=41): albumin solution 4 times per day Treatment two (n=33): human leukocyte interferon 20 million units/ml 4 times per day	
Outcomes	Not given	
Notes	Nonstudy interventions: not given Report language: English Study date: not given Financial support: not given	
Risk of bias		

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.
Yamazaki 1984c		
Methods	Allocation method: not given Masking: single Number of centres: one	
Participants	Country: Japan Number enrolled: 36 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis	
Interventions	Treatment one (n=16): recombinant interferon- α 1000 units/ml 4 times per day Treatment two (n=20): recombinant interferon- α 10 million units/ml 4 times per day	
Outcomes	Not given	
Notes	Nonstudy interventions: not given Report language: English Study date: not given Financial support: not given	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.
Yang 2000		
Methods	Allocation method: not given Masking: double Number of centres: one	
Participants	Country: China Number enrolled: 137 Average age (range): 33 (1–65) Sex: 93 males, 44 females Inclusion criteria: dendritic (55) epithelial keratitis	

Interventions	Treatment one (n=70): acyclovir 0.1% solution Treatment two (n=67): ganciclovir 0.1% solution
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: not given Report language: Chinese Study date: not given Financial support: governmental agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information.

Yeakley 1981

Methods	Allocation method: randomised by code Masking: double Number of centres: one HSV isolation (conjunctiva): 13 positive of 40 tested
Participants	Country: United States Number enrolled: 40 Average age (range): 49 (7–81) Sex: 27 males, 13 females Inclusion criteria: dendritic (38) or geographic (2) epithelial keratitis
Interventions	Treatment one (n=21): vidarabine 3% ointment 5 times per day Treatment two (n=19): acyclovir 3% ointment 5 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: none Report language: English Study date: not given Financial support: not given Adverse reactions (Quote): "Diffuse superficial punctate epitheliopathy was noted in one patient on acyclovir... and resolved within two days after the drug was discontinued. No other adverse effects were noted in either drug treatment group during the course of therapy."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "The drugs were packaged in sequential order by random code number designation and were dispensed sequentially."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients used the medication as directed, and no patient was lost to follow-up prior to complete corneal re-epithelialization."

Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Young 1982		
Methods	Allocation method: randomised Masking: double Number of centres: one HSV isolation (conjunctiva): 35 positive of 93 tested	
Participants	Country: Great Britain Number enrolled: 93 Average age (range): 51 (range not given) Sex: 62 males, 31 females Inclusion criteria: dendritic (85) or geographic (8) epithelial keratitis	
Interventions	Treatment one (n=45): vidarabine 3% ointment 5 times per day Treatment two (n=48): acyclovir 3% ointment 5 times per day	
Outcomes	Not given	
Notes	Nonstudy interventions: atropine Report language: English Study date: not given Financial support: pharmaceutical industry Adverse reactions (Quote): “Two patients developed adverse symptoms during therapy possibly due to their antiviral therapy. One patient on acyclovir experienced an allergic response; this could also have been caused by the atropine drops being administered concurrently. One patient on ara-A complained of grittiness after application of the ointment. No other adverse effect was seen in this group of patients.”	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: “The ophthalmic ointments were provided in identical tubes bearing a trial number, and the entire study was carried out in a double-blind manner.”
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (reporting bias)	Low risk	The prespecified primary outcome was adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abboud 1967	Non-concurrent treatment allocation Treatment one (n=39): idoxuridine 0.1% solution Treatment two (n=24, subset of treatment one following failure to heal within one week using idoxuridine): iodine cauterization
Akberova 2000	Non-concurrent treatment allocation Treatment one (n=118): para-aminobenzoic acid 0.007% (aktipal), an interferon inducer, 4 to 6 times per day Treatment two (n=34): idoxuridine solution 8 to 10 times per day Treatment three (n=41): acyclovir ointment 5 times per day
Assetto 1981	Insufficient data provided Treatment one (n=8): wiping débridement Treatment two (n=8): idoxuridine 0.1% solution 5 times per day Treatment three (n=8): cytarabine solution 5 times per day Treatment four (n=8): idoxuridine 0.1% solution and oral isoprinosine 3 times per day Treatment five (n=8): cytarabine solution and oral isoprinosine 3 times per day Treatment six (n=8): trifluridine 1% solution 5 times per day
Babushkin 1993	Insufficient data provided Treatment one (n=60): idoxuridine 0.1% solution Treatment two (n=24): acyclovir 3% ointment
Bianchetti 1964	Non-concurrent treatment allocation Treatment one (n=31): idoxuridine 0.1% solution (Stoxil or Dispersa) Treatment two (n=33): idoxuridine ointment or gel (Dispersa or Chauvin-Blache)
Butikova 1990	Non-concurrent treatment allocation Control (n=10): historical controls Treatment one (n=18): antiherpetic immunoglobulin
Chen 2000	Botanical or herbal preparation Treatment one (n=80): antiviral solution Treatment two (n=86): antiviral solution and botanical extract
Chen 2007	Insufficient data provided Treatment one (n=43): acyclovir 0.1% solution Treatment two (n=69): acyclovir 0.1% solution and recombinant interferon- α -2b and intravenous acyclovir
Chen 2009	Botanical or herbal preparation Treatment one (n=54): antiviral Treatment two (n=46): antiviral and botanical extract
Corina 1998	Outcome not based on epithelial healing Treatment one (n=65): idoxuridine Treatment two (n=76): acyclovir ointment
Corina 1999	Botanical or herbal preparation Treatment one (n=26): acyclovir ointment Treatment two (n=26): acyclovir ointment with botanical extract
Deng 2003	Botanical or herbal preparation Treatment one (n=53): acyclovir 0.1% solution Treatment two (n=53): acyclovir 0.1% solution and subconjunctival ribavirin and botanical extract
Du 2008	Botanical or herbal preparation Treatment one (n=71): antiviral Treatment two (n=78): antiviral and traditional Chinese medicine
Dundarov 1998	Non-concurrent treatment allocation Control (n=19): "symptomatic medicines" Treatment one (n=55): pandavir (nigericin 0.001%) 2 times on first day then 10 to 12 times per day Treatment two (n=52): pandavir (nigericin 0.001%) with interferon- α 10,000 to 50,000 IU/ml 2 times on first day then 10 to 12 times per day
Elze 1979	Non-concurrent treatment allocation Treatment one (n=97): ethyldeoxyuridine 0.15% solution topically and 0.5% subconjunctivally daily Treatment two (n=71): ethyldeoxyuridine 2% solution topically and 0.5% subconjunctivally and 0.3% gel, with initial iodination débridement
Fellinger 1980	Insufficient data provided Treatment one (n=13): idoxuridine 0.1% solution and 0.5% ointment Treatment two (n=16): trifluridine 1% solution and 2% ointment

Study	Reason for exclusion
	Treatment three (n=13): iodination débridement and idoxuridine Treatment four (n=18): iodination débridement and trifluridine
Feng 2004	Botanical or herbal preparation Treatment one (n=52): acyclovir 0.1% solution Treatment two (n=52): acyclovir 0.1% solution and botanical extract
Galin 1976	Insufficient data provided Treatment one (n=20): idoxuridine 0.5% solution Treatment two (n=19): polyinosinic:polycytidylic acid 0.1% solution
Gao 2006	Botanical or herbal preparation Treatment one (n=42): antiviral therapy Treatment two (n=44): antiviral therapy and botanical extract
Gilkes 1963	Non-concurrent treatment allocation Treatment one (n=77): historical controls treated by "carbolicization or iodization" débridement Treatment two (n=82): idoxuridine 0.1% solution hourly or 0.5% ointment 2-hourly
Gu 2005	Insufficient data provided Treatment one (n=20): acyclovir 0.1% solution 4 to 6 times per day Treatment two (n=19): acyclovir 0.1% solution 4 to 6 times per day and recombinant interferon- α 2b 3 to 4 times per day
Gundersen 1936	Non-concurrent treatment allocation Control (n=53): historical controls using "various mydriatics and antiseptics" Treatment one (n=97): focal iodination débridement Treatment two (n=45): entire corneal iodination débridement
Guo 2003	Insufficient data provided Treatment one: (n=34): "conventional antiviral therapy" Treatment two (n=35): cryotherapy and "conventional antiviral therapy"
Hao 2008	Botanical or herbal preparation Treatment one (n=60): antiviral Treatment two (n=68): antiviral and botanical extract
Herbert 1987	Non-concurrent treatment allocation Treatment one (n=20): scraping débridement with trifluridine 1% solution 8 times daily for one day then 5 times daily Treatment two (n=11): trifluridine 1% solution 8 times daily for one day then 5 times daily
Hilsdorf 1969	Insufficient data provided Treatment one (n=20): iodination débridement with idoxuridine ointment Treatment two (n=20): cryotherapy with idoxuridine ointment
Horoden scy 1979	Non-concurrent treatment allocation Treatment one (n=17): idoxuridine 0.1% solution Treatment two (n=17): cytarabine 0.1% solution
Hua 1997	Botanical or herbal preparation Treatment one (n=52): acyclovir 0.1% solution every 2 hours Treatment two (n=60): botanical extract one time per day
Huang 2008b	Botanical or herbal preparation Treatment one (n=33): antiviral Treatment two (n=33): antiviral and botanical extract
Huang 2009	Insufficient data provided Treatment one (n=36): acyclovir 0.1% solution Treatment two (n=29): acyclovir 0.1% solution and recombinant interferon- α solution
Inocencio 1982	Insufficient data provided Treatment one (n=9): idoxuridine 0.5% ointment 5 times daily Treatment two (n=14): acyclovir 3% ointment 5 times daily
Jin 1992	Insufficient data provided Treatment one (n=41): acyclovir 0.1% solution Treatment two (n=59): recombinant human interferon- α 1 million IU/ml
Jones 1979	Outcome not based on epithelial healing Treatment one (n=12): wiping débridement and placebo ointment 5 times per day Treatment two (n=13): wiping débridement and acyclovir 3% ointment 5 times per day
Kasparov 1972	Insufficient data provided Treatment one (n=16): idoxuridine

Study	Reason for exclusion
	Treatment two (n=43): polyadenylic:polyuridylic acid solution Treatment three (n=167): various immunomodulators such as mebavin (IBC) Treatment four (n=33): immunomodulator(s) with débridement by either diathermy or cryotherapy
Kasparov 1974	Insufficient data provided Control (n=30): "nonspecific drugs, such as antibiotics, sulphonyl amides, vitamins" Treatment one (n=28): idoxuridine 0.1% solution Treatment two (n=27): polyadenylic:polyuridylic acid solution Treatment three (n=15): idoxuridine 0.1% solution and polyadenylic:polyuridylic acid solution
Kasparov 1990	Non-concurrent treatment allocation Treatment one (n=46): idoxuridine Treatment two (n=80): thermal débridement and polyadenylic:polyuridylic acid solution in soft contact lens
Kasparov 1991	Insufficient data provided Treatment one (n=45): acyclovir 3% ointment Treatment two (n=65): polyadenylic:polyuridylic acid solution Treatment three (n=40): acyclovir 3% ointment and polyadenylic:polyuridylic acid solution
Koev 2007	Insufficient data provided Treatment one (n=25): acyclovir ointment Treatment two (n=24): acyclovir ointment and pandavir Treatment three (n=26): acyclovir ointment and pandavir and laser débridement
Kolomiets 1986	Insufficient data provided Treatment one (n=10): non-specific immunoglobulin Treatment two (n=14): antiherpetic immunoglobulin
Kuyama 1979	Insufficient data provided Treatment one (n=not stated): interferon- α 1 million IU/ml Treatment two (n=not stated): interferon- β 1 million IU/ml
Leopold 1965	Insufficient data provided Treatment one (n=5): idoxuridine solution Treatment two (n=5): cytarabine solution
Li 1998	Botanical or herbal preparation Treatment one (n=30): acyclovir 0.1% solution and botanical extract (Ban Lan Gen) by subconjunctival and intramuscular injection Treatment two (n=31): acyclovir 0.1% solution and ribavirin by subconjunctival injection
Lin 2009	Insufficient data provided Treatment one (n=27): acyclovir Treatment two (n=22): acyclovir and polyinosinic-polycytidylic acid injection
Liu 2003	Insufficient data provided Treatment one (n=21): topical antiviral Treatment two (n=21): topical antiviral and subconjunctival interferon
Liu 2007	Insufficient data provided Treatment one (n=50): acyclovir 0.1% solution Treatment two (n=46): acyclovir 0.1% solution and fibroblast growth factor
Liu 2009b	Botanical or herbal preparation Treatment one (n=48): acyclovir Treatment two (n=48): acyclovir and botanical extract
Ma 1982	Non-concurrent treatment allocation Treatment one (n=29): idoxuridine 0.1% solution Treatment two (n=8): vidarabine 0.5% solution Treatment three (n=8): acyclovir 0.1% solution Treatment four (n=11): foscarnet 1% to 5% solution Treatment five (n=58): cyclocytidine 0.05% solution Treatment six (n=14): cyclocytidine 0.1% solution Treatment seven (n=6): cytarabine 0.025% solution Treatment eight (n=4): cyclocytidine monophosphate 0.5% solution
Ma 2006a	Botanical or herbal preparation Treatment one (n=60): acyclovir 0.1% solution 4 times per day Treatment two (n=60): acyclovir 0.1% solution 4 times per day and botanical extract 4 times per day

Study	Reason for exclusion
Mal'khanov 1991	Varied eligibility criteria Treatment one (n=15): thymalin (thymic peptide) Treatment two (n=12): tactivin (thymic peptide) Treatment three (n=48): pirogenal (bacterial lipopolysaccharide) Treatment four (n=20): gamma-globulin
Marquardt 1971	Non-concurrent treatment allocation Treatment one (n=87): thermocauterization débridement Treatment two (n=75): scraping débridement Treatment three (n=64): idoxuridine Treatment four (n=64): unspecified treatment
Martenet 1979	Non-concurrent treatment allocation Treatment one (n=8): idoxuridine 0.1% solution hourly during day and 0.25% ointment at night Treatment two (n=1): iododeoxycytidine 0.15% solution hourly during day and 1% ointment at night
Matalia 1987	Non-concurrent treatment allocation Treatment one (n=102, eyes with epithelial keratitis): idoxuridine Treatment two (n=104, eyes with epithelial keratitis): vidarabine Treatment three (n=22, eyes with epithelial keratitis): trifluridine Treatment four (n=100, eyes with epithelial keratitis): acyclovir Treatment five (n=36, eyes with epithelial keratitis): vidarabine and idoxuridine Treatment six (n=52, eyes with epithelial keratitis): vidarabine and acyclovir
Mathur 1984	Insufficient data provided Treatment one (n=50): iodination débridement Treatment two (n=20): cryotherapy débridement Treatment three (n=24): cryotherapy débridement and topical autologous serum Treatment four (n=30): wiping débridement Treatment five (n=30): wiping débridement and idoxuridine 0.1% solution 3 times per day
Maychuk 1990	Varied eligibility criteria Treatment one (n=28): oral pirprofen Treatment two (n=24): intramuscular pirprofen Treatment three (n=29): oral indomethacin
McGill 1981	Insufficient data provided Treatment one (n=29): vidarabine 3% ointment 5 times per day Treatment two (n=28): acyclovir 3% ointment 5 times per day
Mohan 1987	Insufficient data provided Treatment one (n=19): vidarabine 3% ointment 5 times per day Treatment two (n=21): acyclovir 3 ointment 5 times per day
Morimoto 1986	Non-concurrent treatment allocation Treatment one (n=22): idoxuridine ointment Treatment two (n=15): acyclovir 3% ointment
Patterson 1967c	Insufficient data provided (steroid-enhanced dendritic keratitis) Treatment one (n=9): cauterization/débridement Treatment two (n=15): idoxuridine ointment 5 times per day
Pavan-Langston 1972	Insufficient data provided Treatment one (n=14): idoxuridine 0.5% ointment 3 to 5 times per day Treatment two (n=15): vidarabine 3.3% ointment 3 to 5 times per day
Pavan-Langston 1977	Insufficient data provided Treatment one (n=17): idoxuridine 0.1% solution 19 times per day Treatment two (n=23): trifluridine 1% solution 9 times per day
Pietruschka 1968	Insufficient data provided Treatment one (n=30): para-fluorophenylalanine 0.1% solution hourly Treatment two (n=28): idoxuridine 0.1% solution hourly Treatment three (n=40): para-fluorophenylalanine 0.1 % solution and idoxuridine 0.1% solution hourly, alternating
Pintér 1973	Non-concurrent treatment allocation Treatment one (n=16): photoinactivation with acridine orange Treatment two (n=6): idoxuridine with or without oral moroxydine Treatment three (n=2): idoxuridine and thermal débridement Treatment four (n=8): iodination débridement Treatment five (n=2): miscellaneous interventions including autologous blood injection (1)
Pivetti-Pezzi 1985	Insufficient data provided Treatment one (n=13): intramuscular placebo daily with "local conventional therapy" Treatment two (n=11): intramuscular thymic extract daily with "local conventional therapy"

Study	Reason for exclusion
Prost 1986	Insufficient data provided Treatment one (n=20): cryotherapy and oral placebo Treatment two (n=19): cryotherapy and oral isoprinosine
Salcedo Hernandez 2007	Insufficient data provided Treatment one (n=9): diluted autologous serum 4 times per day Treatment two (n=8): acyclovir 3% ointment 4 times per day
Scialdone 1986	Insufficient data provided Treatment one (n=8): idoxuridine solution 6 times per day and oral isoprinosine and intramuscular thymic extract Treatment two (n=12): interferon- β solution 6 times per day and oral isoprinosine and intramuscular thymic extract
Sellitti 1982	Insufficient data provided Treatment one (n=20): isoprinosine solution and oral isoprinosine and cytosine solution every 2 hours Treatment two (n=20): oral isoprinosine and cytosine solution every 2 hours
Shimomura 1987	Insufficient data provided Treatment one (n=16): wiping débridement and idoxuridine solution every hour Treatment two (n=15): idoxuridine solution every hour
Shiota 1979	Non-concurrent treatment allocation Treatment one (n=16): vidarabine 3% ointment Treatment two (n=9): trifluridine 1% solution
Shiota 1988	Insufficient data provided Treatment one (n=14): interferon- β 100,000 IU/ml Treatment two (n=46): interferon- β 1 million IU/ml
Sozen 2006	Varied eligibility criteria Treatment one (n=15): acyclovir 3% ointment 5 times per day Treatment two (n=15, of 13 patients): oral valacyclovir 1 g 2 times per day
Stambuk 1995	Outcome not based on epithelial healing Treatment one (n=8): idoxuridine ointment or acyclovir ointment Treatment two (n=12): bovine thymic extract and either idoxuridine ointment or acyclovir ointment
Tamburi 1990	Insufficient data provided Treatment one (n=8): acyclovir 3% ointment 4 times per day Treatment two (n=8): interferon- α 3 million IU/ml 8 times per day Treatment three (n=8): acyclovir 3% ointment 4 times per day and interferon- α 3 million IU/ml 8 times per day Note: 3 randomised groups were also compared to a historical group treated with idoxuridine (n=8)
Tarakji 1978	Insufficient data provided Treatment one (n=21): cryotherapy Treatment two (n=14): idoxuridine solution hourly and ointment at night
Tommila 1963	Non-concurrent treatment allocation Treatment one (n=17): iodination débridement Treatment two (n=17): interferon- β solution every 1 to 3 hours
Topciu 1992	Insufficient data provided Treatment one (n=120): idoxuridine and foscarnet Treatment two (n=113): idoxuridine and foscarnet and oral moroxydine and percutaneous vaccinia virus antigens and subcutaneous heat-killed <i>Corynebacterium parvum</i>
Wang 2009	Insufficient data provided Treatment one (n=39): acyclovir 0.1% solution 10 times per day Treatment two (n=39): ganciclovir 0.15% gel 5 times per day
Whitcher 1976	Insufficient data provided Treatment one (n=20): wiping débridement Treatment two (n=31): idoxuridine solution hourly day and ointment at night
Xiao 1998	Varied eligibility criteria Treatment one (n=10, epithelial type): acyclovir 0.1% solution Treatment two (n=20, epithelial type): acyclovir 0.1% solution and recombinant interleukin-2
Xie 2005	Botanical or herbal preparation Treatment one (n=34): acyclovir solution Treatment two (n=26): botanical extract
Xu 2009b	Insufficient data provided Treatment one (n=30): acyclovir 0.1% solution Treatment two (n=32): acyclovir 0.1% solution and recombinant interleukin-2
Yamamoto 1984	Non-concurrent treatment allocation

Study	Reason for exclusion
	Treatment one (n=7): zinc sulfate 0.3% Treatment two (n=7): zinc sulfate 0.3% and idoxuridine Treatment three (n=2): zinc sulfate 0.3% and collagenase
Yu 1999	Botanical or herbal preparation Treatment one (n=51): acyclovir 0.1% solution every 2 hours Treatment two (n=53): botanical extract (miedulin 0.8%) every 2 hours
Zagaigora 1971	Non-concurrent treatment allocation Treatment one (n=41): gamma-globulin Treatment two (n=37): desoxyribonuclease Treatment three (n=28): idoxuridine 0.1% solution
Zajác 1968	Non-concurrent treatment allocation Control (n=84): "conservative treatment" with chloramphenicol Treatment one (n=20): corneal scraping débridement with chloramphenicol Treatment two (n=42): thermocoagulation with chloramphenicol ointment
Zhai 2007	Botanical or herbal preparation Treatment one (n=58): acyclovir 0.1% solution and oral acyclovir Treatment two (n=57): acyclovir 0.1% solution and oral acyclovir and intravenous botanical extract
Zhang 1992	Insufficient data provided Treatment one (n=20): acyclovir and interferon Treatment two (n=21): acyclovir and interferon and transfer factor
Zhang 1995	Botanical or herbal preparation Treatment one (n=20): idoxuridine 0.1% solution every 3 to 4 hours Treatment two (n=20): herbal extract
Zhang 2003	Insufficient data provided Treatment one (n=29): interferon- α -1b Treatment two (n=17): interferon- α -2b
Zhang 2008	Botanical or herbal preparation Treatment one (n=50): acyclovir solution Treatment two (n=100): acyclovir solution and oral botanical extract
Zhao 2001	Insufficient data provided Treatment one (n=89): acyclovir 0.1% solution Treatment two (n=97): acyclovir 0.1% solution and recombinant interferon- α 10 μ g/ml and diclofenac 0.1% solution
Zhao 2007	Botanical or herbal preparation Treatment one (n=111): acyclovir 0.1% solution Treatment two (n=112): topical botanical extract
Zheng 2008	Botanical or herbal preparation Treatment one (n=45): topical antiviral Treatment two (n=45): topical antiviral and systemic botanical extracts
Zhi 2001	Insufficient data provided Treatment one (n=30): topical acyclovir Treatment two (n=38): topical acyclovir and systemic interleukin-2
Zhou 2007	Botanical or herbal preparation Treatment one (n=34): acyclovir 0.1% solution Treatment two (n=38): acyclovir 0.1% solution and botanical extract
Zhou 2008	Insufficient data provided Treatment one (n=35): acyclovir Treatment two (n=66): acyclovir and recombinant interferon- α -2b
Zirm 1981	Non-concurrent treatment allocation Treatment one (n=23): iodination débridement Treatment two (n=14): trifluridine or idoxuridine 3 to 5 times per day Treatment three (n=49): scraping débridement and trifluridine or idoxuridine Treatment four (n=33): trifluridine and antiherpetic immunoglobulin

Characteristics of studies awaiting assessment *[ordered by study ID]*

Anonymous 2003	
Methods	Allocation method: randomised
Participants	Country: United States
Interventions	Treatment one: cidofovir 0.3% solution five times per day Treatment two: cidofovir 0.5% solution five times per day Treatment three: trifluridine 1.0% solution five times per day
Outcomes	Corneal epithelial healing and adverse reactions (e.g., punctal occlusion)
Notes	Financial support: pharmaceutical industry

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Therapy of herpes simplex virus epithelial keratitis		
Patient population: trial participants with dendritic or geographic epithelial keratitis		
Outcomes: healing rate throughout 15 or more days following trial enrolment		
Treatment comparisons	Hazard ratio (95% Confidence Interval)	No. of participants (studies)
Idoxuridine vs. inactive control	2.02 (1.16–3.49)	95 (3)
Vidarabine vs. inactive control	2.47 (1.14–5.33)	43 (1)
Vidarabine vs. idoxuridine	1.36 (0.81–2.28)	74 (2)
Trifluridine vs. idoxuridine	2.29 (1.37–3.83)	78 (1)
Acyclovir vs. idoxuridine	2.15 (1.70–2.72)	355 (8)
Trifluridine vs. vidarabine	1.31 (0.96–1.79)	188 (3)
Acyclovir vs. vidarabine	1.13 (0.86–1.47)	259 (5)
Acyclovir vs. trifluridine	0.92 (0.65–1.32)	140 (3)
Brivudine vs. trifluridine	0.60 (0.35–1.02)	60 (1)
Interferon + antiviral vs. antiviral	2.84 (2.13–3.79)	229 (5)
Débridement + antiviral vs. antiviral	1.76 (1.32–2.35)	248 (6)

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Topical antiviral therapy of herpes simplex virus epithelial keratitis						
Patient population: trial participants with dendritic or geographic epithelial keratitis						
Outcomes: corneal epithelial healing after 7 days and after 14 days						
Treatment comparisons	Illustrative comparative healing percentages *		Relative risk ** (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed healing	Corresponding healing				
	Treatment A	Treatment B				
Idoxuridine (B) vs. inactive control (A)	7 days				Moderate ^{1,2}	Different substances used as inactive control
	25%	57% (43%–75%)	2.26 (1.71–3.00)	392 (10)		
	14 days					
	45%	59% (36%–97%)	1.31 (0.80–2.15)	63 (2)		
Vidarabine (B) vs. idoxuridine (A)	7 days				Moderate ⁴	Combined direct and indirect comparisons indicate vidarabine more effective than idoxuridine; neither antiviral commercially marketed
	40%	44% (34%–56%)	1.10 (0.85–1.42)	243 (3)		
	14 days					
	77%	80% (71%–90%)	1.04 (0.92–1.18)	243 (3)		
Trifluridine (B) vs. idoxuridine (A)	7 days				Moderate ^{1,2}	Adjusted indirect comparison shows similar results
	20%	49% (34%–71%)	2.52 (1.74–3.63)	223 (4)		
	14 days					
	64%	89% (76%–100%)	1.38 (1.19–1.60)	256 (5)		
Acyclovir (B) vs. idoxuridine (A)	7 days				Moderate ^{1,2,5}	Adjusted indirect comparison shows similar results
	33%	64% (54%–77%)	1.96 (1.64–2.34)	468 (9)		
	14 days					
	68%	84% (78%–90%)	1.23 (1.14–1.32)	606 (11)		
Brivudine (B) vs. (A)	7 days				Moderate ⁴	Few studies, with slow healing of idoxuridine-treated eyes, but indirect analysis yields similar relative effect
	5%	43% (15%–100%)	7.94 (2.80–22.53)	99 (2)		
	14 days					
	59%	81% (61%–100%)	1.38 (1.05–1.81)	99 (2)		
Trifluridine (B) vs. vidarabine (A)	7 days				Moderate ^{1,2}	Results partly influenced by one study restricted to geographic epithelial keratitis
	55%	58% (50%–67%)	1.05 (0.91–1.22)	288 (4)		

Acyclovir (B) vs. vidarabine (A)	14 days				
	71%	77% (70%–87%)	1.09 (0.98–1.22)	188 (3)	Indirect analysis also favours acyclovir but one study restricted to geographic epithelial keratitis does not
	7 days				
	68%	84% (71%–98%)	1.23 (1.05–1.44)	314 (6)	
Acyclovir (B) vs. trifluridine (A)	14 days				Studies differ in trifluridine formulation, in solution and as ointment
	84%	92% (84%–99%)	1.09 (1.00–1.18)	342 (7)	
	7 days				
	73%	73% (60%–88%)	0.99 (0.82–1.20)	178 (4)	
Brivudine (B) vs. trifluridine (A)	14 days				Moderate ²
	91%	90% (82%–99%)	0.99 (0.90–1.09)	178 (4)	
	7 days				
	59%	55% (42%–71%)	0.93 (0.71–1.21)	147 (3)	
Brivudine (B) vs. acyclovir (A)	14 days				Moderate ⁴
	85%	85% (75%–97%)	1.00 (0.88–1.14)	147 (3)	
	7 days				
	80%	95% (74%–100%)	1.19 (0.93–1.51)	40 (1)	
Ganciclovir (B) vs. acyclovir (A)	14 days				Moderate ^{1,2,5}
	95%	100% (87%–100%)	1.05 (0.92–1.20)	40 (1)	
	7 days				
	33%	35% (28%–43%)	1.05 (0.84–1.31)	378 (5)	
	14 days				Slow healing in some studies; no significant difference found in random-effects model
	57%	64% (59%–70%)	1.13 (1.04–1.23)	672 (10)	

* The basis for each **assumed risk** is the mean 7-day and 14-day healing percentages among included studies for patients who received treatment A. Each **corresponding risk** (and its 95% confidence interval) is based on the assumed risk and the **risk ratio** comparing treatment B to treatment A (and its 95% CI), with upper limits bounded at 100%.

** The **relative risk** is the pooled risk ratio.

CI: Confidence interval.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹ Some studies had a potential risk of bias

- ² Pooling was limited by inconsistent results at either 7-day or 14-day outcome
- ³ Analysis based only on adjusted indirect comparison
- ⁴ Few studies
- ⁵ Possible publication bias (Figure 4, Figure 5)

Oral antiviral therapy of herpes simplex virus epithelial keratitis						
Patient population: trial participants with dendritic or geographic epithelial keratitis						
Outcomes: corneal epithelial healing after 7 days and after 14 days						
Treatment comparisons	Illustrative comparative healing percentages* (95% CI)			Relative risk** (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed healing		Corresponding healing			
	Treatment A		Treatment B			
	7 days					
Oral antiviral (B) vs. topical antiviral (A)	53%		80% (60%–100%)	1.51 (1.13–2.02)	116 (2)	Low ^I
	14 days					
	97%		89% (77%–100%)	0.92 (0.79–1.07)	56 (1)	
Oral antiviral + topical antiviral (B) vs. topical antiviral (A)	7 days					Low ^I
	63%		71% (60%–83%)	1.13 (0.95–1.33)	287 (1)	
	14 days					
	70%		75% (69%–82%)	1.08 (0.99–1.17)	327 (2)	
Only oral and topical acyclovir studied in comparative treatment trials						
Oral acyclovir was studied with topical trifluridine and with topical idoxuridine						

* The basis for the **assumed risk** is the mean 7-day and 14-day healing percentages among included studies for patients who received treatment A. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk and the **risk ratio** comparing treatment B to treatment A (and its 95% CI), with upper limits bounded at 100%

** The **relative risk** is the pooled risk ratio.

CI: Confidence interval.

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Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^I Inconsistent and insufficient studies

Interferon therapy of herpes simplex virus epithelial keratitis						
Patient population: trial participants with dendritic or geographic epithelial keratitis						
Outcomes: corneal epithelial healing after 7 days and after 14 days						
Treatment comparisons	Illustrative comparative healing percentages* (95% CI)		Relative risk** (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Corresponding healing					
	Assumed healing	Treatment B				
	Treatment A					
Interferon (B) vs. inactive control (A)	7 days				Low ^I	One study used debridement
	38%	56% (40%–78%)	1.48 (1.07–2.06)	178 (3)		
	14 days					
	65%	86% (69%–100%)	1.32 (1.06–1.64)	110 (2)		
Interferon (B) vs. antiviral (A)	7 days				Low ^I	Different antiviral agents used as comparative treatment; no significant difference found in random-effects model
	55%	57% (45%–70%)	1.03 (0.82–1.28)	85 (3)		
	14 days					
	75%	92% (76%–100%)	1.23 (1.01–1.49)	85 (3)		
Interferon + antiviral (B) vs. antiviral (A)	7 days				High	Similar result in sensitivity analysis
	43%	84% (72%–99%)	1.96 (1.67–2.31)	401 (8)		
	14 days					
	93%	95% (92%–99%)	1.03 (0.99–1.07)	476 (9)		

* The basis for the **assumed risk** is the mean 7-day and 14-day healing percentages among included studies for patients who received treatment A. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk and the **risk ratio** comparing treatment B to treatment A (and its 95% CI), with upper limits bounded at 100%

** The **relative risk** is the pooled risk ratio.

CI: Confidence interval.

GRADE Working Group grades of evidence

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Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^I Inconsistent results among studies using different interferon dosages

Corneal epithelial débridement of herpes simplex virus epithelial keratitis						
Patient population: trial participants with dendritic or geographic epithelial keratitis						
Outcomes: corneal epithelial healing after 7 days and after 14 days						
Treatment comparisons	Illustrative comparative healing percentages* (95% CI)			Relative risk** (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed healing		Corresponding healing			
	Treatment A	Treatment B				
	7 days					
Antiviral (B) vs. débridement (A)	7 days			0.89 (0.75–1.06)	372 (7)	Low ^{I-2}
	60%	54% (45%–64%)				
	14 days					
	75%	73% (63%–85%)				
Débridement + antiviral or interferon (B) vs. débridement (A)	7 days			1.15 (1.03–1.28)	347 (8)	Moderate ^I
	66%	76% (68%–84%)				
	14 days					
	73%	89% (76%–100%)				
Débridement + antiviral (B) vs. antiviral (A)	7 days			1.21 (1.04–1.42)	99 (3)	Moderate ^I
	53%	68% (56%–81%)				
	14 days					
	85%	88% (81%–97%)				
				1.04 (0.95–1.14)	248 (6)	
Débridement limited by recurrent epithelial keratitis during healing stage						
Débridement limited by recurrent epithelial keratitis during healing stage; no significant difference found in random-effects model						
Different antiviral agents and different interferon dosages; no significant difference found in random-effects model						

* The basis for the **assumed risk** is the mean 7-day and 14-day healing percentages among included studies for patients who received treatment A. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk and the **risk ratio** comparing treatment B to treatment A (and its 95% CI), with upper limits bounded at 100%.

** The **relative risk** is the pooled risk ratio.

CI: Confidence interval.

GRADE Working Group grades of evidence

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Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^I Inconsistent results among studies using different physicochemical methods of corneal epithelial débridement

² Disparate relative effect found in sensitivity analysis