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

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[Intervention Review]

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 which, though usually self-limiting, may persist or progress without treatment.

Objectives

To compare the relative effectiveness of antiviral agents, interferon, and corneal debridement in the treatment of HSV epithelial keratitis.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 12), PubMed (January 1946 to 31 December 2014), EMBASE (January 1980 to 31 December 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to 31 December 2014), System for Information on Grey Literature in Europe (OpenGrey) (January 1995 to 31 December 2014), BIOSIS (January 1926 to 5 May 2014), Scopus (January 1966 to 31 December 2014), Japan Science and Technology Institute (J-Global) (January 1975 to 31 December 2014), China National Knowledge Infrastructure (CNKI) (January 1979 to 31 December 2014), British Library's Electronic Table of Contents (Zetoc) (January 1993 to 7 May 2014). We looked for trials listed on the the *meta*Register of Controlled Trials (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en), Chinese Clinical Trial Registry, the U.S. Food and Drug Administration (FDA) (www.fda.gov/), National Institute for Health and Clinical Excellence (NICE) (www.evidence.nhs.uk) and the European Medicines Agency (EMA) (www.ema.europa.eu/ema/) as of 31 December 2014. There were no language or date restrictions in the search for trials. We also culled literature digests and conference proceedings as of 15 April 2014. There were no language or date restrictions in the search for trials.

Selection criteria

Randomised and quasi-randomised trials of HSV dendritic or geographic epithelial keratitis were included that reported the proportion of eyes healed at one week, two weeks, or both after enrolment.

Data collection and analysis

We tabulated data on study characteristics, risk of bias, and outcomes and used direct comparisons to estimate a risk ratio (RR) and, when feasible, a hazard ratio (HR) with a 95% confidence interval (CI). Heterogeneity was assessed by an inconsistency index. A multiple treatment comparison meta-analysis consolidated direct and indirect comparisons of relative healing at 14 days.

Main results

One hundred thirty-seven studies involving 8333 eyes met the inclusion criteria. Placebo-controlled studies were heterogeneous in comparison with idoxuridine (RR 1.74; 95% CI 1.03 to 2.91) and few in number for vidarabine (RR 1.81; 95% CI 1.09 to 3.01), interferon (RR 1.32; 95% CI 1.06 to 1.64), and debridement. Vidarabine (RR 1.13; 95% CI 1.02 to 1.25), trifluridine (RR 1.30; 95% CI 1.18 to 1.43), acyclovir (RR 1.23; 95% CI 1.14 to 1.34), and brivudine (RR 1.34; 95% CI 1.18 to 1.51) were more effective than idoxuridine. Trifluridine (RR 1.17; 95% CI 1.03 to 1.32) and acyclovir (RR 1.11; 95% CI 1.03 to 1.19) were more effective than vidarabine. No significant differences in healing emerged among trifluridine, acyclovir, brivudine, and foscarnet although few studies compared brivudine or foscarnet with other antivirals. Any potential advantage of ganciclovir compared to acyclovir was mitigated by study heterogeneity and possible publication bias. Only one study evaluated the joint use of two topical antivirals. In a limited number of studies, oral acyclovir (RR 0.92; 95% CI 0.79 to 1.07) or the combination of oral acyclovir with a topical antiviral (RR 1.36; 95% CI 0.68 to 2.74) appeared as effective as a single topical antiviral agent. Compared to topical antiviral monotherapy, the combination of an antiviral with either interferon or debridement had inconsistent effects on expediting healing and improving outcome.

Authors' conclusions

Placebo-controlled studies of HSV epithelial keratitis are limited to superseded interventions. Trifluridine and acyclovir are more effective than idoxuridine or vidarabine and similar in therapeutic effectiveness. Brivudine and foscarnet do not substantially differ in effectiveness from trifluridine or acyclovir. Ganciclovir is at least as effective as acyclovir. The addition of interferon to a nucleoside antiviral agent and the combination of debridement with antiviral treatment need to be further assessed to substantiate any possible advantage in healing.

PLAIN LANGUAGE SUMMARY

Antiviral medicines, interferon, and corneal surface removal in the treatment of herpes simplex virus infection of the eye

Review question
We compared different treatments of people's eyes infected with herpes simplex virus (HSV).

Background
HSV infection of the eye causes pain and hazy vision. Antiviral eye medicines, interferon drops, and superficial wiping have been used to cure HSV infection of the corneal surface.

Study characteristics
This update, current to December 2014, uses a network of 137 studies of 8333 eyes to compare antiviral medicines and to find out if interferon or debridement would help. Between one and 28 studies were available to compare seven ophthalmic antiviral drugs, an antiviral taken by mouth, interferon, office procedures to remove the eye's infected surface, and other medicines.

Key results
The first antivirals, idoxuridine and vidarabine, seem better than no treatment in healing HSV dendritic keratitis within two weeks. Topically applied trifluridine, acyclovir, or brivudine are better and safer than idoxuridine, cure about 90% of treated eyes within two weeks, and have no significant differences in effectiveness. The evidence is conflicting whether ganciclovir is as good as or better than acyclovir. Determining the role of antiviral pills is limited by few studies and inconsistent findings. Interferon, a natural part of the immune system that can be given as an eye drop, is active against HSV infection of the cornea. The integrated use of interferon and an antiviral drug might be slightly better than an antiviral drug by itself. Another treatment is to rub off the infected surface of the eye, but using a wiping method followed by an antiviral drug is not consistently better than just an antiviral medication.

Quality of the evidence
Comparisons of one ophthalmic antiviral drug to another have a moderate quality of evidence, except for the appraisal comparing ganciclovir and acyclovir where studies are inconsistent. The quality of the evidence is moderate to low when an ophthalmic antiviral drug was compared to combined antiviral and interferon treatments or to combined antiviral treatment and debridement. Evidence is scarce or poor for placebo-controlled comparisons, comparisons of antiviral treatment to interferon or to debridement, and evaluations of antiviral pills. Proper randomisation could not be assured in nearly a quarter of the studies. Patients or examiners could have known which treatment was assigned in at least half of the studies.

Summary of findings for the main comparison. Network analysis of antiviral agents and combination interventions

Network analysis of antiviral agents and combination interventions					
Study population: trial participants with dendritic or geographic epithelial keratitis					
Outcomes: relative corneal epithelial healing at two weeks following trial enrolment					
Treatment	**Comparison**	**Pooling method [1]**	**Risk ratio (95% CI)[2]**	**No. trials (no. participants) of direct comparisons**	**No. indirect network intermediates studied**
Idoxuridine	**Inactive control**	Combined	1.74 (1.03-2.91)[8]	2 (63)	1
Vidarabine	**Inactive control**	Combined	1.81 (1.09-3.01)	1 (43)	1
	Idoxuridine	Combined	1.13 (1.02-1.25)	3 (243)	3
Trifluridine	**Idoxuridine**	Combined	1.30 (1.18-1.43)	5 (256)	3
	Vidarabine	Combined	1.17 (1.03-1.32)[8]	3 (188)	2
Acyclovir	**Idoxuridine**	Combined	1.23 (1.14-1.34)[8]	11 (606)	3
	Vidarabine	Combined	1.11 (1.03-1.19)	7 (342)	2
	Trifluridine	Combined	0.96 (0.90-1.04)	4 (178)	3
Brivudine	**Idoxuridine**	Combined	1.34 (1.18-1.51)	2 (99)	2
	Trifluridine	Combined	1.01 (0.92-1.12)	3 (147)	2
	Acyclovir	Combined	1.04 (0.95-1.15)	1 (40)	2
Ganciclovir	**Acyclovir**	Combined	1.34 (1.20-1.51)[8]	28 (2062)	1
Foscarnet	**Trifluridine**	Combined	1.09 (0.92-1.29)	1 (20)	1
	Acyclovir	Combined	1.15 (1.01-1.32)	1 (104)	2
	Ganciclovir	Combined	0.92 (0.75-1.13)	1 (60)	1

Interferon	**Inactive control**	Direct	1.32 (1.06-1.64)	2 (110)	0
	Antiviral [3]	Direct	1.22 (0.91-1.62)	4 (222)	0
Interferon + antiviral [4]	**Antiviral** [4]	Direct	1.06 (0.99-1.13)[8]	12 (718)	0
Antiviral [5]	**Debridement**	Direct	0.98 (0.72-1.32)[8]	7 (317)	0
Debridement + Antiviral [6]	**Debridement**	Direct	1.25 (0.78-2.00)[8]	3 (99)	0
Debridement + Antiviral [7]	**Antiviral** [7]	Direct	1.05 (0.94-1.17)[8]	7 (334)	0

[1] Combined method uses direct and indirect risk ratios in a multiple treatment meta-analysis; direct method is the risk ratio of the direct meta-analysis.
[2] Adjusted RRs of antiviral comparisons are taken from Table 1 for combined direct and indirect estimates in network meta-analysis. Corresponding direct RRs for antiviral comparisons are tabulated in Summary of findings 2 and are supplemented with HRs in Summary of findings 3. Direct RRs of interferon comparisons are taken from Analysis 3.1; Analysis 3.5; and Analysis 3.7. Direct RRs of debridement comparisons are taken from Analysis 4.2; Analysis 4.4; and Analysis 4.6. Direct comparisons that are restricted to studies of randomized, double-masked trials are tabulated in Table 2.
[3] Idoxuridine or acyclovir
[4] Trifluridine, acyclovir, brivudine, or ganciclovir
[5] Idoxuridine, trifluridine, acyclovir, or brivudine
[6] Trifluridine or interferon
[7] Idoxuridine, trifluridine, brivudine, or ganciclovir
[8] I^2 > 50% of direct comparison suggests diversity among studies

Summary of findings 2. Relative healing outcomes with topical antiviral therapy

Relative healing outcomes with topical antiviral therapy						
Study population: trial participants with dendritic or geographic epithelial keratitis **Outcomes:** corneal epithelial healing at 7 and 14 days						
Treatment comparisons	**Illustrative comparative healing percentages* (95% CI)**		**Relative risk** (95% CI)**	**No. of participants (no. studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed healing	**Corresponding healing**				

	Treatment A	Treatment B				
Idoxuridine (B) versus inactive control (A)	**7 days**				⊕⊕⊖⊖ low[1,2]	Different substances used as inactive control; random-effects model used
	25%	52% (31%-88%)	2.09 (1.24-3.51)	392 (10)		
	14 days					
	50%	65% (22%-100%)	1.31 (0.45-3.84)	63 (2)		
Vidarabine (B) versus inactive control (A)	**7 days**				⊕⊕⊖⊖ low[4]	Direct analysis limited to one study
	25%	54% (20%-100%)	2.17 (0.81-5.87)	23 (1)		
	14 days					
	50%	98% (55%-100%)	1.96 (1.10-3.49)	23 (1)		
Vidarabine (B) versus idoxuridine (A)	**7 days**				⊕⊕⊕⊖ moderate[4]	Combined direct and indirect comparisons indicate vidarabine more effective than idoxuridine; neither antiviral commercially marketed
	50%	55% (43%-71%)	1.10 (0.85-1.42)	243 (3)		
	14 days					
	75%	78% (69%-89%)	1.04 (0.92-1.18)	243 (3)		
Trifluridine (B) versus idoxuridine (A)	**7 days**				⊕⊕⊕⊖ moderate[1,2]	Indirect comparison shows similar results
	50%	100% (87%-100%)	2.52 (1.74-3.63)	223 (4)		
	14 days					
	75%	100% (89%-100%)	1.38 (1.19-1.60)	256 (5)		
Acyclovir (B) versus idoxuridine (A)	**7 days**				⊕⊕⊕⊖ moderate[1,2]	Indirect comparison shows similar results; random-effects model used
	50%	99% (68%-100%)	1.98 (1.35-2.90)	468 (9)		
	14 days					
	75%	92% (81%-100%)	1.22 (1.08-1.38)	606 (11)		

Brivudine (B) versus idoxuridine (A)	**7 days**				⊕⊕⊕⊖ moderate[4]	Few studies, with slow healing of idoxuridine-treated eyes, but indirect analysis yields similar relative effect at 14 days
	50%	100% (100%-100%)	7.94 (2.80-22.53)	99 (2)		
	14 days					
	75%	100% (79%-100%)	1.38 (1.05-1.81)	99 (2)		
Trifluridine (B) versus vidarabine (A)	**7 days**				⊕⊕⊕⊖ moderate[1,2]	Results partly influenced by one study restricted to geographic epithelial keratitis; random-effects model used
	65%	70% (61%-80%)	1.08 (0.94-1.23)	288 (4)		
	14 days					
	82%	92% (69%-100%)	1.12 (0.84-1.49)	188 (3)		
Acyclovir (B) versus vidarabine (A)	**7 days**				⊕⊕⊕⊖ moderate[2]	Indirect analysis also favours acyclovir but one study restricted to geographic epithelial keratitis does not
	58%	71% (61%-84%)	1.23 (1.05-1.44)	314 (6)		
	14 days					
	84%	92% (84%-99%)	1.09 (1.00-1.18)	342 (7)		
Acyclovir (B) versus trifluridine (A)	**7 days**				⊕⊕⊕⊖ moderate	Studies differ in trifluridine formulation, in solution and as ointment
	71%	70% (58%-85%)	0.99 (0.82-1.20)	178 (4)		
	14 days					
	90%	89% (81%-98%)	0.99 (0.90-1.09)	178 (4)		
Brivudine (B) versus trifluridine (A)	**7 days**				⊕⊕⊕⊖ moderate[1,2]	Heterogeneity among studies at 7-day outcome
	61%	57% (43%-74%)	0.93 (0.71-1.21)	147 (3)		
	14 days					
	88%	88% (77%-100%)	1.00 (0.88-1.14)	147 (3)		
Brivudine (B) versus acyclovir (A)	**7 days**				⊕⊕⊕⊖	Direct analysis limited to one study, but indirect analysis yields similar relative effect

	80%	95% (74%-100%)	1.19 (0.93-1.51)	40 (1)	moderate[4]	
	14 days					
	95%	100% (87%-100%)	1.05 (0.92-1.20)	40 (1)		
Ganciclovir (B) versus acyclovir (A)	**7 days**				⊕⊕⊖⊖ low[1,2,5]	Slow healing in some studies results in unusually low assumed healing rate with acyclovir; substantial heterogeneity among studies; random-effects model used to estimate relative risk
	43%	49% (41%-58%)	1.14 (0.96-1.35)	551 (7)		
	14 days					
	55%	76% (67%-86%)	1.38 (1.22-1.57)	2062 (28)		
Foscarnet (B) versus trifluridine (A)	**7 days**				⊕⊕⊕⊖ moderate[4]	Direct analysis limited to one study
	-	-	-	-		
	14 days					
	90%	90% (68%-100%)	1.00 (0.75-1.34)	20 (1)		
Foscarnet (B) versus acyclovir (A)	**7 days**				⊕⊕⊕⊖ moderate[4]	Direct analysis limited to one study
	-	-	-	-		
	14 days					
	75%	86% (71%-100%)	1.15 (0.95-1.40)	104 (1)		
Foscarnet (B) versus ganciclovir (A)	**7 days**				⊕⊕⊕⊖ moderate[4]	Direct analysis limited to one study
	83%	80% (63%-100%)	0.96 (0.76-1.22)	60 (1)		
	14 days					
	90%	86% (72%-100%)	0.96 (0.80-1.16)	60 (1)		

*The **assumed risk** for inactive control is chosen to be 25% at 7 days and 50% at 14 days. The **assumed risk** for idoxuridine, based on observational studies and trials using idoxuridine as a control, is chosen to be 50% at 7 days and 75% at 14 days. For other comparisons, the basis for each **assumed risk** is the mean baseline risk estimated as the overall healing percentage, at 7 and 14 days respectively, among all included studies for participants who received treatment A. Each **corresponding risk** (and its 95% confidence interval, with an upper bound of 100%) is based on the assumed risk and the **risk ratio** directly comparing treatment B to treatment A.

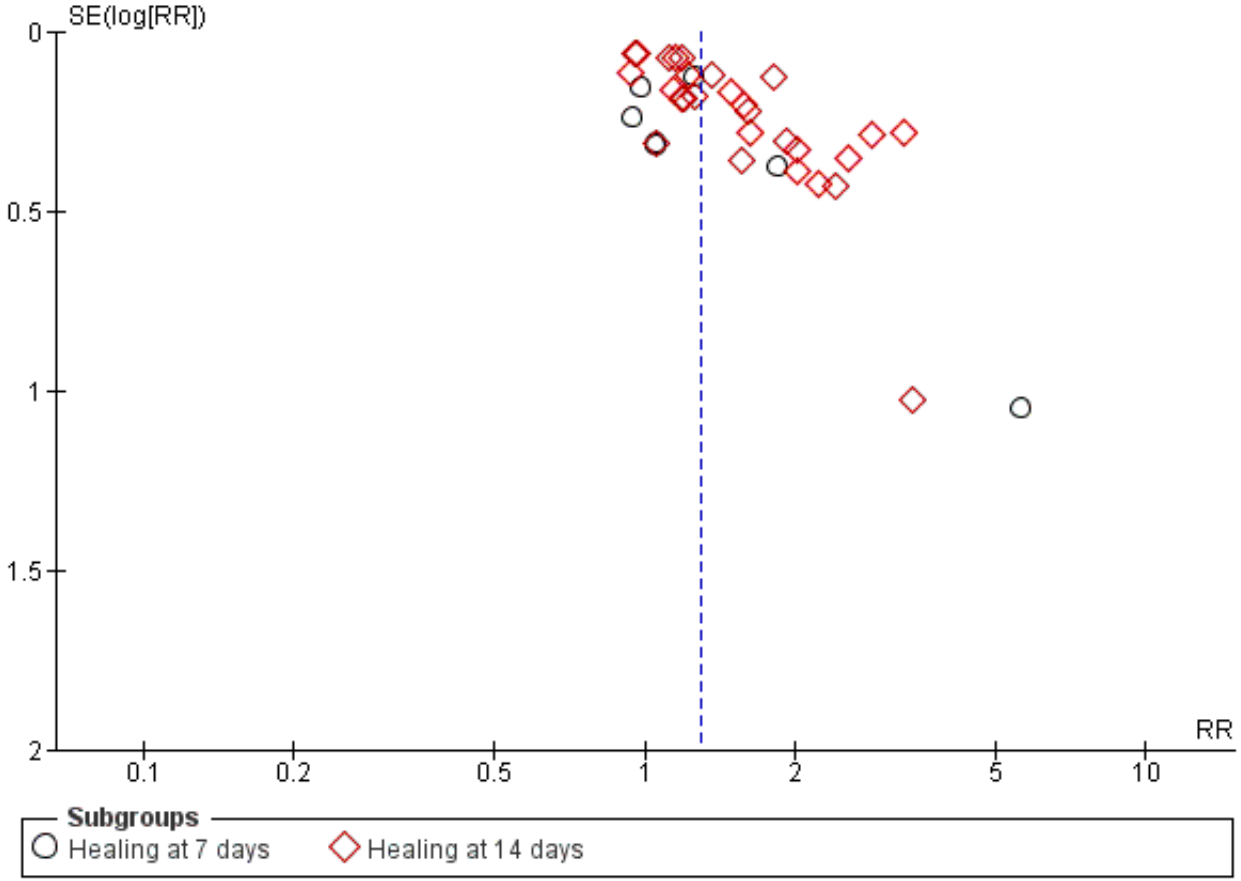
The **relative risk is the pooled risk ratio. Pooling was based on fixed-effects models except for heterogenous comparisons in which a random-effects model was used.

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 for either the 7-day or 14-day outcome
[3] Analysis based only on indirect comparison
[4] Few studies
[5] Possible publication bias (Figure 1)

Figure 1. Funnel plot of studies comparing ganciclovir to acyclovir.



Summary of findings 3. Relative healing rates with antiviral agents and combination interventions

Relative healing rates with antiviral agents and combination interventions			
Study population: trial participants with dendritic or geographic epithelial keratitis **Outcomes:** rate of corneal epithelial healing following trial enrolment			
Treatment	**Comparison**	**Hazard ratio (95% CI)**	**No. of participants (no. studies)**

Idoxuridine	**Inactive control**	1.62 (1.00-2.65)[1]	95 (3)
Vidarabine	**Inactive control**	2.47 (1.14-5.33)	43 (1)
	Idoxuridine	1.36 (0.81-2.28)	74 (2)
Trifluridine	**Idoxuridine**	2.29 (1.37-3.83)	78 (1)
	Vidarabine	1.31 (0.96-1.79)[1]	188 (3)
Acyclovir	**Idoxuridine**	2.15 (1.70-2.72)[1]	355 (8)
	Vidarabine	1.13 (0.86-1.47)	259 (5)
	Trifluridine	0.92 (0.65-1.32)	140 (3)
Brivudine	**Trifluridine**	0.60 (0.35-1.02)	60 (1)
Interferon + antiviral [2]	**Antiviral** [2]	2.84 (2.13-3.79)[1]	229 (5)
Debridement + antiviral [3]	**Antiviral** [3]	1.76 (1.32-2.35)[1]	248 (6)

[1] $I^2 > 50\%$
[2] Trifluridine or acyclovir
[3] Idoxuridine, trifluridine, or acyclovir

Summary of findings 4. Relative healing outcomes with combined topical or topical and oral antiviral therapy

Relative healing outcomes with combined topical and/or oral antiviral therapy						
Study population: trial participants with dendritic or geographic epithelial keratitis **Outcomes:** corneal epithelial healing at 7 and 14 days						
Treatment comparisons	**Illustrative comparative healing percentages* (95% CI)**		**Relative risk** (95% CI)**	**No. of participants (no. studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed healing	**Corresponding healing**				
	Treatment A	**Treatment B**				

Topical acyclovir/vidarabine (B) versus topical acyclovir (A)	**7 days**				⊕⊕⊕⊖ moderate	Analysis limited to one study
	62%	93% (63%-100%	1.50 (1.01-2.24)	32 (1)		
	14 days					
	100%	100% (89%-100%)	1.00 (0.89-1.12)	32 (1)		
Oral antiviral (B) versus topical antiviral (A)	**7 days**				⊕⊕⊖⊖ low[1]	Only oral and topical acyclovir studied in comparative treatment trials; substantial heterogeneity between 2 trials at 7-day outcome
	52%	79% (59%-100%)	1.51 (1.13-2.02)	116 (2)		
	14 days					
	97%	89% (77%-100%)	0.92 (0.79-1.07)	56 (1)		
Oral antiviral + topical antiviral (B) versus topical antiviral (A)	**7 days**				⊕⊕⊖⊖ low[1]	Oral acyclovir was studied with topical trifluridine and with topical idoxuridine; random-effects model used
	63%	71% (60%-84%)	1.13 (0.95-1.33)	287 (1)		
	14 days					
	84%	100% (57%-100%)	1.36 (0.68-2.74)	327 (2)		

*The basis for the **assumed risk** is the overall 7-day or 14-day healing percentage among included studies for participants who received treatment A of both treatment comparisons (oral versus topical and oral/topical versus topical). 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
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] Inconsistent and insufficient studies

Summary of findings 5. Relative healing outcomes with topical interferon

Relative healing outcomes with topical interferon						
Study population: trial participants with dendritic or geographic epithelial keratitis **Outcomes:** corneal epithelial healing at 7 and 14 days						
Treatment comparisons	**Illustrative comparative healing percentages* (95% CI)**		**Relative risk** (95% CI)**	**No. of participants (no. studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed healing	**Corresponding healing**				
	Treatment A	**Treatment B**				
Interferon (B) versus inactive control (A)	**7 days**				⊕⊖⊖⊖ very low[1]	One study used debridement
	25%	37% (27%-52%)	1.48 (1.07-2.06)	178 (3)		
	14 days					
	50%	66% (53%-82%)	1.32 (1.06-1.64)	110 (2)		
Interferon (B) versus antiviral (A)	**7 days**				⊕⊕⊖⊖ low[1,2]	Different antiviral agents used as comparative treatment; random-effects model used
	55%	57% (45%-70%)	0.99 (0.81-1.21)	85 (3)		
	14 days					
	69%	84% (63%-100%)	1.22 (0.91-1.62)	222 (4)		
Interferon + antiviral (B) versus antiviral (A)	**7 days**				⊕⊕⊕⊖ moderate[2]	Heterogeneity among trials at 7 and 14 days; slow healing with antiviral monotherapy in some trials; smaller relative effect size in sensitivity analyses
	44%	83% (72%-96%)	1.64 (1.35-2.55)	475 (9)		
	14 days					
	86%	95% (90%-100%)	1.06 (0.99-1.13)	718 (12)		

*The **assumed risk** for inactive control is chosen to be 25% at 7 days and 50% at 14 days. The basis for the **assumed risk** of antiviral therapy is the overall 7-day or 14-day healing percentage among included studies for participants 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
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] Inconsistent results among studies using different interferon dosages
[2] Different antiviral agents and different types and routes of interferon administration among studies

Summary of findings 6. Relative healing outcomes with corneal debridement

Relative healing outcomes with corneal debridement

Study population: trial participants with dendritic or geographic epithelial keratitis

Outcomes: corneal epithelial healing at 7 and 14 days

Treatment comparisons	Illustrative comparative healing percentages* (95% CI)		Relative risk** (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed healing	Corresponding healing				
	Treatment A	Treatment B				
Antiviral (B) versus debridement (A)	**7 days**				⊕⊕⊖⊖ low[1,2]	Debridement limited by recrudescent epithelial keratitis during healing stage; random-effects model used
	61%	57% (45%-73%)	0.94 (0.74-1.20)	372 (7)		
	14 days					
	72%	71% (52%-95%)	0.98 (0.72-1.32)	317 (7)		
Debridement + antiviral or interferon (B) versus debridement (A)	**7 days**				⊕⊕⊕⊖ moderate[1]	Debridement limited by recrudescent epithelial keratitis during healing stage; random-effects model used
	71%	80% (67%-97%)	1.13 (0.94-1.36)	347 (8)		
	14 days					

	81%	100% (63%-100%)	1.25 (0.78-2.00)	99 (3)		
Debridement + antiviral (B) versus antiviral (A)	**7 days**				⊕⊕⊕⊖ moderate[1]	Different antiviral agents and different interferon dosages; random-effects model used
	53%	68% (57%-81%)	1.28 (1.07-1.53)	305 (7)		
	14 days					
	75%	79% (70%-88%)	1.05 (0.94-1.17)	334 (7)		

*The basis for the **assumed risk** is the overall 7-day or 14-day healing percentage among included studies for participants 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
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] Inconsistent results among studies using different physicochemical methods of corneal epithelial debridement
[2] Disparate relative effect found in sensitivity analysis

BACKGROUND

Herpes simplex virus (HSV) affects most people (Smith 2002). Upon initial exposure, HSV type 1 often infects subclinically but sometimes produces a primary viral syndrome afflicting the eyelids and ocular surface. After establishing latency within neurons of the trigeminal ganglion, periodic shedding of HSV into the tear film is commonly asymptomatic. On occasion, usually years to decades after initial exposure, reactivation of latent HSV erupts into infection and inflammation of the eye. Epithelial keratitis is its most frequent and conspicuous manifestation.

Description of the condition

Epidemiology

Public health importance

HSV is an epidemiologically important cause of infectious and inflammatory eye disease among children, adolescents, adults, and the elderly (Liesegang 2001; Wilhelmus 2008a). The incidence of first-episode ocular HSV in population studies from Europe, North America, and South America is 4 to 13 per 100,000 person-years (Adhin 2012; Labetoulle 2005; Liesegang 1989b; Mortensen 1979; Ribaric 1976; Stanzel 2014; Young 2010). The incidence of subsequent HSV keratitis is 6 to 18 per 100,000 person-years (Labetoulle 2005; Liesegang 1989b; Stanzel 2014). The joint incidence of new or recurrent HSV keratitis is 12.5 to 31.5 people per 100,000 person-years (Labetoulle 2005; Liesegang 1989b; Stanzel 2014). Worldwide, an estimated 1.5 million people experience HSV keratitis each year (Farooq 2012).

The prevalence of a history of ocular HSV disease is about 2 to 15 per 10,000 in the U.S. population (Liesegang 1989a; Stanzel 2014). Approximately 3% have visual acuity of the previously diseased eye worse than 20/200 (Wilhelmus 1981b; Young 2010). Globally, between one and ten million persons have had herpetic eye disease, and many are left with severely impaired vision of the affected eye. Ocular herpes is an important infective cause of corneal blindness.

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 5 to 22 people per 100,000 person-years (Labetoulle 2005; Liesegang 1989b; Mortensen 1979; Stanzel 2014). On a global scale, about one million people suffer a new or repeat episode of HSV epithelial keratitis 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 macroulcerative form of corneal HSV infection that complicates topical corticosteroid use or systemic immunosuppression.

HSV epithelial keratitis is typically unilateral. The contralateral eye is infrequently affected, either simultaneously or subsequently (Liesegang 2001), in healthy individuals. People with atopy or an immune deviation may be predisposed to HSV epithelial keratitis of both eyes (Souza 2003; Wilhelmus 1981c).

Etiology

Clinical virology

Branching corneal disease was first mentioned in a 10th-century medical text (Wood 1936) and redescribed in the 19th century with febrile illness (Kipp 1880) or as a spontaneous episode (Hansen Grut 1886) to which the term "keratitis dendritica" was given (Emmert 1885). Onset of dendritic corneal inflammation was realised to be part of an acute syndrome (Horner 1871; Verhoeff 1909) and by 1920 was shown to be due to a transmissible virus (Grüter 1920).

HSV-1 is the cause of nearly all infective dendritic epithelial keratitis. HSV-2 is much less commonly isolated from the cornea than HSV-1 (Kaneko 2008; Neumann-Haefelin 1978; Vannini 1986). Varicella-zoster virus epithelial keratitis can resemble HSV epithelial keratitis (Bierly 1994; Hu 2010; Pavan-Langston 1973) and may occur with or without dermatoblepharitis during chickenpox or shingles. Rare causes of dendritic epithelial keratitis include cytomegalovirus (Wilhelmus 1996b), Epstein-Barr virus (Pflugfelder 1990), human herpesvirus 6 (Boto-de-los-Bueis 2013; Okuno 2011), and adenovirus (Chodosh 1995). Laboratory testing can help to establish the etiology of atypical cases (Chanzy 2002; Farhatullah 2004; Kowalski 1993).

Differential diagnosis

Dendritiform keratopathy is a condition of the corneal surface characterized by a curvilinear or arborescent pattern that may simulate HSV epithelial keratitis but is due to various noninfective causes. Ramous epithelial changes can be associated with various disorders of the ocular surface. For example, a pseudodendrite can be made up of regenerating or hypertrophic epithelium. Whorling epithelial granularity may be due to dysfunction of the limbal stem cells. Intraepithelial deposits and drug-induced changes can also take on a vortex formation. Fungal and amœbic infections of the cornea have been mistaken as HSV keratitis.

Reactivation and recurrence

Primary ocular herpes may cause dendritic keratitis in susceptible children and adults (Darougar 1985). HSV epithelial keratitis can occur following primary transmission from mother to neonate (Liesegang 2001) and from donor to corneal transplant recipient (Borderie 2004; Hassan 2009; Remeijer 1997; Robert 2005). Reinfection with a different HSV strain is also possible (Remeijer 2002). Much more commonly, HSV epithelial keratitis follows viral reactivation in a latently infected person. After a recurrence, 5% to 10% of people develop a subsequent recurrence of epithelial keratitis each year (Stanzel 2014; Young 2010), regardless of gender or ethnicity (HEDS Group 2001). Events that induce viral reactivation and shedding or that enhance susceptibility of the eye to viral infection can precipitate an infective episode (Webre 2012). Identifying triggers is difficult since any suspected causal association that is made in hindsight is liable to be faulty. For example, a suspected link between psychological stress and herpetic keratitis remains indecisive (HEDS Group 2000a; Kip 2001). With the caveat of recall bias, the following are situations thought to instigate HSV epithelial keratitis:

Reactivation of latent virus

Altered homeostasis

- Fever (Ashaye 2008; Yorston 1992)

- Advancing age (Young 2010; Stanzel 2014)

Radiation exposure

- Excess sunlight (Ludema 2014a; Stan 2000)
- Photodynamic therapy of corneal neovascularisation (Dantas 1997; Yoon 2010)
- Corneal cross-linking with ultraviolet light (Kymionis 2007; Yuksel 2011)

Ocular irritants or injections

- Contact lens wear (Hamroush 2014; Mucci 2009)
- Corneal injury with a foreign body (Sundmacher 1986)
- Periocular injection (Lingua 1985)
- Intraocular injection (Khalili 2009)

Topical ophthalmic drugs

- Prostaglandin analogues and other glaucoma drugs (Alm 2008; Villegas 2008)
- Mitomycin-C and other cytotoxic agents (Rao 2009; Siddique 2011)

Anterior segment surgery

- Laser iridotomy (Hou 2004)
- Cataract extraction (Du 2010; Gu 2014; Lu 2011; Patel 2009; Sun 2013b; Yang 2011)
- Keratorefractive surgery (Santos 1983)
- Laser-assisted in situ keratomileusis (LASIK), photorefractive keratectomy (PRK), laser astigmatic keratotomy, and phototherapeutic keratectomy (PTK) (Di 2011; Gómez García 2004; Hamoudi 2013; Lu 2006; Nagy 2003; Nataneli 2013)
- Lamellar keratoplasty (Jezegabel 1967)
- Penetrating keratoplasty (Ambrósio 2001; Miyajima 2003; Rezende 2004)
- Endothelial keratoplasty (Prasher 2009)

Susceptibility to reactivated virus

Ophthalmic corticosteroids

- Topical corticosteroid (Patterson 1967a; Sundmacher 1978c; Williams 1977)
- Subconjunctival or subtenon corticosteroid (Hashizume 2009; Inoue 2014)
- Intravitreal corticosteroid (Gulkilik 2007; Shtein 2007)

Other immunosuppressive treatment

- Topical ophthalmic calcineurin inhibitor (Field 1995; Joseph 2005)
- Inhaled corticosteroid (Garcia-Medina 2011; McDonald 2015)
- Systemic immunosuppressants following organ or bone marrow transplantation (Hayashi 2008; Kremer 1991; Ng 1998)
- Systemic immunosuppressants given for autoimmune disorders (Larrañaga Fragoso 2015)

Immune dysregulation

- Atopy (Borkar 2014; Kaiserman 2006; Prabriputaloong 2006; Rezende 2006)
- HIV infection (Hodge 1997)
- Diabetes mellitus (Kaiserman 2005)
- Malnutrition (Ukety 1991)

Natural history

Without treatment, dendritic epithelial keratitis tends to be self-limited (Thygeson 1976). Some eyes heal in a few days, but natural healing often takes longer than two weeks (Liesegang 1989a). Inappropriate treatment can worsen corneal inflammation and contribute to visual loss. Any treatment that speeds healing would reduce the opportunity for unsuitable management (Kaufman 1972).

Description of the intervention

Antiviral drugs

Antiviral compounds emerged as potential treatments for herpetic keratitis during the last half of the 20th century (Bauer 1985; Graupner 1969). In 1962 idoxuridine (iododeoxyuridine, IDU), a pyrimidine analogue, was the first effective antiherpetic drug (Kaufman 1962). In the following decade a purine analogue, vidarabine (adenine arabinoside, ARA-A), entered ophthalmic practice (Whitley 1980). Idoxuridine and vidarabine were then progressively superseded by other nucleoside analogues: trifluridine (trifluorothymidine, TFT) (Carmine 1982), acyclovir (acycloguanosine, ACV) (Richards 1983; Wagstaff 1994), brivudine (bromovinyldeoxyuridine, BVDU) (De Clerq 2005), and ganciclovir (dihydroxypropoxymethylguanine, DHPG) (Chou 2014; Croxtall 2011; Tabbara 2010). Cidofovir (hydroxyphosphonylmethoxypropylcytosine, HPMPC) is an acyclic nucleotide analogue. Foscarnet (phosphonoformic acid, PFA) is a non-nucleoside antiviral compound.

Interferon

As synthetic antivirals were under development, a cytokine that could interfere with viral replication was discovered in 1957. Interferon, found to be active against HSV in 1960, was first evaluated for HSV epithelial keratitis in 1963 (Tommila 1963) and emerged as a novel management strategy for viral eye disease (Jones 1967). Comparative treatment trials of topical interferon that began in 1976 showed type I interferons—interferon-α (leukocyte interferon) and interferon-β (fibroblast interferon)—to be effective for treating HSV epithelial keratitis (Pollard 1982; Sundmacher 1982). Several formulations and dosages of exogenous interferon were tested: alone, with an antiviral nucleoside, and after debridement (Cantell 1995; Sundmacher 1983). Formerly available in limited amounts, purified interferon is now produced by recombinant DNA technology. Though not marketed for ophthalmic use, interferon eye drops can be prepared extemporaneously (Ruiz 2007).

Corneal surface debridement

Curettage and cauterisation of the ocular surface came into use in 1890 (Kipp 1890), followed by the application of cytotoxic reagents in 1900 (Friedenwald 1900). Corneal epithelial removal, usually by iodinisation or carbolisation, became a customary remedy for dendritic keratitis during the first half of the 20th century. Initial clinical trials of corneal epithelial removal 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), sometimes in combination with mechanical scraping. Subsequent methods of corneal debridement included cryoapplication (Fulhorst 1972; Struck 1989), photoinactivation (Bartholomew 1977; Daniel 1972; O'Day 1975), and thermocautery (Sundmacher 1976a; Sundmacher 1976b; Sundmacher 1978a; Sundmacher 1978b). Minimal wiping debridement (Whitcher 1976) offered a simpler, safer procedure and was used in several clinical studies (Altinisik 1987; Coster 1977a; Hung 1984; Jensen 1982; Kato 1979; Parlato 1985; Richter 1986; Serifoglu 1987; Uchida 1981; Wilhelmus 1981a; Yamazaki 1984a).

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; pyrimidine analogues such as idoxuridine, trifluridine, and brivudine; and acyclic analogues such as acyclovir and ganciclovir. These prodrugs are phosphorylated by viral thymidine kinase and inhibit HSV replication by interfering with viral DNA synthesis during transcription of the viral genome. Foscarnet and cidofovir directly inhibit viral DNA polymerase. Mutations in viral genes encoding thymidine kinase or DNA polymerase can confer antiviral resistance.

Interferons are cytokines capable of activating an intracellular pathway that upregulates host genes affecting antiviral responses. Interferon and a nucleoside antiviral could have an additive or synergistic interaction.

Corneal epithelial debridement or chemical cauterisation removes or destroys virus-infected cells of the corneal surface and is followed by corneal epithelial regeneration if residual or persistently shed virus does not cause recrudescent ocular infection. A combination of debridement with either a nucleoside antiviral drug or interferon has been suggested to avert early recrudescence. An occlusion patch applied immediately after debridement could affect the epithelial healing rate (Turner 2006) or even raise the corneal temperature by a few degrees to hinder HSV replication (Wheeler 1959).

Ancillary topical ophthalmic agents such as lubricants or growth factors might facilitate corneal epithelial regeneration.

Why it is important to do this review

An antiviral agent is a favoured treatment for HSV epithelial keratitis (Sundmacher 2009). However, controversies persist about the optimal antiviral agent, the role of interferon, and the effectiveness of debridement methods (Epstein 1989; Guess 2007; Kastner 1984). Surveys among ophthalmologists reveal some differences of opinion in treatment preferences for HSV epithelial keratitis (Guess 2010; Labetoulle 2005; McAllum 2003; Sundmacher 1977; Ziahosseini 2009). To provide an evidence-based analysis, this systematic review evaluates the collective evidence on the treatment of HSV epithelial keratitis.

OBJECTIVES

To compare the relative effectiveness of antiviral agents, interferon, and corneal debridement in the treatment of HSV epithelial keratitis.

METHODS

Criteria for considering studies for this review

Types of studies

This review included clinical trials that compared the relative effectiveness of therapeutic interventions on the corneal epithelial healing of participants who had clinically diagnosed or virologically confirmed HSV epithelial keratitis. Trials limited to the prevention of recurrent herpetic eye disease were not considered in this review.

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. Trials of herpes simplex virus stromal keratitis, keratouveitis, or uveitis were not considered in this review.

Types of interventions

Antiviral agents included idoxuridine, vidarabine, trifluridine, acyclovir, ganciclovir, brivudine, foscarnet, and cidofovir. Interferon preparations included interferon-α, interferon-β, and interferon inducers. Debridement of the corneal epithelium was done by wiping, scraping, chemical corrosion, cryotherapy, thermal application, or photoinactivation. Supplemental agents included lubricants, growth factors, anti-inflammatory medications, and immunomodulators. Trials of herbal extracts, traditional medicines, acupuncture, and other alternative interventions were not considered in this review. Studies of gene therapy were not part of this review (Elbadawy 2012).

Types of outcome measures

Primary outcomes

The primary outcome was the proportion of eyes healed at 14 days after study entry.

Secondary outcomes

Two secondary outcomes were used to evaluate the pace of healing: the proportion healed at seven days after study entry and the comparative rate of healing between interventions as estimated by logrank analysis of survival curves or life tables. Ancillary measures that were recorded when available were the effect on viral recovery, the prevalence of adverse events during treatment, the occurrence of episodes of recrudescent keratitis during or immediately after treatment (arbitrarily defining recrudescence as reappearing epithelial keratitis occurring less than two weeks after completing short-term therapy), and the number of episodes of recurrent keratitis during follow up over the ensuing months (arbitrarily defining recurrence as a new episode of epithelial keratitis occurring two weeks or longer after completing short-term therapy).

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. The search for studies was performed with the assistance of the Cochrane Eyes and Vision Group (CEVG) and the United States Cochrane Center (USCC). 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 of a possibly relevant clinical trial. Articles were translated as needed. The sequence of searching and assessment of studies was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 12), PubMed (January 1946 to 31 December 2014), EMBASE (January 1980 to 31 December 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to 31 December 2014), System for Information on Grey Literature in Europe (OpenGrey) (January 1995 to 31 December 2014), BIOSIS (January 1926 to 5 May 2014), Scopus (January 1966 to 31 December 2014), Japan Science and Technology Institute (J-Global) (January 1975 to 31 December 2014), China National Knowledge Infrastructure (CNKI) (January 1979 to 31 December 2014), and British Library's Electronic Table of Contents (Zetoc) (January 1993 to 7 May 2014). The following resources were last searched on 31 December 2014: the *meta*Register of Controlled Trials (mRCT), ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and the Chinese Clinical Trial Registry (ChiCTR). There were no language or date restrictions in the search for trials. Spanish, Portuguese, Japanese, and Chinese databases were searched with English language terms and with pertinent language terms.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), PubMed (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), OpenGrey (Appendix 5), BIOSIS (Appendix 6), Scopus (Appendix 7), J-Global (Appendix 8), CNKI (Appendix 9), Zetoc (Appendix 10), *m*RCT (Appendix 11), ClinicalTrials.gov (Appendix 12), ICTRP (Appendix 13), and ChiCTR (Appendix 14).

Searching other resources

Handsearching

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

Grey literature

We searched titles and abstracts of presentations and posters from 1960 to 2014 for clinical reports of herpetic keratitis submitted to the following meetings: Association for Research in Vision and Ophthalmology (ARVO), World Ophthalmology Congress, American Academy of Ophthalmology (AAO), Ocular Microbiology and Immunology Group (OMIG), and International Conference on Herpetic Eye Diseases. Websites of the U.S.Food and Drug Administration (FDA) (Appendix 15), National Institute for Health and Clinical Excellence (NICE) (Appendix 16), the European Medicines Agency (EMA) (Appendix 17) were searched for unpublished or unregistered clinical trials on herpetic keratitis.

Reference lists

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

Correspondence

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

Data collection and analysis

Selection of studies

Human studies were selected based on study design, type of corneal disease, interventions, and outcome measures. Included studies had an impartial allocation of two or more interventions to participants who were clinically diagnosed or virologically confirmed, or both, 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). This review did not examine the management of HSV stromal keratitis, endotheliitis, keratouveitis, or iritis (Knickelbein 2009).

Data extraction and management

The author recorded relevant information for each included study onto a data collection form. Extracted data comprised attributes of study participants, 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 eyes that healed in each intervention group was recorded for each day of follow up, including days seven and 14. For reports using graphs of healing curves to describe outcome, plotted lines were projected onto the ordinate axis for each follow-up day along the abscissa to estimate the daily proportion healed in each treatment group. Adjustment for censoring was not part of the estimation of risk ratios but was considered when estimating hazard ratios.

Assessment of risk of bias in included studies

Appraisal of study design, analysis, and presentation considered potential sources of selection bias, performance bias, detection bias, and attrition bias. Selection bias was evaluated by examining randomisation of treatment allocation and concealment of assigned treatment group. Studies that did not explain the method of sequence generation but did describe a controlled clinical trial design were considered to have an unclear risk of bias for sequence generation. The remaining studies that did not identify a randomisation process were considered to have a high risk of bias for random sequence generation. Performance bias and detection bias were evaluated by noting the use of masking of participants, trialists, and outcome assessors and by the method that was used to ascertain corneal epithelial healing. Attrition bias was evaluated by the extent of withdrawals and other losses to follow up. Because the primary endpoint of corneal epithelial healing was measured within two weeks of enrolment, withdrawals and losses to follow up were expected to be relatively low. Studies were judged to be liable to have incomplete outcome reporting if the status was not provided for participants who did not achieve healing and who were not assessed at two weeks. Each component of internal validity (sequence generation, allocation concealment, masking,

completeness of outcome data, outcome reporting, and other sources of bias) was categorically judged as having a low, unclear, or high risk of bias.

Measures of treatment effect

Relative measures of corneal healing between treatment groups were estimated by risk ratios at seven days and at 14 days after trial enrolment. A hazard ratio was also estimated when additional time-to-event data could be extracted from tables or cumulative healing curves. Ratios were reported with 95% confidence intervals. 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).

Unit of analysis issues

The unit of analysis was the individual eye with HSV keratitis. If a person with bilateral or recurrent keratitis was enrolled more than once into a trial, the unit of analysis was the eye designated to receive study treatment for each episode. Potential correlation of outcomes between fellow eyes was not considered in pooled analyses.

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

Assessment of heterogeneity

Heterogeneity among trials evaluating similar interventions was investigated using forest plots. The I^2 statistic was used as an index of inconsistency among pooled comparisons of interventions (Higgins 2002). I^2 greater than 50% indicated substantial heterogeneity. Any treatment comparison having high heterogeneity when estimating a pooled risk ratio at 14 days was re-analysed in a random-effects model.

Assessment of reporting biases

Publication bias was explored by funnel plots for treatment comparisons that had at least ten trials.

Data synthesis

Treatment comparisons

Interventions were compared to inactive controls, to each other, or to combinations of interventions. Data from trials with multiple treatment groups were evaluated by selecting paired comparisons of two interventions or by combining data from similar treatment groups.

Placebo controls

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

Combining treatments within studies

Interventions that were considered sufficiently similar and that were amalgamated within studies having more than two treatment groups were photoinactivation and carbolisation; cryotherapy and carbolisation; interferon-α at either 1 million IU/ml or 10 million IU/ml; thermomechanical debridement and thermomechanical debridement with interferon-α 62,500 IU/ml, a dosage probably too low to exert clinical effects; debridement 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.

Combining treatments between studies

Different formulations of the same nucleoside antiviral agent (for example, idoxuridine solution and idoxuridine ointment; acyclovir ointment and acyclovir solution; and ganciclovir gel and ganciclovir solution) were 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. One study (Li 2013a) that compared ganciclovir to acyclovir plus interferon was tabulated in the ganciclovir-acyclovir comparison.

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. Pooled comparisons with $I^2 > 50\%$ for the 14-day outcome were re-estimated in a random-effects model.

Indirect risk ratio

Treatment comparisons were organised into networks. Within the network of antiviral treatment trials, indirect risk ratios were estimated in which different antivirals could be compared by way of a mutual antiviral agent (Bucher 1997; Glenny 2005; Song 2009). Using formulæ (Wells 2009) implemented in software from the Canadian Agency for Drugs and Technologies in Health, indirect risk ratios and corresponding 95% confidence intervals were computed for topical antiviral treatment comparisons at 14 days. Consistency within a set of indirect risk ratios was examined with random-effects meta-regression (White 2012).

Combined direct and indirect risk ratio

An adjusted risk ratio was estimated by pooling direct and indirect relative treatment effects (Song 2003) in a software program using a random-effects model (Harris 2008). The I^2 statistic and graphs (Chaimani 2013) were used to interpret the network meta-analysis.

Hazard ratio

Healing times were estimated for studies that reported outcomes at more than two time points within two weeks 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 to estimate 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 rate

Studies providing healing curves were integrated into a graph to illustrate the relative rates of corneal re-epithelialisation over two weeks of treatment. The cumulative healing probability was estimated by collating participant-level data from a large antiviral treatment trial.

Subgroup analysis and investigation of heterogeneity

Two trials that restricted enrolment to persons with geographic epithelial keratitis were tabulated with other trials but also analysed separately. Studies that enrolled eyes with either dendritic or geographic epithelial keratitis did not undergo stratified analysis by type of keratitis in this systematic review. Other characteristics evaluated as possible prognostic factors of corneal epithelial healing time in any *post hoc* analysis 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 omitted from the meta-analysis if there was a potentially high risk of bias because of possible non-random sequence generation, unconcealed allocation, or lack of masking that could have influenced outcome assessment. Another sensitivity analysis used only studies with an explicit randomised, double-masked trial design. Studies that were excluded because cumulative healing proportions of the treatment arms were not given were tabulated to explore how their findings compared with the pooled results of included studies.

RESULTS

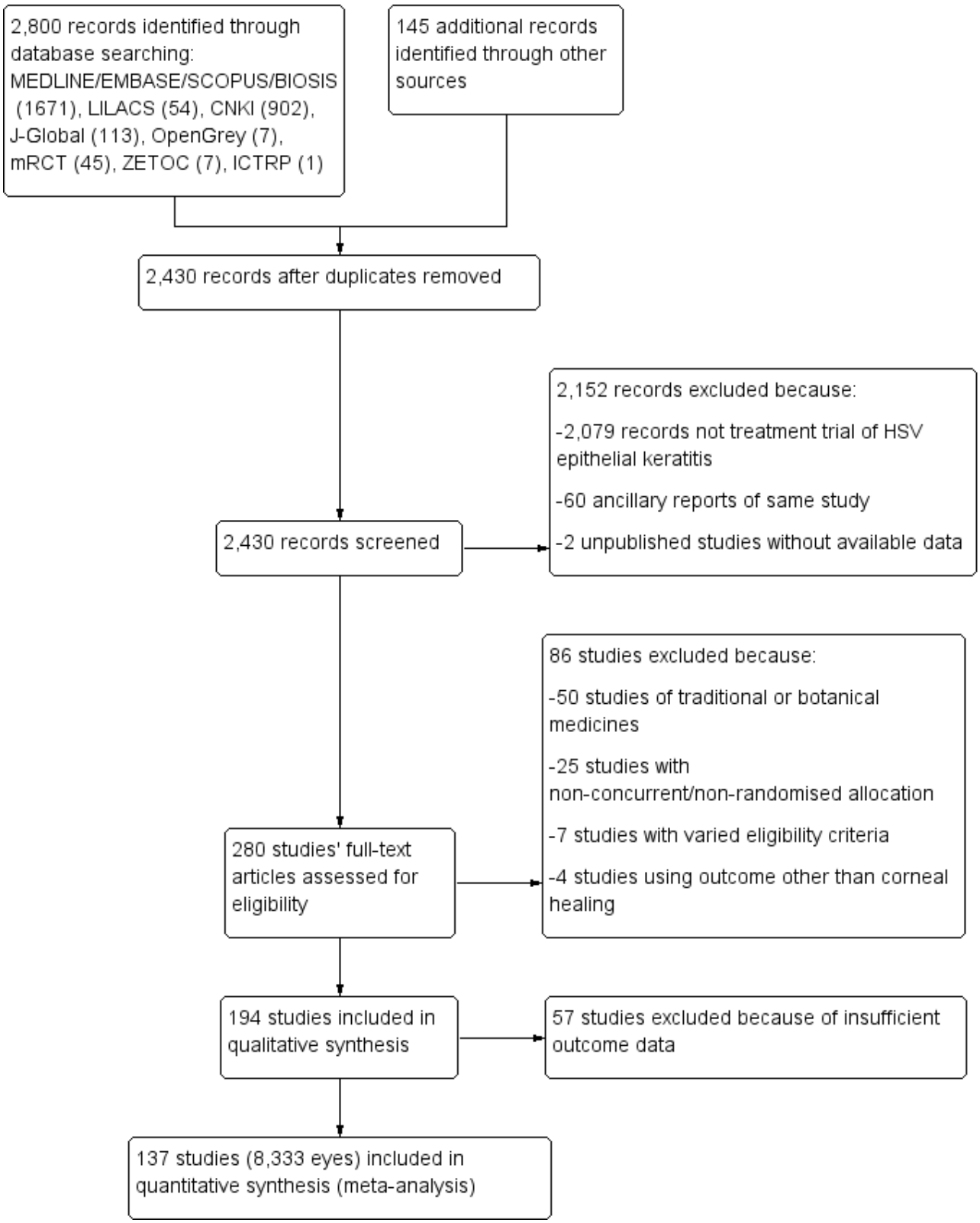
Description of studies

Results of the search

Electronic and manual searches identified 2430 discrete reports of HSV keratitis. After screening, 280 therapeutic studies were identified that compared two or more interventions in the treatment of HSV epithelial keratitis (Figure 2). One hundred thirty-seven studies that met this review's inclusion criteria are tabulated in Characteristics of included studies. Characteristics of excluded studies outlines which of the five main reasons why 143 studies were excluded along with the treatment groups of each excluded study. Two unpublished antiviral treatment trials are listed in Characteristics of studies awaiting classification.

Figure 2.

- **Study flow diagram.**



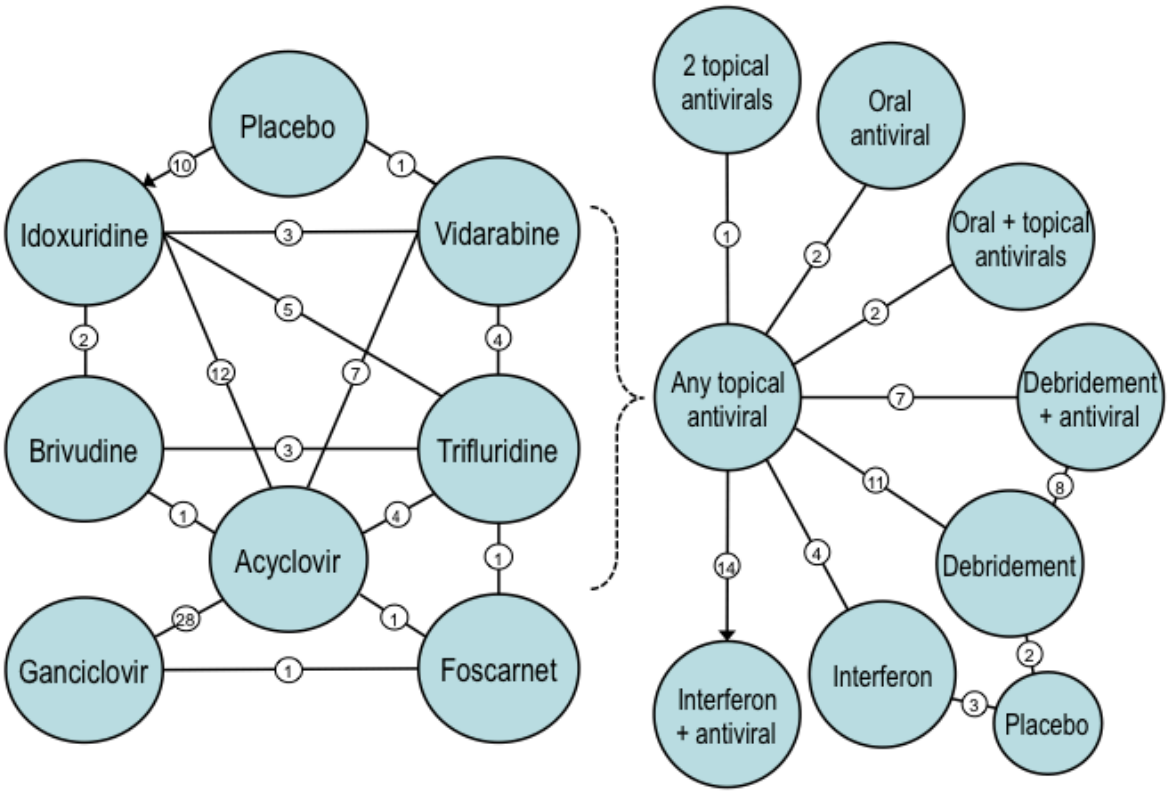
Included studies

Interventions

Trials compared various pharmacological and non-pharmacological interventions. One hundred sixteen trials compared an intervention to a control or compared two interventions. The others had multiple treatment arms: 16 studies had three treatment groups (Altinisik 1987; Bartholomew 1977; Carmassi 1993; Colin 1997a; Colin 2007a; Coster 1977a; Davidson 1964; Huang 2008a; MacKenzie 1964; Maichuk 1988; Markham 1977; Meurs 1985; Parlato 1985; Sundmacher 1976a; Sundmacher 1981b; Uchida 1981), four studies had four groups (Matthäus 1970; Panda 1995; Struck 1989; Sundmacher 1987), and one study had five groups (Fulhorst 1972).

For this systematic review, treatment comparisons were organised into two-way comparisons and allocated into five categories: comparisons of topical antivirals, trials involving oral antiviral treatments, studies examining the effect of interferon, studies of corneal epithelial debridement, and trials of miscellaneous drugs. Among multiple treatment comparisons (Figure 3), the number of direct, two-way comparisons ranged from one to 28 studies.

Figure 3. Networks of clinical trials included in this systematic review. Left diagram shows a network of two-way comparisons among topical antiviral agents. Not shown in the left diagram are trials evaluating *para*-fluorophenylalanine, different trifluridine vehicles, and different ganciclovir concentrations. Right diagram illustrates a network of comparisons between topical antiviral agents and various interventions that included dual antiviral therapy, oral acyclovir, interferon without or with an antiviral, and debridement without or with an antiviral. Not shown in the right diagram are trials evaluating different interferon dosages or types, an interferon inducer, different methods of debridement, debridement with two different antivirals, and miscellaneous agents (hyaluronate, epidermal growth factor, panthenol, methyluracil, oxyphenbutazone, or inosine pranobex). Lines show direct treatment comparisons reporting outcomes at one week or two weeks. Circled numerals indicate the number of direct treatment comparisons that were included in this systematic review. The placebo groups consist of a variety of inactive controls. The number of acyclovir-idoxuridine (IDU) comparisons includes one trial using iododeoxycytidine (IDC), even though IDC was not pooled with IDU in the meta-analysis. The number of direct comparisons exceeds the number of studies because 21 studies compared more than two interventions.



Supplemental medications

Use of a topical cycloplegic agent was reported in 51 included trials: atropine in 29 studies, scopolamine in six, homatropine in five, and a non-specified cycloplegic or mydriatic agent in 11. A concomitant topical antibiotic was dispensed in 19 studies: ofloxacin in seven studies, chloramphenicol in four, gentamicin in one, micronomicin in one, and an unspecified antibiotic in six.

Sample sizes and study statistics

A total of 8333 eyes with HSV epithelial keratitis were enrolled and analysed in 137 studies included for analysis in this systematic review. Study sizes ranged from 15 to 287 participants, and the distribution of study sizes skewed toward small to moderately sized samples. The median number enrolled per study was 53 (interquartile range [IQR] 33 to 78). Multicentre studies enrolled more eyes: the median study size was 50 (IQR 32 to 76) among 118 single-centre studies and 64 (IQR 51 to 109) among 19 multicentre studies.

None of the studies reported a pretrial sample size estimation based on *a priori* assumptions, although one trial did provide a statistical computation that was used to plan enrolment based on recurrence risk rather than epithelial healing (HEDS Group 1997). The statistical analysis of individual studies, when reported, was based on detecting a statistically significant difference between treatment groups in corneal epithelial healing. One study provided a *post hoc* non-inferiority analysis (Colin 2007b). An independent committee monitored accrued data for some multicentre studies (HEDS Group 1997; Tanaka 1988a; Tanaka 1988b).

Study participants

Table 3 summarizes the characteristics of participants and interventions. Among 66 trials that described age statistics of enrolled participants (including one trial (Li 2013b) that gave median rather than mean age), the overall average age was 43 years (standard deviation (SD) 6 years). Of 78 trials reporting the gender of study participants (omitting one trial (Hart 1965) that only gave the gender of cured participants), 71 (91%) enrolled more men than women. The median male-female ratio was 1.5 (IQR 1.2 to 2.1).

Setting

Seventy-one trials included in this review took place in Europe, 51 in Asia, 13 in North America (including one performed in the United States and the United Kingdom), one in Africa, and one in Australia. One hundred seventeen trials included in this review took place at a single centre. The primary report was published in the English language for 79 included trials, Chinese for 33, Japanese for seven, German for seven, French for six, Italian for two, Turkish for two, and Russian for one.

Type of epithelial keratitis

Seventy-four trials specified dendritic epithelial keratitis as an eligibility criterion. Two other trials (Burns 1963; Davidson 1964) provided insufficient information to confirm that all participants had dendritic epithelial keratitis. Fifty-nine trials enrolled participants with either dendritic or geographic epithelial keratitis. In these studies dendritic epithelial keratitis was, on average, five times more prevalent than geographic epithelial keratitis. Two trials were restricted to geographic epithelial keratitis (Collum 1985; Coster 1979).

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). Four trials performed HSV isolation without providing the number of culture-positive eyes (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% (IQR 50% to 78%). HSV-2 was rarely isolated (Vannini 1986). No study reported whether a topical anæsthetic (Goldschmidt 2006; Weinberg 1977) or stain (Roat 1987; Seitzman 2006) might have curtailed viral detection.

Outcome evaluation

Outcome assessment was based on clinical observation using slit-lamp biomicroscopy, except for one study (Hart 1965) that used a magnifying loupe. Of 117 trials specifying the use of a stain, 96 (82%) used fluorescein (including one study stating only that a "stain" was used), nine used rose-Bengal, and 12 used both fluorescein and rose-Bengal.

The description of outcome assessment, when stated, assigned the day of healing as the time when re-epithelialisation of the corneal surface was first verified. If a topical dye was used then the day of healing was the first day when no confluent staining was observed. The following extracts exemplify overlapping ways by which the primary endpoint of resolution of active epithelial keratitis were expressed:

- "Disappearance of [fluorescein] dendritic staining, despite the occasional persistence of fine, superficial punctate keratitis" (Parlato 1985).
- "Fluorescein-negative healing of the corneal epithelium, which was defined as complete closure of all erosions except for some single dye-positive micropunctations" (Sundmacher 1976a).
- "Disappearance of specific Bengal-rose staining of the precise site of the healing dendritic ulceration...[not considering] fine microscopic punctate staining diffusely arranged on the epithelial surface" (Wilhelmus 1981a).
- "2 criteria for healing: (1) partial healing...defined as closure of the epithelial wound only, i.e., no staining with fluorescein; and (2) complete healing...defined as closure of the epithelial wound without any epithelial oedema or cystic changes in the area of the previous dendrite" (de Koning 1982).
- "Healing was defined as the situation in which no staining with fluorescein was observed and no epithelial oedema and cystic changes were present in the epithelium covering the site of the original ulcer" (van Bijsterveld 1980).
- Following fluorescein 1% and rose-Bengal 1%, the initial dendritic pattern "was red, stained by rose bengal, and outlined by a green fluorescent double contour…. The red-stained dendriform pattern represented virus-affected cells, while the green double contour disclosed presence of epithelial defects as well. After on an average five days only uncharacteristic remains were left of the previous dendritic pattern in the form of accumulated vital-stained dots localized within parts of the previous pattern. Some such remains were fluorescein-stained

epithelial defects and others rose-bengal-stained, degenerate epithelial cells…. This second phase was followed by a third one, during which punctate fluorescein and/or rose bengal staining might still be seen, but now only represented by a few dots, as a rule scattered over the whole cornea, also outside the original dendritic pattern" (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 antiviral-treated geographic epithelial keratitis was nine days (Collum 1985; Coster 1979). Based on 49 trials that published survival graphs, the maximum separation of healing curves for different treatments occurred at a median of six days. The healing curve of one large antiviral treatment trial (HEDS Group 1997) was examined in parametric statistical models and found to fit a log-logistic distribution (Wilhelmus 2000). In that study, the cumulative probability of corneal epithelial healing at each day (t) of trifluridine chemotherapy for dendritic epithelial keratitis could be estimated by $[(7/t)^4 + 1]^{-1}$.

Excluded studies

One hundred forty-three comparative treatment trials of HSV epithelial keratitis were excluded from analysis because study treatment, study design, or available data did not meet eligibility criteria (Characteristics of excluded studies). One excluded study did not report the sample size (Kuyama 1979). A total of 12,367 participants with HSV epithelial keratitis were enrolled in the other 142 excluded studies that had study populations ranging from nine to 416 participants.

Alternative study treatment

Fifty studies were ineligible because at least one of two treatment groups included an ethnobotanical preparation or traditional Chinese medication, used either alone or integrated with a synthetic antiviral agent. Several studies of complementary or alternative interventions were pre-emptively identified before full articles were reviewed for eligibility, precluded based on their titles or abstracts, and do not appear in this subtotal.

Ineligible study design

Twenty-five studies were excluded because of non-concurrent or non-randomised treatment allocation. Seven studies were excluded because their eligibility criteria did not ensure that enrolled patients had active epithelial keratitis. Four studies were excluded because outcome was based on an endpoint other than epithelial healing.

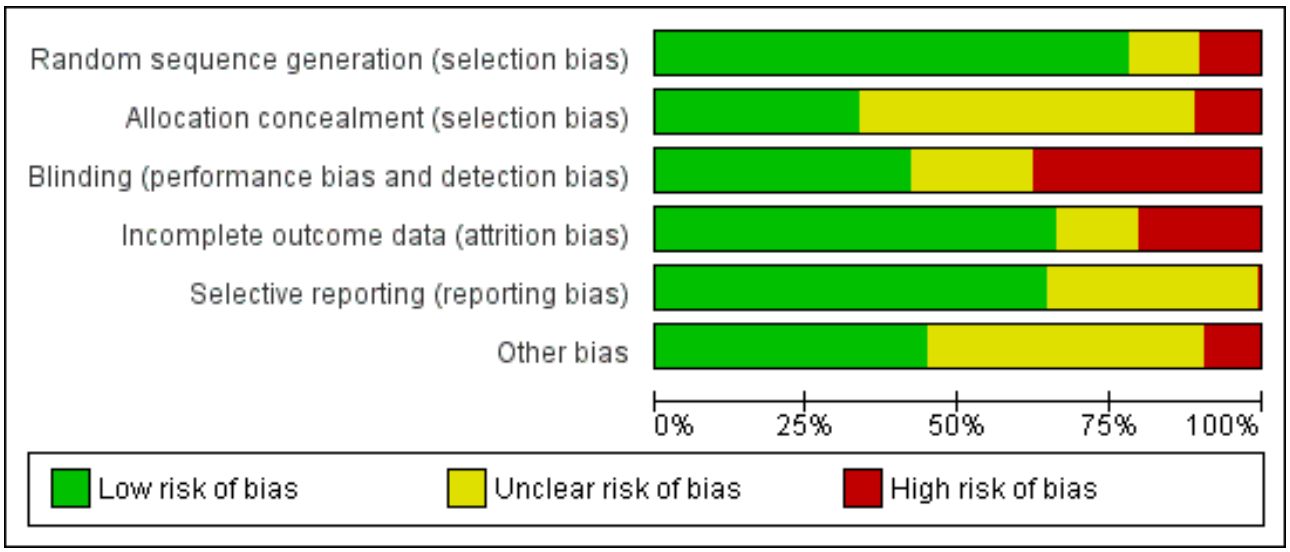
Insufficient outcome information

Fifty-seven studies were excluded because insufficient outcome data were available at seven and 14 days. Trials lacking survival data generally assessed relative outcome by comparing mean healing times or clinical scores of symptoms and signs (Table 4). Thirty-three studies reported mean healing times of treatment groups; 18 studies reported a P value for a different endpoint; and six studies provided neither outcome analysis.

Risk of bias in included studies

Potential biases affected several studies (Figure 4).

Figure 4. Methodological quality graph: review author's judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Among 137 included trials, 107 (78%) stated that a randomisation process was used to allocate study interventions. Sixteen studies had an unclear method of generating the sequence of treatment assignment. Fourteen studies were considered to have a potentially high risk of bias of random sequence generation, including two studies that assigned study treatment to alternating participants (Daniel 1972; Luntz 1963) and two studies that apparently allocated treatment by availability (Abe 1987; Altinisik 1987). Allocation concealment was judged to have a low risk of bias for 46 (34%) of the studies. Seventy-six studies had an unclear risk of bias of allocation concealment, and 15 were considered to have a high risk of bias.

Blinding

Fifty-seven (42%) studies had a double-masked study design, including two triple-masked trials that used a different outcome assessor than the investigator who allocated treatment (Parlato 1985; Sundmacher 1978a). Twenty-eight trials had a single-masked or unclear scheme, and 52 trials used an unmasked design.

Incomplete outcome data

Ninety (66%) of the studies were considered to have a low risk of attrition bias. Nineteen studies had an unclear risk of attrition bias. Among 28 studies considered to have a high risk of having incomplete outcome data, the percentage of missing data varied from 5% to 40%. Eight of these studies provided outcome data only for culture-positive eyes.

Selective reporting

Eighty-eight (64%) of the studies had a low risk of reporting bias. Forty-eight studies had an unclear risk of selective reporting, mainly because study protocols were rarely available and the published report was used to determine relevant events within two weeks of follow up. One study judged to have a high risk of reporting bias apparently enrolled patients with bilateral keratitis but used participants rather than eyes as the unit of analysis (Dai 2009a).

Other potential sources of bias

Thirteen studies were judged to have a high risk of other sources of bias. Two trials added supplemental treatment during follow up: additional debridement in one trial (Sundmacher 1978a) and corticosteroid eye drops in another trial (Luntz 1963). One trial allowed some participants to cross over to the other treatment arm (Patterson 1967a). Two trials were stopped early (Behrens-Baumann 1992; O'Day 1975). In addition to one study that enrolled an unclear number of eyes with stromal keratitis (Zhen 2012), seven studies randomised between 13% and 34% of study eyes having disciform or stromal keratitis; these studies did not separately report healing outcomes by type of keratitis (Li 2009; Lin 2011; Liu 2012a; Liu 2012b; Liu 2014a; Wang 2014a; Zhao 2006).

Investigation of heterogeneity

Substantial heterogeneity (I^2 > 50%) among study findings was found for ten treatment comparisons at the 14-day outcome assessment, including one placebo-controlled comparison (Analysis 1.1), three comparisons of topical nucleoside antivirals (Analysis 1.10; Analysis 1.13; Analysis 1.22), a comparison involving oral acyclovir (Analysis 2.2), the comparison between interferon (Analysis 3.5) or combined interferon and an antiviral (Analysis 3.7) with nucleoside antivirals, and three comparisons examining debridement (Analysis 4.2; Analysis 4.4; Analysis 4.6). Six of these comparisons also showed heterogeneous findings at seven days (Analysis 1.1; Analysis 1.10; Analysis 3.7; Analysis 4.2; Analysis 4.4; Analysis 4.6). Possible treatment-related reasons for inconsistency among studies were differences in dosage or formulation of topical study medicines, non-uniform methods of corneal debridement, dissimilar use of adjunctive drugs, and possible enrolment of some eyes that did not have HSV epithelial keratitis.

Sensitivity analyses

After selectively omitting studies that had a potentially inadequate or indeterminate process of random treatment assignment, studies that may have had unconcealed allocation, and studies that used incomplete masking, precision declined but relative effect measures did not shift substantially (Table 5). The findings of randomised, double-masked trials were also generally comparable to the results of all studies (Table 2).

Assessment of publication bias

Five treatment comparisons had enough studies to assess asymmetry in funnel plots. No obvious publication bias was found for the idoxuridine-placebo comparison. Publication bias may have existed in favour of acyclovir for the acyclovir-idoxuridine comparison at seven days, but no serious publication bias was apparent for the 14-day outcome. Publication bias was possible for the ganciclovir-acyclovir comparison (Figure 1), suggesting a bias toward publication of studies favouring ganciclovir. The comparisons between antiviral treatment and either interferon plus antiviral or debridement did not have apparent publication bias.

Secular variation

To explore whether response to therapy may have changed over time, outcome were examined for 59 studies in which topical acyclovir ointment or solution was assigned to one treatment arm. The 14-day cure rate with acyclovir averaged 91% (SD 10%) among 27 studies published between 1980 and 1989 (Abe 1987; Altinisik 1987; Colin 1981; Colin 1983; Colin 1987; Collum 1980; Collum 1985; Collum 1986; Coster 1980; de Koning 1983; Denis 1983; Genée 1987; Hoang-Xuan 1984; Høvding 1989; Jackson 1984; Jensen 1982; Kitano 1985; Klauber 1982; Kumar 1987; La Lau 1982; Maichuk 1988; McCulley 1982; Meurs 1985; Pavan-Langston 1981; Wilhelmus 1981a; Yeakley 1981; Young 1982), 75% (SD 15%) for four studies published between 1990 and 1999 (Carmassi 1993; Colin 1997a; Colin 1997b; Panda 1995), 56% (SD 27%) for 15 studies published between 2000 and 2009 (Cao 2001; Chen 2008; Colin 2007a; Colin 2007b; Dai 2009a; Dai 2009b; Huang 2008a; Li 2008; Li 2009; Liu 2009a; Ramirez 2002; Xu 2009a; Yang 2000; Yang 2008; Zhao 2006), and 46% (SD 24%) for 13 studies published between 2010 and 2014 (Han 2010; Han 2014; Li 2013a; Lin 2011; Lin 2014; Liu 2010; Liu 2012a; Liu 2012b; Sun 2013a; Wang 2014a; Zhang 2014; Zhen 2012). Among 32 studies evaluating ganciclovir gel, the 14-day outcome with ganciclovir averaged 83% (SD 0.5%) for two studies published in 1997 (Colin 1997a; Colin 1997b), 73% (SD 18%) for 13 studies published between 2000 and 2009 (Chen 2008; Colin 2007a; Colin 2007b; Dai 2009a; Dai 2009b; Huang 2008a; Li 2008; Liu 2009a; Ramirez 2002; Xu 2009a; Yang 2000; Yang 2008; Zhao 2006), and 73% (SD 20%) for 17 studies published between 2010 and 2014 (Fu 2012; Han 2010; Han 2014; Li 2013a; Li 2013b; Lin 2011; Lin 2014; Liu 2010; Liu 2012a; Liu 2012b; Sun 2013a; Wang 2014a; Yu 2012a; Zhang 2014; Zhen 2012; Zheng 2010).

Effects of interventions

See: **Summary of findings for the main comparison** Network analysis of antiviral agents and combination interventions; **Summary of findings 2** Relative healing outcomes with topical antiviral therapy; **Summary of findings 3** Relative healing rates with antiviral agents and combination interventions; **Summary of findings 4** Relative healing outcomes with combined topical or topical and oral antiviral therapy; **Summary of findings 5** Relative healing outcomes with topical interferon; **Summary of findings 6** Relative healing outcomes with corneal debridement

Interventions were divided into five categories: topical antiviral agents, oral antiviral therapy, interferon, corneal epithelial debridement, and adjunctive drugs. The primary treatment effect was assessed by a risk ratio at 14 days, adjusted by available indirect risk ratios for antiviral treatment comparisons (Table 1). Any difference in early resolution was examined by a risk ratio at seven days. The relative pace of healing was examined by a hazard ratio.

Topical antiviral therapy

Eight-three studies made head-to-head comparisons among inactive control, idoxuridine, vidarabine, trifluridine, acyclovir, brivudine, ganciclovir, or foscarnet (Figure 3).

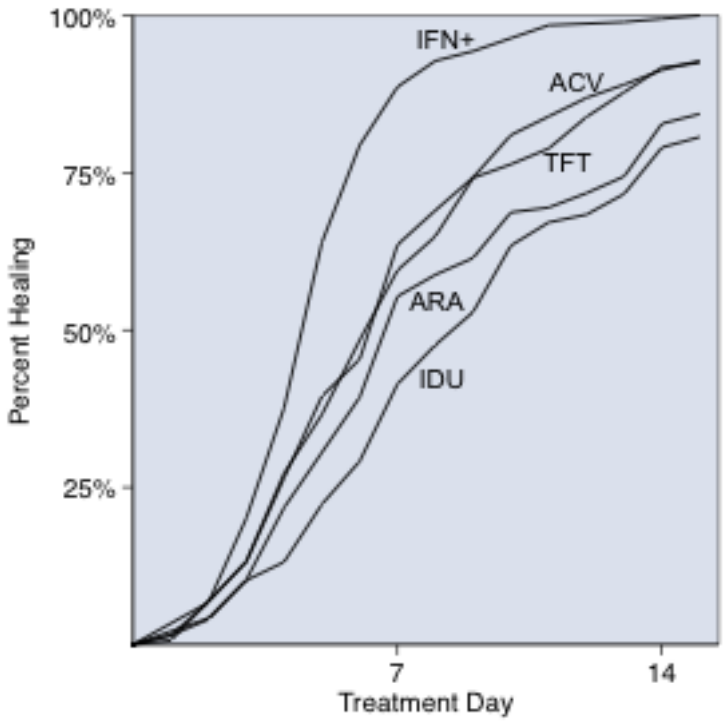
Idoxuridine and vidarabine

The analyses of seven-day and 14-day outcomes (Analysis 1.1) and of relative healing rates (Analysis 1.2) comparing idoxuridine to inactive control were limited by heterogeneity. In one trial, vidarabine was significantly better than inactive control at 14 days (Analysis 1.3) and increased the rate of healing (Analysis 1.4). While direct comparisons of vidarabine to idoxuridine did not show a significant difference in healing outcome (Analysis 1.5) or healing rate (Analysis 1.6), a combined direct and indirect comparison using studies in which vidarabine and idoxuridine were compared to a mutual antiviral suggested that vidarabine might have better therapeutic effectiveness than idoxuridine (Table 1). Additionally, *para*-fluorophenylalanine, an amino acid analogue having antiviral activity, did not significantly differ from idoxuridine (Analysis 1.7).

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) were significantly better, although the acyclovir-idoxuridine comparison had high heterogeneity and possible bias toward publication of trials that showed faster healing with acyclovir. One trial compared acyclovir to iododeoxycytidine, but a significant difference in healing outcome was not detected (Analysis 1.10.3). Network analysis indicated that healing outcomes of trifluridine, acyclovir, or brivudine were significantly better than for idoxuridine (Table 1). Assimilated healing curves also furnished evidence that trifluridine and acyclovir provided faster healing than idoxuridine (Figure 5). Trifluridine (Analysis 1.13; Analysis 1.14) and acyclovir (Analysis 1.15; Analysis 1.16), while not determined to be significantly different from vidarabine in direct comparisons, were more effective than vidarabine in network analyses (Table 1). Neither acyclovir (Analysis 1.17; Analysis 1.18) nor brivudine (Analysis 1.19; Analysis 1.20) was found to be significantly different from trifluridine. Brivudine was not different from acyclovir in one trial (Analysis 1.21) and in network analysis (Table 1). The direct comparison of ganciclovir with acyclovir was limited by heterogeneity among included studies (Analysis 1.22) and a possible publication bias toward studies favouring ganciclovir (Figure 1).

Figure 5. Cumulative healing data from trials evaluating idoxuridine, vidarabine, trifluridine, acyclovir, or interferon plus an antiviral agent. Antiviral healing curves were blended 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; Høvding 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 reported healing data for idoxuridine (278 eyes), vidarabine (262 eyes), trifluridine (279 eyes), or acyclovir (480 eyes). Corneal healing with combined interferon-antiviral was estimated from seven studies (Carmassi 1993; Colin 1983; de Koning 1982; de Koning 1983; Meurs 1985; Sundmacher 1981b; van Bijsterveld 1989) that evaluated 196 participants who received interferon with trifluridine (75), acyclovir (102), or brivudine (19). (ACV, acyclovir; ARA, vidarabine; IDU, idoxuridine; IFN+, interferon with an antiviral (trifluridine, acyclovir, or brivudine); TFT, trifluridine).



Foscarnet

Foscarnet was not significantly different from trifluridine in one trial (Analysis 1.23), from acyclovir in one trial (Analysis 1.24), or from ganciclovir in one trial (Analysis 1.25). Network analysis did not reveal statistically significant differences between foscarnet and trifluridine or ganciclovir (Table 1). The indirect comparison of foscarnet and acyclovir involved a heterogeneous group of studies comparing acyclovir and ganciclovir.

Antiviral combination

Although dual antiviral treatment was more effective at seven days, the combination of topical acyclovir and vidarabine was not significantly different at 14 days than topical acyclovir in one trial (Analysis 1.26).

Formulation and dosage of topical antivirals

No differences were apparent among few studies that evaluated different vehicles (Analysis 1.27) or concentrations (Analysis 1.28) of topical antiviral agents. No study compared different frequencies of administration of the same topical antiviral agent.

Safety of topical antivirals

Forty-four studies reported the prevalence of ocular adverse reactions other than stinging or discomfort that was attributable to topical antiviral medications. Treatment-related effects on the ocular surface that were reported in trials included in this review were allergic blepharoconjunctivitis, toxo-allergic follicular conjunctivitis, and superficial keratopathy. In these antiviral treatment trials the median percentage of eyes that developed superficial keratopathy or punctate epithelial erosions was 10% with idoxuridine, 11% with vidarabine, 4% with trifluridine, 10% with acyclovir, 0% with brivudine, and 4% with ganciclovir (Table 6).

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 (Analysis 2.2) were limited by few trials that tended to be heterogeneous.

Interferon therapy

Interferon monotherapy

Topical interferon therapy was significantly better than inactive control (Analysis 3.1), but few studies were available. A higher interferon concentration (≥ 1 million IU/ml) was more effective than a low concentration (1000 IU/ml) (Analysis 3.2). Interferon-α and interferon-β did not differ significantly when used with debridement (Analysis 3.3). Recombinant interferon was not significantly different from naturally-derived interferon in combination with trifluridine (Analysis 3.4).

Interferon compared to nucleoside antivirals

The comparison of topical interferon to a topical nucleoside antiviral agent (Analysis 3.5) was limited by heterogeneity among included studies. A topical interferon inducer did not differ significantly from a topical antiviral agent in a single study (Analysis 3.6).

Interferon-antiviral combination therapy

The combination of interferon and an antiviral agent appeared to be significantly more effective than antiviral monotherapy (Analysis 3.7) and to offer earlier and significantly faster healing (Analysis 3.8), but these comparisons were limited by heterogeneity among studies.

Safety of topical interferons

Adverse effects attributable to topical interferon were rarely mentioned in studies, although between 5% and 25% of treated patients had a mild, transient reaction (Tanaka 1988a; Tanaka 1988b). Adverse events described with the combined use of interferon and an antiviral drug were limited to punctate keratopathy (Colin 1983; de Koning 1983).

Debridement

Methods of corneal debridement

Few studies of limited duration compared physicochemical debridement with control (Analysis 4.1). The comparison of debridement to topical antiviral therapy was limited by heterogeneity among studies (Analysis 4.2). No clinically significant differences were found in the few studies that compared different methods of taking off the corneal epithelium (Analysis 4.3).

Debridement and antiviral chemotherapy

The comparison of physicochemical debridement followed by an antiviral agent compared to debridement alone was limited by heterogeneity among studies (Analysis 4.4). One trial comparing debridement and acyclovir to debridement and idoxuridine did not show a significant difference in the proportion of participants healed at seven or 14 days (Analysis 4.5). Heterogeneity was present among studies comparing combined debridement-antiviral treatment to antiviral therapy (Analysis 4.6). Evidence that combination therapy might allow faster healing was also constrained by heterogeneity among studies (Analysis 4.7).

Safety of debridement

Most studies that used a method of corneal debridement did not mention side effects. Four studies stated that no adverse reactions occurred (Bartholomew 1977; Jensen 1982; Kato 1979; Parlato 1985). Phototherapy was reported to be painful (Daniel 1972) and was associated with superficial punctate keratopathy and iritis in one study (O'Day 1975). Carbolisation produced superficial punctate keratopathy in 11% of patients in one study (MacKenzie 1964) and one episode of shallow ulceration in another study (Patterson 1967a).

Supplemental agents

Hyaluronate contributed to healing at one week but did not yield a better outcome at two weeks in one trial (Analysis 5.1). The combination of epidermal growth factor with an antiviral did not significantly enhance the antiviral agent's effect on corneal epithelial healing in one trial (Analysis 5.2). Topical panthenol, a precursor to pantothenic acid that might promote epithelial wound healing, was not significantly different from *para*-fluorophenylalanine in one trial (Analysis 5.3). Methyluracil, an antioxidant thought to facilitate cell proliferation, did not have an additive effect with interferon in one trial (Analysis 5.4).

The addition of the nonsteroidal anti-inflammatory agent oxyphenbutazone to idoxuridine treatment did not differ from treatment with idoxuridine alone in one trial (Analysis 5.5). Inosine pranobex, an immune modulator (Campoli-Richards 1986) that has been used both topically and orally (Sellitti 1982), had an uncertain effect on healing at one week and, without or with an antiviral agent, did not significantly affect the 14-day outcome in two included studies (Analysis 5.6). No adverse reactions were reported in this cluster of studies.

DISCUSSION

HSV infection is a prevalent and potentially damaging eye disease that inflicts personal distress and socioeconomic costs. Safe, effective treatment aims to alleviate symptoms, to enable corneal healing, and to expedite visual recovery. This systematic review synthesises an interconnected web of clinical trials comparing therapeutic options for HSV infection of the corneal surface (Figure 3) and presents the direct and indirect evidence on the relative effectiveness of antivirals, interferon, and debridement in the treatment of HSV epithelial keratitis (Summary of findings for the main comparison).

Summary of main results

Antiviral therapy

Placebo-controlled studies were inconsistent for idoxuridine and sparse for vidarabine. No significant difference in effectiveness was found between idoxuridine and vidarabine (Pavan-Langston 1972). Another out-of-use compound, *para*-fluorophenylalanine, did not significantly differ from idoxuridine (Pietruschka 1968). Trifluridine and acyclovir were more effective than either idoxuridine or vidarabine. Excluded studies also suggested that trifluridine was better than idoxuridine (Assetto 1981; Pavan-Langston 1977) and that acyclovir was better than idoxuridine (Babushkin 1993; Inocencio 1982) or vidarabine (McGill 1981; Mohan 1987).

Analysis of a network of antiviral treatment comparisons indicated that trifluridine, acyclovir, and brivudine had no significant differences in treatment (Summary of findings for the main comparison), a finding supported by one-week results (Summary of findings 2) and by their relative rates of healing (Summary of findings 3). 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.

Ganciclovir was possibly as or more effective as acyclovir in included studies and in excluded studies (Huang 2007; Jing 2010; Wang 2009), but interpretation was limited by heterogeneity among the studies. Foscarnet seemed as effective as trifluridine, acyclovir, and ganciclovir but needs further study. The effect of two topical antivirals was examined in only one study. Oral acyclovir may be an alternative to topical antiviral therapy, but few studies examined an oral antiviral or combined oral and topical antivirals in comparison to topical antiviral monotherapy (Summary of findings 4). The dosage, formulation, and frequency of administration of antiviral therapy were evaluated in few studies.

Interferon therapy

Interferon at a concentration of 1 million IU/ml or higher was more effective than control in included studies and an excluded study (Shiota 1988). Used either alone or in combination with debridement (Cantell 1995; Sundmacher 1982; Sundmacher 1984b) interferon was as effective as a nucleoside antiviral agent. Excluded studies (Jin 1992; Scialdone 1986; Tamburi 1990) had insufficient outcome data to adequately determine relative effectiveness between interferon and nucleoside antivirals. A topical interferon inducer did not compare favourably with a topical antiviral agent in a single included study (Analysis 3.6) but had encouraging clinical activity in excluded studies (Galin 1976; Kasparov 1972; Kasparov 1974; Kasparov 1991; Lin 2009). Interferon-α and interferon-β did not differ in included studies or among excluded studies (Kuyama 1979; Zhang 2003).

The combination of interferon and a nucleoside antiviral agent offers the prospect of faster healing than antiviral therapy alone (Summary of findings 5). The possible advantage of combining interferon and an antiviral agent was supported by observational experience (Figure 5) and by several excluded studies (Chen 2007; Gu 2005; Huang 2009; Lin 2013b; Liu 2003; Tamburi 1990; Wan 2014; Weng 2014; Zhao 2001; Zhou 2008), but evidence is limited by heterogeneity among included studies.

Debridement

Trials of physicochemical debridement were relatively few and inconsistent. The comparison of debridement to topical antiviral therapy was limited by heterogeneity among included studies and by different findings among excluded studies (Patterson 1967c; Tarakji 1978; Whitcher 1976). Various methods of curettage, cauterisation, and chemoablation were used to remove the corneal epithelium and likely produced variously sized corneal epithelial defects. Thermomechanical scraping, cryotherapy, and chemical abrasion could leave a large denuded area of the corneal surface while wiping and swabbing aim to selectively remove loosened, infected epithelial cells along the dendrite (Wilhelmus 1989). Potential shortcomings of debridement included damage to Bowman's layer (Coster 1977b) and exacerbation of corneal inflammation and opacification (Parlato 1985).

Epithelial keratitis occurred soon after debridement in some debridement-treated eyes. Presumably, post-debridement viral shedding (Sundmacher 1976a; Sundmacher 1976b) or infection of remaining cells of the ocular surface can lead to recrudescent epithelial keratitis (Coster 1977b). While a relapsing episode could be treated by repeating debridement, recrudescent keratitis is preventable by using an antiviral agent for several days after debridement (Coster 1977b). However, any healing advantage that might be gained by following debridement with an antiviral agent or interferon was uncertain because of study heterogeneity (Summary of findings 6). Excluded studies were also difficult to interpret: some inferred that the combination of debridement and an antiviral agent healed more quickly than antiviral treatment alone (Koev 2007; Mathur 1984) while others found little difference in average healing times (Fellinger 1980; Guo 2003; Shimomura 1987).

Ancillary agents

Trials that evaluated the addition of a lubricant, growth factors, or a nonsteroidal anti-inflammatory drug to topical antiviral therapy were few in number and did not provide convincing evidence of effectiveness. The role of an immunomodulator such as inosine pranobex was uncertain in included studies and in an excluded study (Prost 1986). Studies did not examine justifications for using cycloplegic or antibacterial eye drops. Secondary microbial infection during herpetic epithelial keratitis (Boisjoly 1983; Wilhelmus 1982) was not reported in any included study.

Overall completeness and applicability of evidence

This systematic review aimed to synthesise the relative effectiveness among available interventions that can be used in the treatment of HSV epithelial keratitis. The literature was systematically searched for all relevant comparative clinical trials using electronic databases, handsearching, and personal contact.

Participant characteristics and potential effect modifiers

Age, gender and ethnicity

The incidence of HSV keratitis rises with advancing age (Labetoulle 2005; Young 2010). Participants in studies included in this systematic review averaged 43 years of age, but few studies described the shape of the age distribution. Males outnumbered females in 91% of studies, and studies enrolled, on average, 50% more men than women. While some cohort investigations have suggested that men might be more likely to be diagnosed and treated for HSV epithelial keratitis (Gold 1965; Gundersen 1936; HEDS Group 1997; Liesegang 1989a; Wilhelmus 1981b), population-based studies show that men and women have similar rates of ocular herpes (Labetoulle 2005; Young 2010; Stanzel 2014). Selective enrolment according to age or gender could reflect under-representation of children, the elderly, and women in clinical drug trials (Van Spall 2007). Women of childbearing potential have often been systematically deemed ineligible for topical ophthalmic antiviral trials because of an unproven concern about antiviral teratogenicity during pregnancy (Ahrens 2013; Chung 2004; Itoi 1975; Pasternak 2010). Among studies that examined the effect of patient characteristics on outcome, neither age nor gender influenced the rate of corneal healing during antiviral therapy for HSV epithelial keratitis (de Koning 1982; de Koning 1983; Jackson 1984; McCulley 1982; van Bijsterveld 1980; van Bijsterveld 1989). Observational studies have suggested that some ethnic groups may be susceptible to recurrent HSV epithelial keratitis (McDonald 2015; Wilhelmus 1996a), but ethnicity was not significantly associated with recurrence in a cohort followed for 18 months (HEDS Group

2001). Insufficient information was available to examine age, gender, or ethnicity as possible effect modifiers in this review.

Immune status

Medical conditions may modulate viral eradication and epithelial regeneration during HSV infection. Poorly controlled diabetes (Kaiserman 2005), atopy (Rezende 2006), and immunosuppression (Field 1995; Oshry 1998) might slow resolution of HSV epithelial keratitis. Health status was not examined as a possible effect modifier in studies included in this review.

Previous herpetic eye disease

Neither the number of previous episodes nor the duration of symptoms prior to initiating antiviral treatment affected healing rates in most studies that evaluated these factors (Blake 1977; Høvding 1989; Jensen 1982; La Lau 1982; McCulley 1982; Pavan-Langston 1981; Sugar 1980; van Bijsterveld 1989; Yeakley 1981). Neither the prior use of antiviral agents (Jensen 1982; McCulley 1982) nor the recent use of corticosteroids (McCulley 1982; Pavan-Langston 1981; Sugar 1980; Yeakley 1981) affected relative treatment response.

Duration between onset and treatment

One study found that the interval between the start of symptoms and the beginning of antiviral treatment correlated with healing time: patients who received earlier treatment healed faster (van Bijsterveld 1980).

Pattern of epithelial keratitis

Approximately 90% of eyes enrolled in studies included in this systematic review had dendritic epithelial keratitis. Geographic epithelial keratitis was much less prevalent. In epidemiological studies geographic epithelial keratitis accounts for 5% to 15% of HSV epithelial keratitis (Labetoulle 2005; Liesegang 1989a; Pramod 1999), although a slightly higher frequency was evident in some studies enrolling both dendritic and geographic epithelial keratitis.

Corneal epithelial wound healing follows a distribution function (Callaghan 2006) similar to the logistic healing curve of HSV epithelial keratitis (Wilhelmus 2000). The rate of healing depends on the area of the corneal epithelial defect (Chung 1998). Larger HSV epithelial keratitis re-epithelialises at a greater rate than smaller lesions (Jackson 1984; Sugar 1980; Wellings 1972). Even so, geographic epithelial keratitis resolves more slowly than dendritic epithelial keratitis (Blake 1977; Coster 1976; Jackson 1984) and, on average, takes longer to heal (Altinisik 1987; Blake 1977; Jackson 1984; Wellings 1972; Wilhelmus 1981a; Young 1982). Investigators have stated that eyes with geographic epithelial keratitis "constitute the most difficult therapeutic challenge for antiviral drugs" (Coster 1979), "respond least well to conventional treatment" (Bartholomew 1977), and "frequently require more prolonged therapy than simple dendritic ulcers" (Collum 1985). On the other hand, one study found that the relative effect between antivirals was not necessarily affected by lesion size (Colin 2007b). It is unclear whether geographic epithelial keratitis offers a more stringent test of antiviral effectiveness.

Corneal stromal inflammation

Corneal characteristics of HSV epithelial keratitis that may be associated with slow healing include a peripheral corneal location (Wilhelmus 1981a) and the presence of stromal inflammation (Altinisik 1987; Daniel 1972; Klauber 1982; Wilhelmus 1981a). While inflammatory cells may slow corneal epithelial wound healing (Wagoner 1984), studies have not demonstrated that stromal keratitis impacts the rate of re-epithelialisation (Høvding 1989; Jackson 1984). Insufficient data were available to undertake metaregression of these and other potential effect modifiers.

Virology and antiviral susceptibility

Viral infection

Laboratory methods can detect herpes simplex virus in specimens from the ocular surface (Satpathy 2011). One quarter of studies included in this review undertook viral isolation, including five studies that required viral confirmation before randomisation. The overall 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 eliminates HSV from the ocular surface within the first few days of therapy (Sundmacher 1984a; Sundmacher 1985), although HSV could sometimes be recovered up to ten days after beginning antiviral therapy (Colin 1997a). HSV strains may differ in pathogenicity (Brandt 2005), but how virulence genes might impact the healing rate of herpetic epithelial keratitis remains to be determined.

Antiviral resistance

Genetic mutations of HSV affecting thymidine kinase or DNA polymerase can impart resistance to antiviral agents (Duan 2009). HSV strains that are not readily susceptible to acyclovir can emerge among immunocompromised persons and during antiviral treatment of otherwise healthy individuals (Burrel 2013; van Velzen 2013; Zhang 2007). Mutant HSV strains may recur more frequently and heal more slowly (Pan 2014) but usually respond to an alternative antiviral (Hlinomazová 2012; Turner 2013; Yao 1996), a combination of nucleoside antivirals, or co-administration of an antiviral with interferon (Minkovitz 1995). Susceptibility testing could be considered for treatment-unresponsive infection due to HSV (Choong 2010).

In this review, the 14-day outcome with topical acyclovir declined during a 25-year period while the response rate with topical ganciclovir remained stable over 15 years. Although the emergence of acyclovir resistance is a potential reason for this observed longitudinal trend, studies did not do susceptibility testing. Dissimilarities in defining cure in diverse studies might be a more likely explanation for this ebb in reported responses to topical acyclovir.

Quality of the evidence

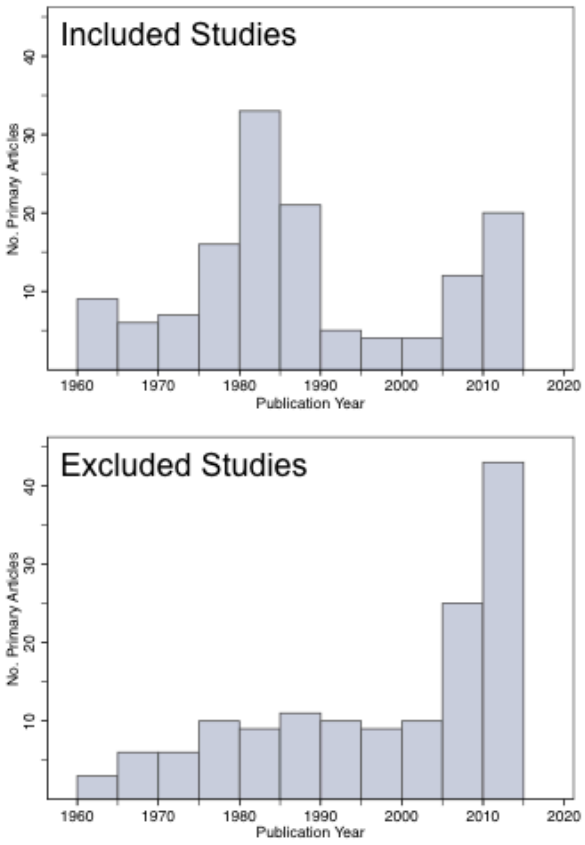
This systematic review endeavoured to encapsulate a pragmatic and quantitative digest of clinical research. Many trials in this review were inconclusive because of inadequate sample size. In addition, trials concluding a similarity between treatments were not designed to demonstrate equivalence (Musch 2006). Systematic pooling of studies and network analysis endeavoured to improve precision through an objective appraisal of clinical evidence.

Data were extracted from journal articles and other sources to estimate relative effect measures of corneal healing for different interventions. Healing curves (Graupner 1968; Wellings 1972) and survival analysis (Coster 1976; Coster 1979) are recommended for

reporting treatment trials of HSV epithelial keratitis, but these analytical methods were unevenly applied. Nearly a third of otherwise eligible studies were not included in this review because of incompletely reported data. The estimation of cumulative risk and the use of hazard functions that consider variable follow-up durations need to be more widely implemented in clinical trials of ophthalmic interventions (Hosmer 2009; Jewell 2009).

Publication of studies included in this review peaked during the 1980s (Figure 6), an era of antiviral discovery and investigation (Gordon 2000). After a brief lull, the number of published studies began to rise again after 2005 with the advent of antiviral trials undertaken in China. In comparison, the number of excluded studies that had remained fairly stable throughout the late 20th century also increased during the early 21st century, largely driven by studies of traditional Chinese medicines. The inclusion of studies that lack adherence to proper study design, random allocation and analysis would dampen the quality of the cumulative evidence (Panagiotou 2013; Wu 2009).

Figure 6. Histograms of publication year for included studies and excluded studies. Most of the studies during the late 20th century took place in Europe or North America. An upswing in studies reported since 2005 is due to trials conducted in China.



Potential biases in the review process

Internal and external validity

Attention to detail in study design and reporting

Methodological rigour varied among studies. Nearly a quarter of studies did not clarify the method of random sequence generation, and authenticating randomisation was problematic for brief reports (Wu 2009). Why the number of study eyes sometimes exceeded the number of participants was unclear; presumably, persons with bilateral keratitis or participants experiencing a recurrence were re-enrolled into some studies. Half of the included studies lacked masking of both patients and trialists. Withdrawals were infrequent during the initial two weeks of observation and therapy, even among studies that had a risk of attrition bias. For studies did not specify censoring times, extrapolation of data from healing curves could have misinterpreted the number of healed eyes. Sensitivity analyses that omitted studies with a higher risk of bias left few trials for each treatment comparison.

Issues of consistency

Heterogeneity of trial results limited the interpretation of some treatment comparisons. Some trials of the ganciclovir trials enrolled patients with disciform or stromal keratitis and did not stratify outcome by type of corneal disease. Diverse treatment

dosages and formulations of antivirals and interferons and varied physical and chemical methods of removing corneal epithelium tempered the comparability of studies. Pooling different antiviral agents in the interferon-antiviral and debridement-antiviral comparisons did not take into consideration potential differences in antiviral effectiveness. The use of a cycloplegic or antibiotic could have affected therapeutic effects since atropine and neomycin are capable of inhibiting HSV (Alarcón 1984; Langeland 1987).

The asymmetric geometry of the network of treatment comparisons was a web of open and closed loops. To contend with multiple treatment comparisons this systematic review integrated direct head-to-head comparisons of antivirals with indirect comparisons. As noted in the Cochrane Handbook, "indirect comparisons are not randomized comparisons, and cannot be interpreted as such" (Higgins 2011). Blending direct and indirect risk ratios offers increased precision but is liable to confounding and bias (Mills 2012). The validity of network analysis depends on homogeneity among studies and consistency between direct and indirect results.

Possible shortcomings in selecting and reviewing studies

Eighty-six of 143 excluded studies were not appropriate for this review due to use of an alternative intervention or problematic design. The remaining 57 studies were excluded because data on cumulative healing proportions at one or two weeks of study treatment were not reported. The exclusion of adequately designed studies because relevant outcome information was not available in the published report could dampen the robustness of the review (Felton 1992).

Safety

Topically applied antivirals and other medications that delay epithelial regeneration (Lass 1984) could impact the assessment of relative treatment effects. Thus, while safety was an auxiliary concern, the evaluation of effectiveness could be affected by side effects. Less than half of the studies included in this review reported the incidence of drug-related ocular allergy or toxicity. The relative safety of antivirals, interferon, and other interventions summarised in this review is likely to be inexact. Ophthalmic studies and case reports have described adverse reactions at the ocular surface due to antivirals (Chen 1989; Falcon 1981; Naito 1987) and interferon (Aldave 2007) that were more serious than those detected in treatment trials. Postmarketing surveillance and pharmacovigilance are needed to define the prevalence of common adverse reactions and to detect uncommon complications such as lacrimal punctal stenosis, conjunctival cicatrisation, corneal dysplasia, and anterior segment ischæmia.

Agreements and disagreements with other studies or reviews

Medical therapy

Literature reviews have deduced that currently available topical ophthalmic antiviral agents are effective for HSV epithelial keratitis (AAO 2013; Barker 2008; Behrens-Baumann 2010; Hergeldzhieva 2012; Labetoulle 2012; Wei 2008). A systematic review of 28 randomised, double-masked, controlled, English-language clinical trials (including two trials that were subsets of larger trials) found 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). While literature reviews have considered ganciclovir gel to be similar in efficacy to acyclovir ointment (Kaufman 2012; Sahin 2012), a systematic review of 14 randomized trials that compared topical ophthalmic acyclovir and ganciclovir in the treatment of HSV epithelial keratitis concluded that despite heterogeneity (I^2=55%) ganciclovir improves the cure rate (RR, 1.22; 95% CI, 1.10, 1.36), has a lower risk of adverse reactions (RR, 0.12; 95% CI, 0.03 to 0.46), and reduces the risk of recurrence during the ensuing year (0.22; 92% CI, 0.11-0.45) (Li 2014d). An evidence-based guideline from the American Academy of Ophthalmology and Ocualr Microbiology and Immunology Group concluded that topical trifluridine, acyclovir, and ganciclovir are effective, that debridement is an alternative treatment, that combining debridement with a topical antiviral agent confers "limited or no benefit," and that oral antiviral agents such as acyclovir, valacyclovir, and famciclovir "appear to be as effective as topical antiviral agents" (White 2014). The therapeutic effect of oral acyclovir for treating herpetic epithelial keratitis is consistent with its efficacy for treating labial or genital herpes (Cernik 2008). and an oral antiviral might be preferred to topical antivirals when treating herpetic keratitis in children (Revere 2013).

Complementary and alternative medicine

This systematic review excluded clinical studies of ethnomedicinal products and alternative practices. A review of traditional herbal 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). Rather than reporting the proportion of eyes healed at each follow-up visit, the outcome was often based on clinical scoring of symptoms and signs, measurements of the length of residual dendrites, or visual acuity. Systematic evaluation is needed to assess how herbal and botanical products and other alternative or complementary interventions such as acupuncture compare to or might integrate with antiviral chemotherapy.

Prevention

This review did not systematically evaluate whether interventions for treating HSV epithelial keratitis influenced subsequent inflammatory episodes or future recurrences. Limited evidence exists that short-term antiviral therapy for dendritic epithelial keratitis can forestall consequent HSV stromal keratitis (Maudgal 1979; Wilhelmus 1981b). The evidence that a topical antiviral might also affect future episodes of epithelial keratitis is conflicting. Several studies included in this systematic review found no differential effect between interventions on later recurrences (HEDS Group 1997; McGill 1981; Patterson 1963a; Power 1991; Wilhelmus 1981a; Yamagami 1998). On the other hand, several included studies comparing ganciclovir and acyclovir observed that topical ganciclovir reduced the risk of ocular recurrence during the year after completing treatment (Han 2010; Lin 2011; Lin 2014; Liu 2012a; Liu 2012b; Liu 2014a; Wang 2014a; Yang 2008; Zhen 2012). Whether a short-term intervention for HSV epithelial keratitis affects future recurrences deserves to be critically evaluated.

The prevention of recurrent ocular herpes is feasible through chronic suppressive antiviral prophylaxis (Jones 1977) and by drugs that inhibit viral reactivation (Kaufman 2002; Luzi 1983). Prolonged use of a topical antiviral (Wilhelmus 1983; Romano 1988) or oral antiviral (HEDS Group 2000b; Uchoa 2003; Wu 2002; Young 2010) can deter recurrent herpetic eye disease. This issue

is examined in another systematic review (de la Parra 2013). Though costly (Lairson 2003), prolonged antiviral use may be helpful for previously infected people who have an increased risk of recurrence, such as with increased sunlight exposure (Ludema 2014b), topical corticosteroid use (Wilhelmus 1996a), or ocular surgery (Bhatt 2009). A safe and effective vaccine is awaited (Chentoufi 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Ophthalmic formulations of trifluridine, acyclovir, ganciclovir, brivudine, and foscarnet are effective in the treatment of HSV epithelial keratitis. The combination of an antiviral with interferon might be considered for clinically recalcitrant dendritic keratitis. Wiping debridement may be an option to avoid chemotherapeutic drugs, but the relative value of debridement accompanied by an antiviral agent is unclear.

Implications for research

The design and reporting of future clinical trials of HSV epithelial keratitis should follow guidelines for Enhancing the Quality and Transparency of Health Research (EQUATOR), including the Consolidated Standards of Reporting Trials (CONSORT). Studies should specify the eligibility and healing criteria, methods of randomisation and allocation concealment, means of masking outcome evaluation, and rationale for the numbers of enrolled eyes and participants. Since dendritic epithelial keratitis heals relatively rapidly with currently available treatment, trialists may consider estimating sample size based on a non-inferiority comparison. The time to corneal re-epithelialisation is a key measure of therapeutic efficacy and days by which healing or censoring occur during the initial weeks of therapy should be given in graphs or tables. The effects of characteristics that might modify healing would be a useful supplementary analysis. Virological evaluation will have increasing relevance if optimal therapy is affected by the emergence of viral strains with enhanced resistance or virulence. Adverse events should be recorded, and a comprehensive evaluation of the safety of antivirals and other interventions should extend to data sources beyond clinical trials. Additional research is needed to clarify the roles of topical ganciclovir, topical foscarnet, oral antiviral treatment, concurrent use of an antiviral with interferon, and corneal epithelial debridement. However, future clinical trials should avoid unnecessarily randomising patients without contributing new information or addressing reasons for heterogeneity among previous studies. The potential value of integrative and alternative therapy with herbal medicines remains to be systematically reviewed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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	

Abe 1987 *(Continued)*

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data
Selective reporting (reporting bias)	Low risk	The pre-specified 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 'punktat 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

Altinisik 1987 *(Continued)*

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 pre-specified 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): iodinisation Treatment two (n=25): idoxuridine
Outcomes	'When no corneal staining remained'
Notes	Nonstudy interventions: mydriatic, antibiotic (iodinisation 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)	High 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 iodinisation group

Austin 1974 *(Continued)*

Selective reporting (reporting bias)	Low risk	The pre-specified primary outcome was adequately reported
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 x 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 Adverse reactions (Quote): "none of our patients experienced any adverse reactions."

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 pre-specified primary outcome was adequately reported
Other bias	Unclear risk	Insufficient information

Bartholomew 1977 *(Continued)*

	Quote: "none of our patients experienced any adverse reactions."

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

Blake 1977 *(Continued)*

	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 pre-specified 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

Burns 1963 *(Continued)*

	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."

Cao 2001

Methods	Allocation method: randomised Masking: none Number of centres: 3
Participants	Country: China Number enrolled: 104 dendritic epithelial keratitis (123 total cases of epithelial or disciform keratitis + 41 others with open allocation of study treatments) Average age (range): 39 (18-65) Sex (imputed from total, for dendritic sample): 75 males, 29 females Inclusion criteria: dendritic (104) epithelial keratitis, geographic epithelial keratitis (11), disciform keratitis (8) in trial; and in open allocation, dendritic (14), geographic (9), and disciform (18) cases, for total population of 164
Interventions	Treatment one (n=52): acyclovir 0.1% solution 6 times per day Treatment two (n=52): foscarnet 3% solution 6 times per day
Outcomes	Fluorescein staining

Cao 2001 *(Continued)*

Notes	Nonstudy interventions: atropine 1% Report language: Chinese Study date: 1999-2000 Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The investigators describe a random component in the sequence generation process. However, additional study groups had open allocation of study treatments
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-masked trial design described but no details of masking
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary outcome data available for dendritic epithelial keratitis but not for other strata (e.g., geographic epithelial keratitis)
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

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

Carmassi 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Insufficient information ("i pazienti sono stati suddivisi in 3 gruppi di 5 pazienti ciascuno e sottoposti a 3 differenti trattamenti")
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 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 Adverse reactions (Quote): "The tolerability of EGF was always good, and there have not been signs of interaction or incompatibility between EGF and the antiviral agent."

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

Cellini 1994 *(Continued)*

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 pre-specified 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

Chen 2008 *(Continued)*

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 epithéliale 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 ponctuée" 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 pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

Colin 1982

Methods	Allocation method: not given ("traitement comparatif") Masking: none Number of centres: one
Participants	Country: France Number enrolled: 24 Average age (range): 55 Sex: 13 males, 11 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=12): trifluridine solution 5 times per day Treatment two (n=12): trifluridine solution 5 times per day + oral isoprinosine 50 mg/kg/day (one tablet per 10 kg body weight per day) for 5 days
Outcomes	Florescein staining: 'l'absence d'ulcération épithéliale après instillation de fluorescéine'
Notes	Nonstudy interventions: atropine 1% 2 times per day Report language: French Study date: not given Financial support: not given Adverse reactions (Quotes): one patient treated with trifluridine had not healed by day 12 when he still had a 2-mm epithelial defect and "kératite ponctuée diffuse et conjonctivite folliculaire." "Tolerance: en dehors de cette observation il n'a pas été noté de signes to toxicité dus à la TFT. Cependant 9 patients ont signalé une sensation de brûlure oculaire lors de l'installation des gouttes. Aucune manifestation générale n'a été signalée pendant cet essai chez les patients recevant de l'Isoprinosine."

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 pre-specified 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

Colin 1983 *(Continued)*

	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

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 pre-specified 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

Colin 1984 *(Continued)*

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 fluorescéïne')
Notes	Nonstudy interventions: atropine Report language: French Study date: not given Financial support: not given Adverse reactions: One case of kératite ponctuée" 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 pre-specified 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, 13 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

Colin 1987 *(Continued)*

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 pre-specified 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

Colin 1997a *(Continued)*

	Adverse reactions (from Colin 2007a, 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
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 were 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 fro the efficacy (per protocol analysis)."
Selective reporting (reporting bias)	Low risk	The pre-specified 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

Colin 1997b *(Continued)*

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 pre-specified 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")

Colin 2007a *(Continued)*

Allocation concealment (selection bias)	Low risk	Centralized distribution process
Blinding (performance bias and detection bias) All outcomes	High 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)	Low risk	No missing primary outcome data

Colin 2007b *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The pre-specified 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 pre-specified 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	High risk	Quote: "Three patients were withdrawn from the study owing to failure of treatment." Quote: "Three patients randomly allocated to acyclovir treatment failed to return after their initial assessment and were excluded from the analysis."
Selective reporting (reporting bias)	Low risk	The pre-specified primary outcome was adequately reported
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

Collum 1986 *(Continued)*

	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 pre-specified 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 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

Coster 1976 *(Continued)*

	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_3T

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 pre-specified 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

Coster 1977a *(Continued)*

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 pre-specified 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_3T."

Risk of bias

Coster 1979 *(Continued)*

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 *versus* 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 pre-specified 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."

Coster 1980 *(Continued)*

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 pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

Dai 2009a

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 58 patients (71 eyes) Average age (range): 38 (15-66) Sex: 40 males, 18 females Inclusion criteria: dendritic (59) or geographic (12) epithelial keratitis
Interventions	Treatment one (n=30 patients, 36 eyes): acyclovir 0.1% solution 4 times per day Treatment two (n=28 patients, 35 eyes): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining ('角膜荧光索染色阴性')
Notes	Nonstudy interventions: atropine 1% for iridocyclitis Report language: Chinese Study date: 2008 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	High risk	Incomplete primary outcome data (outcome day unclear)
Selective reporting (reporting bias)	High risk	Outcomes reported for 58 patients rather than for 71 eyes

Dai 2009a *(Continued)*

Other bias	Unclear risk	Insufficient information

Dai 2009b

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 79 Average age (range): 32 (11-57) Sex: 45 males, 34 females Inclusion criteria: dendritic (51) or geographic (28) epithelial keratitis
Interventions	Treatment one (n=39): acyclovir 0.1% solution 6 times per day Treatment two (n=40): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining ('荧光素染色阴性')
Notes	Nonstudy interventions: ofloxacin 0.3% 4 times per day Report language: Chinese Study date: 2007-2008 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	High risk	Incomplete primary outcome data (outcome day unclear)
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Daniel 1972

Methods	Allocation method: alternate patients Masking: none Number of centres: one

Daniel 1972 *(Continued)*

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 Adverse reactions (Quote): "Considerable pain resulted from the phototherapy, because of the resulting photochemical keratitis....In some patients pain prevented the further exposure that was necessary to achieve a confluent corneal stain."

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 pre-specified 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

Davidson 1964 *(Continued)*

	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 iodinisation (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 pre-specified 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

de Koning 1982 *(Continued)*

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 pre-specified 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 (actually 59, but 8 patients dropped from description and analysis) 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

de Koning 1983 *(Continued)*

	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	High risk	Quote: Of 59 patients who were enrolled and treated, "eight patients were excluded form the trial, two because they did not follow the instructions and four because all herpes simplex virus isolations were negative" and two treatment failures of geographic epithelial keratitis
Selective reporting (reporting bias)	Low risk	The pre-specified 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

Denis 1983 *(Continued)*

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 pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

Fu 2012

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 78 Average age (range): 34 (18-75) Sex: 48 males, 30 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=38): ganciclovir 0.15% gel 4 times per day Treatment two (n=40): ganciclovir 0.15% gel 4 times per day + subconjunctival interferon (0.5 ml of 1 million units/ml every other day for 14 days)
Outcomes	Fluorescein staining ('荧光染色阴性')
Notes	Nonstudy interventions: none Report language: Chinese Study date: 2010-2011 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 likely because one treatment group received subconjunctival injections

Fu 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data, although survival data of healing were not tabulated
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

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 placebo ointment 5 times per day Treatment four (n=13): carbolization (débridement with orange stick followed by touching epithelial edge with phenol) and idoxuridine ointment 5 times per day Treatment five (n=15): carbolization (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

Fulhorst 1972 *(Continued)*

Selective reporting (reporting bias)	Low risk	The pre-specified 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 ("Doppelblindstudie") 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 pre-specified 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	Fluorescein ('Der Behandlungserfolg wurde an Hand der Anfärbbarkeit 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)	High 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: randomised 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

Graupner 1968 *(Continued)*

	Treatment two (n=26): *para*-fluorophenylalanine 0.1% ointment 5 times per day
Outcomes	Fluorescein ('vollständige Epithelisation der Hornhaut')
Notes	Nonstudy interventions: atropine Report language: German Study date: note 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: "Alle Patienten, bei denen in unserer Klinik die Diagnose Keratitis dendritica gestellt werden konnte, wurden zufällig einer der beiden Therapiegruppen zugeordnet."
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 dat
Selective reporting (reporting bias)	Low risk	The pre-specified 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: randomised 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): iodinization /débridement plus idoxuridine 0.1% ointment every 4 hours Treatment two (n=15): iodinization /débridement plus *para*-fluorophenylalanine 0.1% ointment every 4 hours
Outcomes	Fluorescein ('Anfärbbharkeit der Hornhaut mit Fluorescein beurteilt')
Notes	Nonstudy interventions: atropine Report language: German Study date: not given Financial support: not given

Graupner 1969 *(Continued)*

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: "Alle Patienten, bei denen in unserer Klinik die Diagnose Keratitis dendritica gestellt werden konnte, wurden zufällig einer der beiden Therapiegruppen."
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 pre-specified 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

Guerra 1979 *(Continued)*

		Quote: "Il trattamento iniziale è stato assegnato su di una base prerandomizzata con la terz'ultima fila della tabella dei numeri casuali."
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-masked study design Quote: "I due farmaci erano stati preparati della Cattedra di Virologia dell'Università di Siena in contenitori etichettati A e B, l'identità del contenuto dei quali era sconosciuta ai ricercatori clinici."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data
Selective reporting (reporting bias)	Low risk	The pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

Han 2010

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 40 Average age (range): not give Sex: not given Inclusion criteria: epithelial keratitis
Interventions	Treatment one (n=19): acyclovir solution Treatment two (n=21): ganciclovir gel
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: not given Report language: Chinese Study date: not given Financial support: not given Recurrence rate: in one year, 2 episodes in acyclovir group and 1 episode in ganciclovir group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a randomised method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias)	High risk	Lack of masking could have influenced outcome assessment

Han 2010 *(Continued)*

All outcomes		
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

Han 2014

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 96 Average age (range): 40 (22-58) Sex: 58 males, 38 females Inclusion criteria: dendritic or geographic epithelial keratitis (possibly also stromal keratitis)
Interventions	Treatment one (n=48): acyclovir solution hourly and recombinant fibroblast growth factor gel every 2 hours Treatment two (n=48): ganciclovir gel hourly and recombinant fibroblast growth factor every 2 hours (apparent typographical error stating 46 patients enrolled in this treatment arm)
Outcomes	Fluorescein staining ('痊愈：眼部疼痛、畏光、流泪等刺激症状消失，角膜溃疡愈合，荧光素钠染色阴性')
Notes	Nonstudy interventions: not given Report language: Chinese Study date: January 2012 - December 2012 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 method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Unclear 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 pre-specified primary outcome was adequately reported

Han 2014 *(Continued)*

Other bias	Unclear risk	Some patients had concomitant stromal keratitis

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	Quote: "the criterion of epithelial healing being the absence of discrete fluorescein staining of the cornea...in the assessment of epithelial healing, when such staining was no greater on the ulcer region than elsewhere, the ulcer would be deemed healed, but when punctate stains were confined to the ulcer region, it would be deemed not healed."
Notes	Nonstudy interventions: mydriatic ("reserved for those patients in whom iritis was diagnosed"), 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 pre-specified 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 Adverse reactions (Quote): "Nous n'avons remarqué aucun signe secondaire important ni constant, et le produit a été bien toleré par tous les malades."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors describe this study as a "essai clinique en double insue" but do not describe the method of treatment allocation
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 pre-specified 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

HEDS Group 1997 *(Continued)*

	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 pre-specified 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: not given 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

Hoang-Xuan 1984 *(Continued)*

	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	The authors describe this study as "une étude comparative en clinique humaine" but do not describe the method of treatment allocation
Allocation concealment (selection bias)	High 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 pre-specified 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

Huang 2008a *(Continued)*

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)	Unclear risk	Insufficient information

Hung 1984 *(Continued)*

All outcomes		
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 pre-specified 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
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 pre-specified primary outcome was adequately assessed

Høvding 1989 *(Continued)*

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	Using fluorescein and rose bengal staining 'treatment failure was defined as follows: ulceration worse or unchanged by day 7, healing incomplete by day 15 or recurrence between days 15 and 21'
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)	Low risk	The investigators describe a random component of the sequence generation process (personal communication) in this multicentre "double-blind comparative study."
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 pre-specified 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' with fluorescein and rose bengal
Notes	Nonstudy interventions: cycloplegic, chloramphenicol ointment Report language: English Study date: not given Financial support: pharmaceutical industry Adverse reactions: "Superificial 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 pre-specified 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."

Jepson 1964 *(Continued)*

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	The authors describe this study as a "double-blind study" but do not describe the method of treatment allocation
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 pre-specified 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'

Kato 1979 *(Continued)*

Notes	Nonstudy interventions: pad (débridement group) Report language: Japanese Study date: not given Financial support: not given Adverse reactions (Quote): "No adverse reactions were observed in eyes treated with debridement."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Insufficient information
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 pre-specified 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

Kitano 1983 *(Continued)*

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 pre-specified 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	Centralised allocation scheme
Blinding (performance bias and detection bias)	Low risk	Double-masked trial design described

Kitano 1985 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data
Selective reporting (reporting bias)	Low risk	The pre-specified 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: "typical dendritic corneal ulcerations"
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'
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	The authors describe this study as "a double-blind clinical trial" but do not describe the method of treatment allocation
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

Klauber 1982 *(Continued)*

Selective reporting (reporting bias)	Low risk	The pre-specified 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 pre-specified 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 pre-specified 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

Laibson 1964 *(Continued)*

	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)	Low risk	The investigators describe a random component of the sequence generation process (personal communication) in this "double-blind study."
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 pre-specified 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

Laibson 1977 *(Continued)*

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)	Low risk	The investigators describe a random component of the sequence generation process (personal communication) in this "double controlled study."
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

Li 2008 *(Continued)*

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

Li 2009

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 79 Average age (range): 44 (11-66) Sex: 35 males, 44 females Inclusion criteria: dendritic (32) or geographic (29) epithelial keratitis or disciform keratitis (18)
Interventions	Treatment one (n=34): acyclovir 0.1% solution 6 to 8 times per day Treatment two (n=45): acyclovir 0.1% solution 6 to 8 times per day and subconjunctival interferon 100,000 units every 1 to 2 days for 6 to 8 injections and intramuscular interferon (1 million units for adults and 1 million units/square meter for children) every 1 to 2 days for 6 to 8 injections
Outcomes	Fluorescein staining ('治愈或基本治愈: 自觉症状消失, 充血与刺激症状消退, 角膜溃疡愈合, 荧光素染色转阴或残留极少上皮着色点, 角膜实质浸润吸收, 水肿和后弹力层皱褶消失, 角膜光切面厚度恢复正常或变薄, KP 消失或极少, Tyndall征转阴')
Notes	Nonstudy interventions: atropine 1% (if iridocyclitis) Report language: Chinese Study date: November 2005 - January 2008 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 method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information

Li 2009 *(Continued)*

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	Healing outcome presumed to be measured on day 14
Selective reporting (reporting bias)	Unclear risk	The pre-specified primary outcome was adequately reported, but the report did not stratify outcomes for participants treated with topical corticosteroid for stromal keratouveitis
Other bias	High risk	Among 79 eyes, the investigators enrolled 23% of eyes having disciform keratitis and did not separately report outcomes for epithelial keratitis (61) and stromal keratitis (18)

Li 2013a

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 87 Average age (range): 35 (19-56) Sex: 49 males, 38 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=42): acyclovir 0.1% solution 6 times per day + recombinant interferon α-2b 6 times per day + oral acyclovir 200 mg 6 times per day + subconjunctival ribavirin 0.2 ml every other day Treatment two (n=45): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining ('荧光素染色阴性')
Notes	Nonstudy interventions: atropine 1% Report language: Chinese Study date: 2010-2012 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)	High risk	Incomplete primary outcome data (outcome day unclear)

Li 2013a *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Li 2013b

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 85 Average age (range): 38, median (16-67) Sex: 52 males, 33 females Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=46): ganciclovir 0.15% gel 4-6 times per day Treatment two (n=39): ganciclovir 0.15% gel 4-6 times per day + recombinant human interferon α-1b 10 gm/mL 4-6 times per day
Outcomes	Fluorescein staining ('荧光素钠染色阴性')
Notes	Nonstudy interventions: not given Report language: Chinese Study date: 2008-2010 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 method of sequence generation
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	Unclear risk	Healing outcome presumed to be measured on day 15
Selective reporting (reporting bias)	Low risk	The pre-specified primary outcome was adequately reported
Other bias	Unclear risk	The investigators enrolled more eyes (85) than patients (68), making it difficult to determine the primary unit of analysis

Lin 2011

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 68 Average age (range): 36 (17-72) Sex: 39 males, 29 females Inclusion criteria: epithelial keratitis (59, including 6 with stromal keratitis) or stromal keratitis (9)
Interventions	Treatment one (n=34): acyclovir 0.1% solution 10 times per day Treatment two (n=34): ganciclovir 0.15% gel 5 times per day
Outcomes	Fluorescein staining ('治愈或基本治愈：自觉症状消失，充血与刺激症状消退，角膜溃疡愈合，荧光素染色转阴或残留极少上皮着色点，角膜实质浸润吸收，水肿和后弹力层皱褶消失，角膜光切面厚度恢复正常或变薄，KP 消失或极少，Tyndall征转阴')
Notes	Nonstudy interventions: ofloxacin 0.3% 3 times per day Report language: Chinese Study date: January 2006 - September 2009 Financial support: not given Recurrence rate: in one year, 8 episodes in acyclovir group and 2 episodes in ganciclovir group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a randomised method of sequence generation
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	High risk	Healing outcome reported at 3 weeks instead of 2 weeks
Selective reporting (reporting bias)	Unclear risk	The pre-specified primary outcome was adequately reported, but the report did not stratify outcomes for participants treated with topical corticosteroid for stromal keratouveitis
Other bias	High risk	Among 68 eyes, the investigators enrolled 13% of eyes having stromal keratitis and did not separately report outcomes for epithelial keratitis (59) and stromal keratitis (9)

Lin 2014

Methods	Allocation method: randomised Masking: none Number of centres: one

Lin 2014 *(Continued)*

Participants	Country: China Number enrolled: 112 Average age (range): 44 (17-72) Sex: 59 males, 53 females Inclusion criteria: dendritic (60) or geographic (52) epithelial keratitis
Interventions	Treatment one (n=56): acyclovir 0.1% solution 8 times per day Treatment two (n=56): ganciclovir 0.15% gel 8 times per day
Outcomes	Fluorescein staining ('治愈：荧光素染色阴性，流泪、畏光、疼痛、等刺激症状消失，角膜溃疡修复 ')
Notes	Nonstudy interventions: mydriatic if uveitis, oral indomethacin, oral 'antiviral', oral anti-glaucoma drug(s) if increased intraocular pressure Report language: Chinese Study date: February 2011 - February 2013 Financial support: not given Adverse reactions: 7 occurrences in acyclovir group and 2 occurrences in ganciclovir group Recurrence rate: in one year, 12 episodes in acyclovir group and 3 episodes in ganciclovir group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a randomised method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Incomplete 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 pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

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

Liu 2009a *(Continued)*

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)	Unclear risk	The investigators describe a random component in the sequence generation process ("随机选择"); however, no explanation for imbalance in the numbers of eyes assigned to each intervention
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 2010

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 67 eyes (50 patients) Average age (range): 30 (16-68 Sex: 30 males, 20 females (based on estimation of GCV group's eye data) Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=28 eyes, 20 patients): acyclovir 0.1% solution 6 times per day Treatment two (n=39 eyes, 30 patients): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: ofloxacin 0.3% 4 times per day Report language: Chinese Study date: not given Financial support: not given

Liu 2010 *(Continued)*

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 but do not account for the unequal group sizes
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 pre-specified primary outcome was adequately reported
Other bias	Unclear risk	Insufficient information

Liu 2011

Methods	Allocation method: randomised Masking: single Number of centres: one
Participants	Country: China Number enrolled: 26 Average age (range): not given (21-53) Sex: 14 males, 12 females Inclusion criteria: dendritic or geographic epithelial keratitis
Interventions	Treatment one (n=12): ganciclovir 0.15% gel 4 times per day + ofloxacin 0.3% 4 times per day Treatment two (n=14): ganciclovir 0.15% gel 4 times per day + sodium hyaluronate 0.1% 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

Liu 2011 *(Continued)*

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 pre-specified primary outcome was adequately reported
Other bias	Unclear risk	Insufficient information

Liu 2012a

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 80 Average age (range): not given (17-46) Sex: 48 males, 32 females Inclusion criteria: dendritic (38) or geographic (21) epithelial keratitis or disciform keratitis (21)
Interventions	Treatment one (n=40): acyclovir 0.1% solution 6 times per day and intravenous ribavirin 500 mg/day Treatment two (n=40): ganciclovir 0.15% gel 4 times per day and intramuscular interferon every other day and oral vitamin C 200 mg 3 times per day
Outcomes	Fluorescein staining, with disappearance of signs of corneal inflammation
Notes	Nonstudy interventions: oral indomethacin Report language: Chinese Study date: January 2010 - January 2012 Financial support: not given Recurrence rate: in one year, 7 episodes in acyclovir group and 1 episode in ganciclovir group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The investigators describe a randomised method of sequence generation
Allocation concealment (selection bias)	High risk	Possible open enrolment since treatment plans were complex, involving different topical and systemic medications for each study arm
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	Healing outcome reported for combined cured and improved criteria

Liu 2012a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The pre-specified primary outcome was adequately reported, but the report did not stratify outcomes for participants treated with topical corticosteroid for stromal keratouveitis
Other bias	High risk	Among 80 eyes, the investigators enrolled 26% of eyes having disciform keratitis and did not separately report outcomes for epithelial keratitis (59) and stromal keratitis (21)

Liu 2012b

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 76 Average age (range): 35 (21-67) Sex: 35 males, 41 females Inclusion criteria: epithelial keratitis (51, including 15 with stromal keratitis) or stromal keratitis (25)
Interventions	Treatment one (n=38): acyclovir 0.1% solution 8 times per day Treatment two (n=38): ganciclovir 0.15% gel 5 times per day (presumed typographic error of 0.5% gel)
Outcomes	Fluorescein staining ('治愈：患者不存在眼部刺激症状，同时其眼部充血情况消退，对其进行荧光素染色，呈阴性，患者角膜基质的水肿及浸润情况消失，角膜后沉着物减退等')
Notes	Nonstudy interventions: ofloxacin 0.3% 3 times per day Report language: Chinese Study date: October 2009 - June 2011 Financial support: not given Recurrence rate: in six months, 10 episodes in acyclovir group and 2 episodes in ganciclovir group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a randomised method of sequence generation
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	High risk	Healing outcome reported at 3 weeks instead of 2 weeks
Selective reporting (reporting bias)	Unclear risk	The pre-specified primary outcome was adequately reported, but the report did not stratify outcomes for participants treated with topical corticosteroid for stromal keratouveitis

Liu 2012b *(Continued)*

Other bias	High risk	Among 76 eyes, the investigators enrolled 33% of eyes having stromal keratitis without epithelial keratitis and did not separately report outcomes for epithelial keratitis (36), combined epithelial and stromal keratitis (15), and stromal keratitis (25)

Liu 2014a

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 64 Average age (range): 38 (not given) Sex: 38 males, 28 females Inclusion criteria: dendritic (34) or geographic (19) epithelial keratitis or disciform keratitis (11)
Interventions	Treatment one (n=32): acyclovir 0.1% solution 4 times per day Treatment two (n=32): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining ('痊愈：治疗后眼部刺激，充血症状完全消失，角膜溃疡完全修复，突光素染色转阴，角膜后沉着物消失或呈色素性')
Notes	Nonstudy interventions: ofloxacin 0.3% 4 times per day Report language: Chinese Study date: January 2007 - July 2011 Financial support: not given Adverse reactions: 5 occurrences in acyclovir group and 3 occurrences in ganciclovir group Recurrence rate: in one year, 6 episodes in acyclovir group and 2 episodes in ganciclovir group; in two years, 10 episodes in acyclovir group and 4 episodes in ganciclovir group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a randomised method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Incomplete masking could have influenced outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Healing outcome reported at 3 weeks instead of 2 weeks
Selective reporting (reporting bias)	Unclear risk	The pre-specified primary outcome was adequately reported, but the report did not stratify outcomes for participants treated with topical corticosteroid for stromal keratouveitis

Liu 2014a *(Continued)*

Other bias	High risk	Among 64 eyes, the investigators enrolled 17% of eyes having disciform keratitis and did not separately report outcomes for epithelial keratitis (53) and disciform keratitis (11)

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 pre-specified 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

MacKenzie 1964 *(Continued)*

	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): carbolisation "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 carbolisation group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Insufficient information on how "the eighty eyes were divided into three groups."
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 pre-specified primary outcome was adequately reported
Other bias	Unclear risk	Insufficient information

Maichuk 1980

Methods	Allocation method: not given Masking: none Number of centres: one
Participants	Country: Russia Number enrolled: 39 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis

Maichuk 1980 *(Continued)*

Interventions	Treatment one (n=20): human leukocyte interferon 500-700 units/mL 5-6 times per day Treatment two (n=19): human leukocyte interferon 500-700 units/mL + methacil (methyluracil) 3 times per day
Outcomes	Quote: "corneal epithelialization"
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)	High 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

Maichuk 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

Maichuk 1988 *(Continued)*

	Financial support: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High 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

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

Markham 1977 *(Continued)*

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	No other sources of bias were found

Matthäus 1970

Methods	Allocation method: randomised ("wurden zufällig...zugeordnet") 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): iodinisation plus panthenol ointment Treatment two (n=27): iodinisation plus *para*-fluorophenylalanine 0.1% ointment Treatment three (n=26): cryotherapy plus panthenol ointment Treatment four (n=34): cryotherapy plus *para*-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 einer der folgenden 4 Therapiegruppen."
Allocation concealment (selection bias)	Unclear risk	Insufficient information

Matthäus 1970 *(Continued)*

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 pre-specified primary outcome was adequately reported
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% (*sic*) of patients receiving ACV and 42.4% (*sic*) 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)	Low risk	No missing primary outcome data

McCulley 1982 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The pre-specified 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: randomised 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 ('no staining of the epithelium of the cornea with fluorescein') and complete healing ('absence of the epidelial oedema and microcystic 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	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 pre-specified primary outcome was adequately reported
Other bias	Unclear risk	Study limited to virologically confirmed participants

Norn 1973

Methods	Allocation method: not given Masking: double Number of centres: one Quote: "Virus culture was not performed."
Participants	Country: Denmark

Norn 1973 *(Continued)*

	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 Adverse reactions (Quote): "No instances were observed of allergy caused by Tanderil or ointment base."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The author describes this study as "a prospective study, based on double-blind trials" but does not describe the method of treatment allocation
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 pre-specified 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: randomised 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

O'Day 1975 *(Continued)*

	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
Random sequence generation (selection bias)	Low risk	The investigators describe an allocation sequence process that aimed "to evaluate photoinactivation in comparison with IDU by random selection," although 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 pre-specified 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." These consisted "of a generalized epithelial keratitis and an anterior uveitis, possibly of phototoxic origin."

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"

Panda 1995 *(Continued)*

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 pre-specified 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 corneal specimens and 1 of 9 conjunctival specimens
Participants	Country: United States Number enrolled: 34 (actually 39, but 5 dropped from description and analysis) 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 lesions were stained with fluorescein.' '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

Parlato 1985 *(Continued)*

	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 pre-specified 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: randomised (personal communication) "in a double-blind controlled trial" 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 1% twice daily, hot bathings three times daily, pad Report language: English Study date: 1962 Financial support: not given

Risk of bias

Patterson 1963a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators used a random component in the sequence generation process (personal communication)
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described ("in accordance with the design of a double-blind trial the observer was at no time conversant with the type of medication being administered"
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: randomised 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% solution 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, heat, 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)	Low risk	The investigators used a random component in the sequence generation process (personal communication)
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias)	Low risk	Double-masked trial design described

Patterson 1963b *(Continued)*

All outcomes		
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: randomised 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, heat, 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)	Low risk	The investigators used a random component in the sequence generation process (personal communication)
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: randomised 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 Quote: "the 77 cases of simplex dendritic ulceration were divided randomly into groups."
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)	Unclear risk	Insufficient information
Other 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."

Patterson 1967b

Methods	Allocation method: randomised Masking: none Number of centres: one

Patterson 1967b *(Continued)*

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)	High risk	Insufficient information. No explanation for the imbalance in numbers of participants assigned to each intervention
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

Pavan-Langston 1976 *(Continued)*

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."
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 pre-specified 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

Pavan-Langston 1981 *(Continued)*

	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)
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 pre-specified 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

Power 1991 *(Continued)*

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 pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

Ramirez 2002

Methods	Allocation method: randomised Masking: not given Number of centres: one
Participants	Country: Mexico Number enrolled: 19 Average age (range): not given Sex: not given Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=9): acyclovir 3% ointment 5 times per day Treatment two (n=10): ganciclovir 0.15% gel 5 times per day
Outcomes	Fluorescein staining
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)	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)	High risk	Unmasked study design could have influenced outcome assessment

Ramirez 2002 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data
Selective reporting (reporting bias)	Low risk	The pre-specified 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: not given 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)	High risk	Insufficient information on how patients "2 Gruppen zugeordnet."
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 pre-specified primary outcome was adequately reported
Other bias	Unclear risk	Insufficient information

Serifoglu 1987

Methods	Allocation method: not given 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)	High 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 pre-specified primary outcome was adequately reported
Other bias	Unclear risk	Insufficient information

Shen 2014

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 86 Average age (range): not given (8-72) Sex: 40 males, 38 females (78 patients; 86 eyes)

Shen 2014 *(Continued)*

	Inclusion criteria: punctate or dendritic epithelial keratitis
Interventions	Treatment one (n=43): ganciclovir gel 4 times per day + bovine fibroblast growth factor solution 4 times per day + oral acyclovir Treatment two (n=43): debridement with sterile needle + ganciclovir gel 4 times per day + bovine fibroblast growth factor solution 4 times per day + oral acyclovir
Outcomes	Fluorescein staining ('治愈 : 角膜刺激症状消失 , 溃疡愈合 , 荧光素染色(-), 基质水肿消失 , KP(-), 部分遗留角膜云翳 ')
Notes	Nonstudy interventions: ofloxacin eye drops 4 times per day; atropine 1% if uveitis; gatifloxacin ointment following debridement Report language: Chinese Study date: January 2009 - June 2013 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	High risk	Incomplete primary outcome data (outcome day unclear)
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Srinivas 1993

Methods	Allocation method: not given 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

Srinivas 1993 *(Continued)*

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)	Unclear risk	The investigators state that this was a "clinical trial" but do not describe whether a random component was used 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." It is unclear whether this statement means an unconcealed (i.e., open) allocation process or whether the authors are merely summarizing the number of participants (20 per group)
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 iodinisation, 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

Struck 1989 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors describe this study "Im Rahmen einer multizentrischen Prüfung" but do not provide information about the method of treatment allocation
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 F_3T."

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

Sugar 1980 *(Continued)*

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 pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

Sun 2013a

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 75 Average age (range): 30 (17-63) Sex: 51 males, 25 females (no explanation for total of 76 instead of 75) Inclusion criteria: dendritic (51) or geographic (25) epithelial keratitis (no explanation for total of 76 instead of 75)
Interventions	Treatment one (n=37): acyclovir 0.1% solution 4 times per day Treatment two (n=38): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: ofloxacin 4 times per day Report language: Chinese Study date: September 2010 - January 2013 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 method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Incomplete masking could have influenced outcome assessment
Incomplete outcome data (attrition bias)	High risk	Healing outcome reported at 3 weeks instead of 2 weeks

Sun 2013a *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The pre-specified primary outcome was adequately reported
Other bias	Unclear risk	75 eyes were allocated to two treatment groups but demographic information (gender and type of epithelial keratitis) were given for 76 eyes

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 (actually 73, but only 55 were culture-positive) 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 random component in the sequence generation process
Allocation concealment (selection bias)	Low 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
Blinding (performance bias and detection bias) All outcomes	High risk	"Group 1 was treated with human leukocyte interferon...[while] groups 2 and 2 were studied on a double-blind basis." However, the same investigators who performed débridement performed the outcome assessment
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 pre-specified primary outcome was adequately reported

Sundmacher 1976a *(Continued)*

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	Centralised allocation of coded vials, although "one vial could be used for more than one patient." Quote: "After the treatment of 51 cases, the coded results were mailed from Freiburg to Helskinki and the code from Helsinki to Freiburg on the same day."
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 pre-specified 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
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 pre-specified 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 (actually 53, but only 38 were culture-positive) Average age (range): not given

Sundmacher 1978b *(Continued)*

	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

Sundmacher 1981a *(Continued)*

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

Sundmacher 1981b *(Continued)*

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	High risk	Quote: "For final evaluation, only the results of those patients were used who had delivered positive virus cultures before initiation of therapy."
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

Sundmacher 1984a *(Continued)*

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, 19 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 interferon-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	Centralised allocation facility
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-masked trial design described

Sundmacher 1985 *(Continued)*

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 (actually 75, but only 45 were culture-positive and compliant) 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."

Sundmacher 1987 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Tanaka 1988a

Methods	Allocation method: randomised Masking: double Number of centres: 18
Participants	Country: Japan Number enrolled: 36 Average age (range): 47 (not given) Sex: 19 males, 17 females Inclusion criteria: dendritic (33) or geographic (3) epithelial keratitis
Interventions	Treatment one (n=16): recombinant interferon-α-2a (Ro22-8181) 1000 IU/ml 4 times per day Treatment two (n=20): recombinant interferon-α-2a (Ro22-8181) 10 million IU/ml 4 times per day
Outcomes	Fluorescein staining
Notes	Nonstudy interventions: atropine, micronomicin Report language: Japanese Study date: 1983 Financial support: not given (study medicines were provided by pharmaceutical firm)

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	Uncertain masking despite double-blind method
Incomplete outcome data (attrition bias) All outcomes	High risk	Three patients withdrew from the study, and after the study was completed a judgment committee that reviewed eligibility forms and photographs decided to exclude 11 patients
Selective reporting (reporting bias)	Low risk	The pre-specified primary outcome was adequately reported
Other bias	Unclear risk	Insufficient information

Tanaka 1988b

Methods	Allocation method: randomised

Tanaka 1988b *(Continued)*

	Masking: single (partial "double blind method") Number of centres: 31
Participants	Country: Japan Number enrolled: 137 Average age (range): not given Sex: 75 males, 62 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=71): idoxuridine solution every 1 or 2 hours Treatment two (n=30): recombinant interferon-α (Ro22-8181) 10 million 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 despite "double blind method."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data
Selective reporting (reporting bias)	Low risk	The pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

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

Travers 1978 *(Continued)*

Outcomes	Rose-Bengal staining
Notes	Nonstudy interventions: "mydriatics and antiglaucoma therapy was given when 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	The authors describe this study as "a controlled trial" but do not describe the method of treatment allocation
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 pre-specified 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

Uchida 1981 *(Continued)*

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."

Uchida 1982 *(Continued)*

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 pre-specified 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, 20 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)	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."

van Bijsterveld 1980 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The pre-specified 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 interferon-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 pre-specified 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 (*sic*), 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 pre-specified 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

Wang 2004 *(Continued)*

	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 pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

Wang 2014a

Methods	Allocation method: randomised Masking: single Number of centres: one
Participants	Country: China Number enrolled: 104 Average age (range): 38 (18-71) Sex: 76 males, 28 females Inclusion criteria: epithelial keratitis (shallow, deep, combined)
Interventions	Treatment one (n=52): topical acyclovir solution 8 times per day Treatment two (n=52): topical ganciclovir gel 5 times per day
Outcomes	Fluorescein staining ('治愈:患者患眼的刺激症状消失,充血消退,角膜基质无水肿和浸润,后弹力层褶皱消退,角膜后沉着物吸收,溃疡愈合良好,荧光色染色呈阴性,房水闪辉呈阴性')

Wang 2014a *(Continued)*

Notes	Nonstudy interventions: none Report language: Chinese Study date: December 2011 to December 2013 Financial support: not given Adverse reactions: 11 occurrences of pain or discomfort in acyclovir group and 3 occurrences of pain or discomfort in ganciclovir group Recurrence rate: in one year, 11 episodes in acyclovir group and 3 episodes in ganciclovir group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a randomised method of sequence generation
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	High risk	Healing outcome reported at 3 weeks instead of 2 weeks
Selective reporting (reporting bias)	Unclear risk	The pre-specified primary outcome was adequately reported, but the report did not stratify outcomes for participants treated with topical corticosteroid for stromal keratouveitis
Other bias	High risk	Among 104 eyes, the investigators enrolled 41 eyes with shallow keratitis, 35 eyes with deep keratitis, and 28 eyes with mixed type.

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

Wellings 1972 *(Continued)*

	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 débridement 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 pre-specified 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

Wilhelmus 1981a *(Continued)*

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
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 pre-specified 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)	High risk	Lack of masking could have influenced outcome assessment

Xu 2009a *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data
Selective reporting (reporting bias)	Low risk	The pre-specified 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	The authors describe these studies as "clinical trials" (and reference collaborators whose trial was randomised) but do not provide sufficient information on the method of treatment allocation
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	The authors describe these studies as "clinical trials" (and reference collaborators whose trial was randomised) but do not provide sufficient information on the method of treatment allocation
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

Yamazaki 1984c *(Continued)*

	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	The authors describe these studies as "clinical trials" (and reference collaborators whose trial was randomised) but do not provide sufficient information on the method of treatment allocation
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

Yang 2000 *(Continued)*

	Financial support: governmental agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors describe "a double blind clinical investigation" but do not describe the method of treatment allocation
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

Yang 2008

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 62 Average age (range): 40 (20-73) Sex: 27 males, 35 females Inclusion criteria: dendritic (49) or geographic (13) epithelial keratitis
Interventions	Treatment one (n=30): acyclovir 0.1% solution 6 times per day Treatment two (n=32): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining ('荧光素钠染色阴性')
Notes	Nonstudy interventions: atropine 1% for iridocyclitis; oral indomethacin 25 mg 3 times per day Report language: Chinese Study date: 2010-2012 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

Yang 2008 *(Continued)*

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	Incomplete primary outcome data (outcome day unclear)
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)	Low risk	Quote: "All patients used the medication as directed, and no patient was lost to follow-up prior to complete corneal re-epithelialization."

Yeakley 1981 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The pre-specified 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	Rose Bengal
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 pre-specified primary outcome was adequately reported

Young 1982 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Yu 2012a

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 60 Average age (range): 39 (17-60) Sex: 32 males, 28 females Inclusion criteria: dendritic (36) or geographic (24) epithelial keratitis
Interventions	Treatment one (n=30): ganciclovir 0.1% solution 8 times per day Treatment two (n=30): foscarnet 3% solution 6 times per day
Outcomes	Epithelial healing
Notes	Nonstudy interventions: none Report language: Chinese Study date: 2008-2009 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 pre-specified primary outcome was adequately reported
Other bias	Unclear risk	Insufficient information

Zhang 2014

Methods	Allocation method: randomised Masking: none Number of centres: one

Zhang 2014 *(Continued)*

Participants	Country: China Number enrolled: 84 Average age (range): 39 (22-60) Sex: 46 males, 38 females Inclusion criteria: dendritic (55) or geographic (29) epithelial keratitis
Interventions	Treatment one (n=42): acyclovir 0.1% solution every 2 hours Treatment two (n=42): ganciclovir 0.15% gel 5 times per day
Outcomes	Fluorescein staining ('患者的眼部刺激症状消失, 角膜充血消退, 溃疡得到修复, 并且荧光素染色转为阴性, 浸润和水肿消失, 角膜后的沉着物呈现色素性或者消失')
Notes	Nonstudy interventions: none Report language: Chinese Study date: January 2012 - June 2013 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 method of sequence generation
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 pre-specified primary outcome was adequately reported
Other bias	Low risk	The study appears to be free of other sources of bias

Zhao 2006

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 124 Average age (range): 37 (12-64) Sex: 81 males, 43 females Inclusion criteria: epithelial keratitis (106) or stromal keratitis (18)
Interventions	Treatment one (n=62): acyclovir solution every 1-2 hours Treatment two (n=62): ganciclovir gel 4 times per day

Zhao 2006 *(Continued)*

Outcomes	Fluorescein staining ('刺激症状消失, 知觉恢复 , 溃疡面愈合 , 基质层水肿消失, 荧光素染色阴性 ')
Notes	Nonstudy interventions: atropine 1% and "antibiotic eye drop" 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 randomised method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	High risk	Incomplete masking could have influenced outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Uncertain time when healing outcome reported
Selective reporting (reporting bias)	Unclear risk	The pre-specified primary outcome was adequately reported, but the report did not stratify outcomes for participants treated with topical corticosteroid for stromal keratouveitis
Other bias	High risk	Among 124 eyes, the investigators enrolled 15% of eyes having stromal keratitis and did not separately report outcomes for epithelial keratitis (106) and disciform keratitis (18)

Zhen 2012

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 128 Average age (range): not given (15-65) Sex: 55 males, 73 females Inclusion criteria: dendritic or geographic epithelial keratitis (some eyes may have had disciform stromal keratitis)
Interventions	Treatment one (n=64): acyclovir 0.1% solution 8 times per day Treatment two (n=64): ganciclovir 0.15% gel 4 times per day
Outcomes	Fluorescein staining ('荧光素染色阴性 ')
Notes	Nonstudy interventions: atropine 1% for iridocyclitis; dexamethasone 0.05% for keratouveitis Report language: Chinese Study date: 2009-2012 Financial support: university

Zhen 2012 *(Continued)*

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	High risk	Incomplete primary outcome data (outcome day unclear)
Selective reporting (reporting bias)	Unclear risk	The pre-specified primary outcome was adequately reported, but the report did not stratify outcomes for participants treated with topical corticosteroid for stromal keratouveitis
Other bias	High risk	Insufficient information

Zheng 2010

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 210 (not including 38 cases of stromal keratitis) Average age (range): not given (18-65) Sex: 185 males, 62 females (gender distribution for epithelial keratitis patients not reported separately) Inclusion criteria: dendritic (178) or geographic (31) epithelial keratitis (38 cases, including 35 disciform keratitis and 3 necrotizing keratitis, are being excluded from this analysis)
Interventions	Treatment one (n=104): ganciclovir 0.1% solution 6 times per day Treatment two (n=105): ganciclovir 0.15% gel 4 times per day
Outcomes	Healing ('治愈: 刺激症状消失, 知觉恢复, 溃疡面愈合')
Notes	Nonstudy interventions: mydriatic and subconjunctival dexamethasone 3 mg for stromal keratitis 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 randomised method of sequence generation

Zheng 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	High risk	Incomplete 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	Vague description of assessing healing
Other bias	Unclear risk	Among 247 eyes, outcome data for 209 eyes having epithelial keratitis were extracted while ignoring 38 eyes with corticosteroid-treated disciform or stromal keratitis

Zhu 2012

Methods	Allocation method: randomised Masking: none Number of centres: one
Participants	Country: China Number enrolled: 74 eyes (68 participants) Average age (range): not given (16-67) Sex: 32 males, 36 females Inclusion criteria: dendritic epithelial keratitis
Interventions	Treatment one (n=38): ganciclovir 0.15% gel 4 times per day Treatment two (n=36): ganciclovir 0.15% gel 4 times per day + interferon 1 million units/ml (0.5 ml) subconjunctival injection every other 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

Zhu 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete primary outcome data (outcome day unclear)
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

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 cauterisation
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 debridement 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
Cao 2012	Botanical or herbal preparation Treatment one (n=30): ganciclovir 0.15% gel Treatment two (n=30): ganciclovir 0.15% gel and botanical extract
Cao 2013	Botanical or herbal preparation

Study	Reason for exclusion
	Treatment one (n=28): acyclovir 0.1% solution 4 times daily and oral antiviral (plus dexamethsone and tobramycin for stromal keratitis) Treatment two (n=30): acyclovir 0.1% solution 4 times daily and oral antiviral and oral botanical extract twice daily (plus dexamethonse and tobramycin for stromal keratitis)
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 iodinisation debridement
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 Treatment three (n=13): iodinisation debridement and idoxuridine Treatment four (n=18): iodinisation debridement and trifluridine

Study	Reason for exclusion
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 "carbolization or iodization" debridement Treatment two (n=82): idoxuridine 0.1% solution hourly or 0.5% ointment 2-hourly
Gong 2013	Botanical or herbal preparation Treatment one (n=55): antiviral Treatment two (n=55): antiviral and botanical extract
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
Gulinuer 2011	Non-concurrent/non-randomised treatment allocation Treatment one (n=37): acyclovir 0.1% solution 6 times per day Treatment two (n=48): ganciclovir 0.15% gel 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 iodinisation debridement Treatment two (n=45): entire corneal iodinisation debridement
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
He 2014	Insufficient data provided Treatment one (n=34): antiviral Treatment two (n=34): autologous serum
Herbort 1987	Non-concurrent treatment allocation

Study	Reason for exclusion
	Treatment one (n=20): scraping debridement 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): iodinisation debridement with idoxuridine ointment Treatment two (n=20): cryotherapy with idoxuridine ointment
Horodeňscy 1979	Non-concurrent treatment allocation Treatment one (n=17): idoxuridine 0.1% solution Treatment two (n=17): cytarabine 0.1% solution
Hu 2013	Botanical or herbal preparation Treatment one (n=30): ganciclovir Treatment two (n=40): ganciclovir and botanical extract
Huang 2007	Insufficient data provided Treatment one (n=62): acyclovir 0.1% solution Treatment two (n=62): ganciclovir 0.15% gel
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
Huang 2013	Botanical or herbal preparation Treatment one (n=34): ganciclovir 0.15% gel 4 times daily Treatment two (n=34): ganciclovir 0.15% gel 4 times daily and oral botanical extract (qinggan jiedu)
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
Jiang 2011	Varied eligibility criteria (both shallow and deep forms) Treatment one (n=22, shallow type): acyclovir 0.1% solution + basic fibroblast growth factor Treatment two (n=23, shallow type): acyclovir 0.1% solution + tobramycin-dexamethasone
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
Jing 2010	Insufficient data provided Treatment one (n=22): acyclovir 0.1% solution 5 times daily Treatment two (n=24): ganciclovir 0.15% gel 5 times daily

Study	Reason for exclusion
Jones 1979	Outcome not based on epithelial healing Treatment one (n=12): wiping debridement and placebo ointment 5 times per day Treatment two (n=13): wiping debridement and acyclovir 3% ointment 5 times per day
Kasparov 1972	Insufficient data provided Treatment one (n=16): idoxuridine 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 debridement by either diathermy or cryotherapy
Kasparov 1974	Insufficient data provided Control (n=30): "nonspecific drugs, such as antibiotics, sulphanyl 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 debridement 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 debridement
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
Li 2012	Botanical or herbal preparation

Study	Reason for exclusion
	Treatment one (n=39): acyclovir 0.1% solution Treatment two (n=41): acyclovir 0.1% solution and botanical extract
Li 2013c	Botanical or herbal preparation Treatment one (n=85): acyclovir Treatment two (n=90): acyclovir and botanical extract
Li 2014a	Botanical or herbal preparation Treatment one (n=44): antiviral Treatment two (n=48): antiviral and botanical extract and oral transfer factor
Li 2014b	Botanical or herbal preparation Treatment one (n=40): antiviral Treatment two (n=40): botanical extract
Li 2014c	Insufficient data provided Treatment one (n=21): ganciclovir gel and acyclovir solution Treatment two (n=21): ganciclovir gel and basic fibroblast growth factor
Lin 2009	Insufficient data provided Treatment one (n=27): acyclovir Treatment two (n=22): acyclovir and polyinosinic-polycytidylic acid injection
Lin 2013a	Outcome not based on epithelial healing (total score of symptoms and signs) Treatment one (n=114): ganciclovir 0.15% gel Treatment two (n=116): ganciclovir 0.15% in situ gel
Lin 2013b	Insufficient data provided (unclear time until outcome assessment) Treatment one (n=33): ganciclovir 0.1% solution 4 times daily + levofloxacin solution 4 times daily Treatment two (n=33): ganciclovir 0.1% solution 4 times daily + levofloxacin solution 4 times daily + subconjunctival interferon one million units/ml (0.3 ml) every other day
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
Liu 2014b	Insufficient data provided Treatment one (n=not given): acyclovir solution Treatment two (n=not given): periocular injection of polyinosinic acid 0.5 mg every other day

Study	Reason for exclusion
	Treatment three (n=not given): acyclovir solution and periocular polyinosinic acid 0.5 mg every other day (Total enrolled=38 patients, 60 eyes)
Long 2011	Varied eligibility criteria (25 eyes with HSV keratitis and 19 eyes with herpes zoster keratitis) Treatment one (n=13, HSV keratitis): acyclovir 0.1% solution 6-8 times per day Treatment two (n=12, HSV keratitis): acyclovir 0.1% solution 6-8 times per day + interferon eye drops 4 times per day + subconjunctival (1 mL) interferon one million units/mL every 1-2 days (6-8 injections)
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
Ma 2010	Botanical or herbal preparation Treatment one (n=42): acyclovir solution Treatment two (n=40): botanical extract
Ma 2011	Botanical or herbal preparation Treatment one (n=34): acyclovir solution Treatment two (n=34): botanical extract
Ma 2013	Botanical or herbal preparation Treatment one (n=29): antiviral Treatment two (n=29): botanical extract
Maichuk 1990	Varied eligibility criteria Treatment one (n=28): oral pirprofen Treatment two (n=24): intramuscular pirprofen Treatment three (n=29): oral indomethacin
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): thermocauterisation debridement

Study	Reason for exclusion
	Treatment two (n=75): scraping debridement 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): iodinisation debridement Treatment two (n=20): cryotherapy debridement Treatment three (n=24): cryotherapy debridement and topical autologous serum Treatment four (n=30): wiping debridement Treatment five (n=30): wiping debridement and idoxuridine 0.1% solution 3 times per day
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 Inclusion criteria: 24 eyes with corticosteroid-enhanced epithelial keratitis: 22 eyes with geographic "amoeboid" epithelial keratitis and two eyes with "multiple linear ulcers"; "a severe stromal keratitis was often present." Treatment one (n=9): cauterisation, debridement 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

Study	Reason for exclusion
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 debridement Treatment four (n=8): iodinisation debridement 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"
Prost 1986	Insufficient data provided Treatment one (n=20): cryotherapy and oral placebo Treatment two (n=19): cryotherapy and oral isoprinosine
Rykun 1988	Non-concurrent, non-randomised treatment allocation Treatment one (n=38, dendritic type): antiviral (idoxuridine) Treatment two (n=22, dendritic type): antiviral + α-tocopherol 10% solution
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 debridement 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

Study	Reason for exclusion
	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
Su 2010	Insufficient data provided Treatment one (n=40 eyes, 29 patients): ganciclovir 0.15% gel 4 times per day Treatment two (n=38 eyes, 30 patients): ganciclovir 0.15% gel 4 times per day + subconjunctival interferon one million units/mL (1 ml) every other day (6-8 injections)
Sun 2012	Botanical or herbal preparation Treatment one (n=35): acyclovir solution 4-6 times per day Treatment two (n=33): acyclovir solution 4-6 times per day + intravenous yan hu ning (dehydroandrographolide succinate) 400 mg in 250 mL saline, repeated every third day for 10 days
Sun 2014	Botanical or herbal preparation Treatment one (n=34): acyclovir solution Treatment two (n=34): acyclovir solution + oral vitamin C
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): iodinisation debridement 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 *Corynebacterium parvum*
Wan 2014	Insufficient data provided (average healing time and outcome assessment at 4 weeks) Treatment one (n=24): ganciclovir 0.15% gel 6 times daily

Study	Reason for exclusion
	Treatment two (n=26): ganciclovir 0.15% gel 6 times daily + recombinant human interferon α-2b solution 6 times daily
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
Wang 2010a	Botanical or herbal preparation Treatment one (n=102): ganciclovir gel + intravenous acyclovir Treatment two (n=111): ganciclovir gel + intravenous acyclovir + botanical extract
Wang 2010b	Botanical or herbal preparation Treatment one (n=42): acyclovir 0.1% solution + subconjunctival acyclovir Treatment two (n=45): acyclovir 0.1% solution + subconjunctival acyclovir + botanical extract
Wang 2011	Botanical or herbal preparation Treatment one (n=48): acyclovir 0.1% solution Treatment two (n=108): acyclovir 0.1% solution + botanical extract
Wang 2014b	Botanical or herbal preparation Treatment one (n=106): ganciclovir 0.15% gel Treatment two (n=107): ganciclovir 0.15% gel and botanical extract (yiqi jiedu)
Wei 2012	Insufficient data provided Treatment one (n=24): ganciclovir 0.15% gel 6 times per day Treatment two (n=24): ganciclovir 0.15% gel 6 times per day + polyinosinic acid (poly I:C) 0.5 mg subconjunctival injection every 3 days + poly I:C 1.5 mg intramuscular injection every other day
Wen 2011	Botanical or herbal preparation Treatment one (n=41): acyclovir 0.1% solution Treatment two (n=40): acyclovir 0.1% solution + botanical extract
Weng 2014	Insufficient data provided (outcome assessment at 6 weeks) Treatment one (n=35): acyclovir 0.1% solution 6-8 times daily + tobramycin 0.3% 3 times daily Treatment two (n=35): acyclovir 0.1% solution 6-8 times daily + tobramycin 0.3% 3 times daily + subconjunctival recombinant human interferon α-2b one million U
Whitcher 1976	Insufficient data provided Treatment one (n=20): wiping debridement 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

Study	Reason for exclusion
	Treatment one (n=30): acyclovir 0.1% solution Treatment two (n=32): acyclovir 0.1% solution and recombinant interleukin-2
Xu 2012	Botanical or herbal preparation Treatment one (n=43): acyclovir 0.1% solution + intravenous acyclovir Treatment two (n=67): acyclovir 0.1% solution + intravenous acyclovir + botanical extract
Yamamoto 1984	Non-concurrent treatment allocation 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
Yang 2012	Botanical or herbal preparation Treatment one (n=33): acyclovir 0.1% solution Treatment two (n=35): botanical extract
Yi 2011	Botanical or herbal preparation Treatment one (n=60): acyclovir 0.1% solution + ganciclovir gel + intravenous acyclovir Treatment two (n=67): acyclovir 0.1% solution + botanical extract + acupuncture
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
Yu 2012b	Insufficient data provided (outcome based on clinical scores and corneal sensation) Treatment one (n=30): ganciclovir 0.15% gel 8 times per day Treatment two (n=30): ganciclovir 0.15% gel 8 times per day + subconjunctival live attenuated measles vaccine (0.5 ml) every other day
Yu 2014	Botanical or herbal preparation Treatment one (n=46): acyclovir Treatment two (n=50): acyclovir and botanical extract
Yuan 2011	Varied eligibility criteria (both epithelial and stromal keratitis) Treatment one (n=35, epithelial type): acyclovir 0.1% solution 4 times per day + interferon 1 million units/mL (0.5 ml) subconjunctival injection every other day Treatment two (n=34, epithelial type): ganciclovir 0.15% gel 4 times per day + interferon 1 million units/mL (0.5 ml) subconjunctival injection every other day
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
Zajácz 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

Study	Reason for exclusion
	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
Zhan 2011	Botanical or herbal preparation Treatment one (n=50): acyclovir 0.1% solution + oral acyclovir Treatment two (n=50): 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 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
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
Zhang 2010	Botanical or herbal preparation Treatment one (n=57): acyclovir 0.1% solution (or ganciclovir gel) Treatment two (n=61): acyclovir 0.1% solution (or ganciclovir gel) + 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 µg/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
Zhao 2010	Botanical or herbal preparation Treatment one (n=54): botanical extract Treatment two (n=52): periocular injection of polyinosinic acid
Zhao 2013	Botanical or herbal preparation Treatment one (n=48): antiviral Treatment two (n=48): antiviral and botanical extract (yu ping feng)
Zheng 2008	Botanical or herbal preparation

Study	Reason for exclusion
	Treatment one (n=45): topical antiviral Treatment two (n=45): topical antiviral and systemic botanical extracts
Zheng 2014	Botanical or herbal preparation Treatment one (n=39): acyclovir solution Treatment two (n=45): acyclovir solution and botanical extract
Zhi 2001	Insufficient data provided Treatment one (n=30): topical acyclovir Treatment two (n=38): topical acyclovir and systemic interleukin-2
Zhong 2003	Botanical or herbal preparation Treatment one (n=30): acyclovir 0.1% solution 6 times per day + intramuscular polyinosinic acid Treatment two (n=30): re du qing solution 6 times per day + intramuscular polyinosinic acid Treatment three (n=50): re du qing nebuliser for 15 minutes 2 times per day + intramuscular polyinosinic acid
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): iodinisation debridement Treatment two (n=14): trifluridine or idoxuridine 3 to 5 times per day Treatment three (n=49): scraping debridement and trifluridine or idoxuridine Treatment four (n=33): trifluridine and antiherpetic immunoglobulin

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

Ajanta Pharma 2013

Methods	Allocation method: randomised
Participants	Country: India
Interventions	Treatment one: acyclovir 3% ointment five times per day Treatment two: ganciclovir 0.15% gel five times per day
Outcomes	Corneal epithelial healing
Notes	Financial support: pharmaceutical industry

Bausch & Lomb 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

DATA AND ANALYSES

Comparison 1. Topical antiviral agents

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Idoxuridine *versus* inactive control: 7-day & 14-day healing	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Healing at 7 days	10	392	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.24, 3.51]
1.2 Healing at 14 days	2	63	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.45, 3.84]
2 Idoxuridine *versus* inactive control: healing rate	3	95	Hazard Ratio (95% CI)	1.62 [1.00, 2.65]
3 Vidarabine *versus* 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 *versus* inactive control: healing rate	1	43	Hazard Ratio (95% CI)	2.47 [1.14, 5.33]
5 Vidarabine *versus* 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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Vidarabine *versus* idoxuridine: healing rate	2	74	Hazard Ratio (95% CI)	1.36 [0.81, 2.28]
7 *para*-Fluorophenylalanine *versus* idoxuridine: 7-day & 14-day healing	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Healing at 7 days: without debridement	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.59, 1.54]
7.2 Healing at 14 days: without debridement	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.14]
7.3 Healing at 7 days: with debridement	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.87, 1.43]
7.4 Healing at 14 days: with debridement	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.18]
8 Trifluridine *versus* 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 *versus* idoxuridine: healing rate	1	78	Hazard Ratio (95% CI)	2.29 [1.37, 3.83]
10 Acyclovir *versus* idoxuridine: 7-day & 14-day healing	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Healing at 7 days: acyclovir *versus* idoxuridine	9	468	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.35, 2.90]
10.2 Healing at 14 days: acyclovir *versus* idoxuridine	11	606	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.08, 1.38]
10.3 Healing at 7 days: acyclovir *versus* iododeoxycytidine	1	32	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.76, 2.63]
10.4 Healing at 14 days: acyclovir *versus* iododeoxycytidine	1	32	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.89, 1.12]
11 Acyclovir *versus* idoxuridine: healing rate	8	355	Hazard Ratio (95% CI)	2.15 [1.70, 2.72]
12 Brivudine *versus* 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]

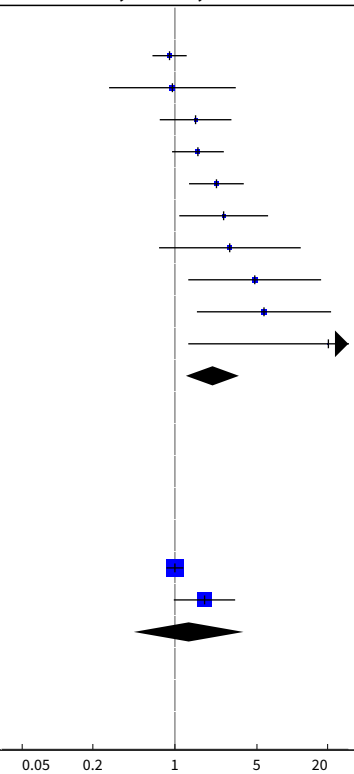
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 Healing at 14 days	2	99	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.05, 1.81]
13 Trifluridine *versus* vidarabine: 7-day & 14-day healing	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Healing at 7 days: all groups	4	288	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.94, 1.23]
13.2 Healing at 14 days: all groups	3	188	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.84, 1.49]
13.3 Healing at 7 days: geographic epithelial keratitis	1	30	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.55, 3.13]
13.4 Healing at 14 days: geographic epithelial keratitis	1	30	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.16, 3.33]
14 Trifluridine *versus* vidarabine: healing rate	3	188	Hazard Ratio (95% CI)	1.31 [0.96, 1.79]
15 Acyclovir *versus* 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 *versus* vidarabine: healing rate	5	259	Hazard Ratio (95% CI)	1.13 [0.86, 1.47]
17 Acyclovir *versus* 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 *versus* trifluridine: healing rate	3	140	Hazard Ratio (95% CI)	0.92 [0.65, 1.32]
19 Brivudine *versus* trifluridine: 7-day & 14-day healing	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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 *versus* trifluridine: healing rate	1	60	Hazard Ratio (95% CI)	0.60 [0.35, 1.02]
21 Brivudine *versus* 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 *versus* acyclovir: 7-day & 14-day healing	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 Healing at 7 days	7	551	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.96, 1.35]
22.2 Healing at 14 days	28	2062	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.22, 1.57]
23 Foscarnet *versus* 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 Foscarnet *versus* acyclovir: 14-day healing	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 Healing at 14 days	1	104	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.95, 1.40]
25 Foscarnet *versus* ganciclovir: 7-day & 14-day healing	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 Healing at 7 days	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.76, 1.22]
25.2 Healing at 14 days	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.16]
26 Acyclovir/vidarabine *versus* acyclovir: 7-day & 14-day healing	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 Healing at 7 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [1.01, 2.24]

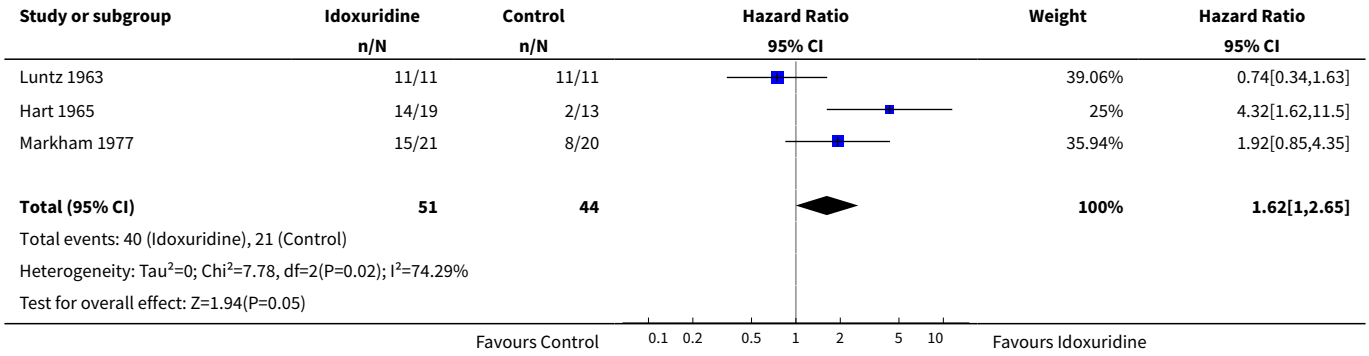
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.2 Healing at 14 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.89, 1.12]
27 Trifluridine (aqueous) *versus* trifluridine (viscous)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 Healing at 7 days	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.58, 4.05]
27.2 Healing at 14 days	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.96, 2.41]
28 Ganciclovir 0.15% gel *versus* ganciclovir 0.05% gel or 0.1% solution	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 Healing at 7 days	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.53, 1.74]
28.2 Healing at 14 days	4	355	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.98, 1.14]

Analysis 1.1. Comparison 1 Topical antiviral agents, Outcome 1 Idoxuridine *versus* inactive control: 7-day & 14-day healing.

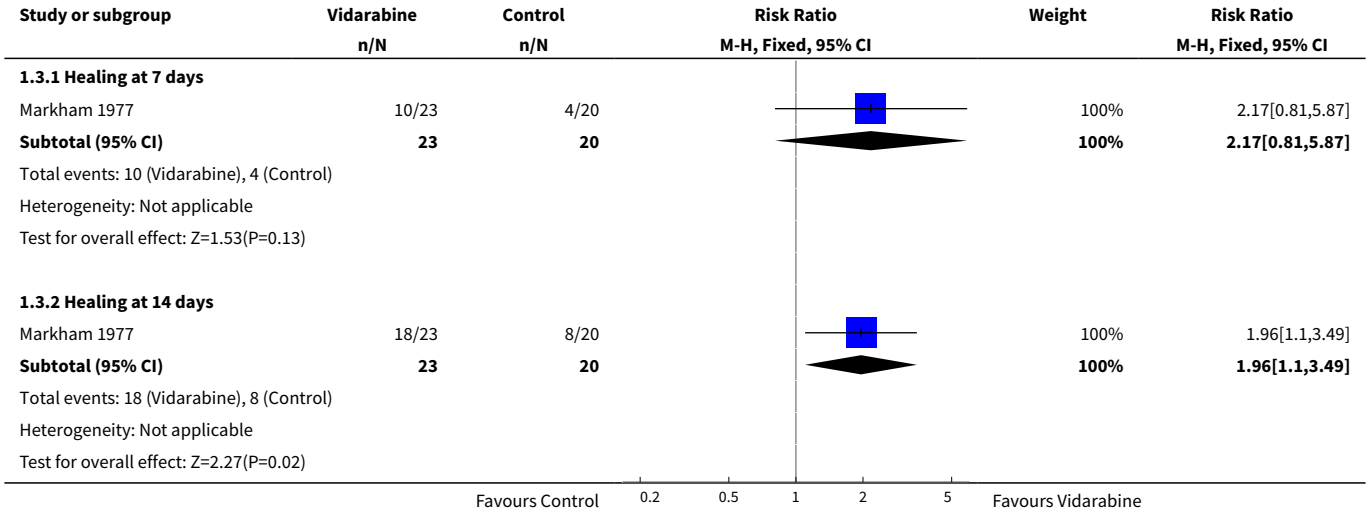
Study or subgroup	Idoxuridine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Healing at 7 days					
Luntz 1963	9/11	10/11		14.92%	0.9[0.64,1.26]
Markham 1977	4/21	4/20		8.3%	0.95[0.27,3.3]
Davidson 1964	12/25	8/25		12.31%	1.5[0.74,3.03]
Jepson 1964	11/12	7/12		13.8%	1.57[0.95,2.61]
Laibson 1964	26/47	13/53		13.58%	2.26[1.32,3.86]
Patterson 1963a	8/10	4/13		10.96%	2.6[1.09,6.22]
Burns 1963	9/23	2/15		7.43%	2.93[0.73,11.75]
Hart 1965	14/19	2/13		7.93%	4.79[1.3,17.62]
Patterson 1963b	13/17	2/15		7.85%	5.74[1.54,21.4]
Patterson 1963c	11/16	0/14		2.91%	20.29[1.3,315.86]
Subtotal (95% CI)	**201**	**191**		**100%**	**2.09[1.24,3.51]**
Total events: 117 (Idoxuridine), 52 (Control)					
Heterogeneity: Tau^2=0.44; Chi^2=37.5, df=9(P<0.0001); I^2=76%					
Test for overall effect: Z=2.79(P=0.01)					
1.1.2 Healing at 14 days					
Luntz 1963	11/11	11/11		53.58%	1[0.85,1.18]
Markham 1977	15/21	8/20		46.42%	1.79[0.98,3.26]
Subtotal (95% CI)	**32**	**31**		**100%**	**1.31[0.45,3.84]**
Total events: 26 (Idoxuridine), 19 (Control)					
Heterogeneity: Tau^2=0.56; Chi^2=11.98, df=1(P=0); I^2=91.65%					
Test for overall effect: Z=0.49(P=0.62)					



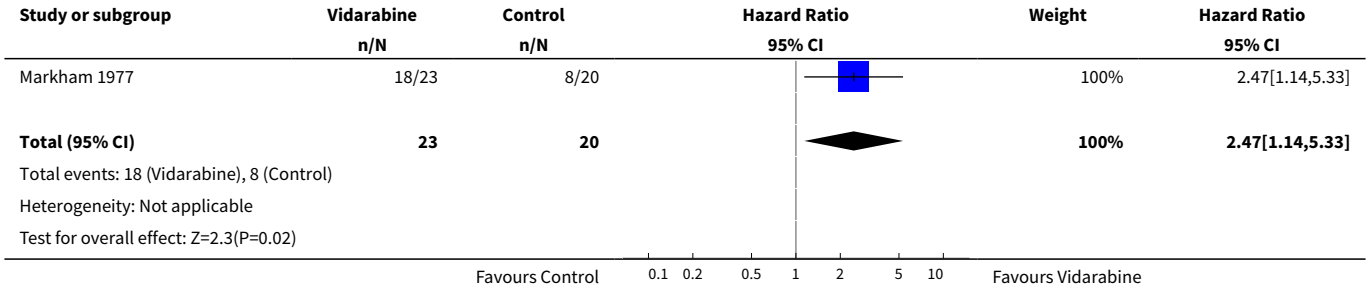
Analysis 1.2. Comparison 1 Topical antiviral agents, Outcome 2 Idoxuridine *versus* inactive control: healing rate.



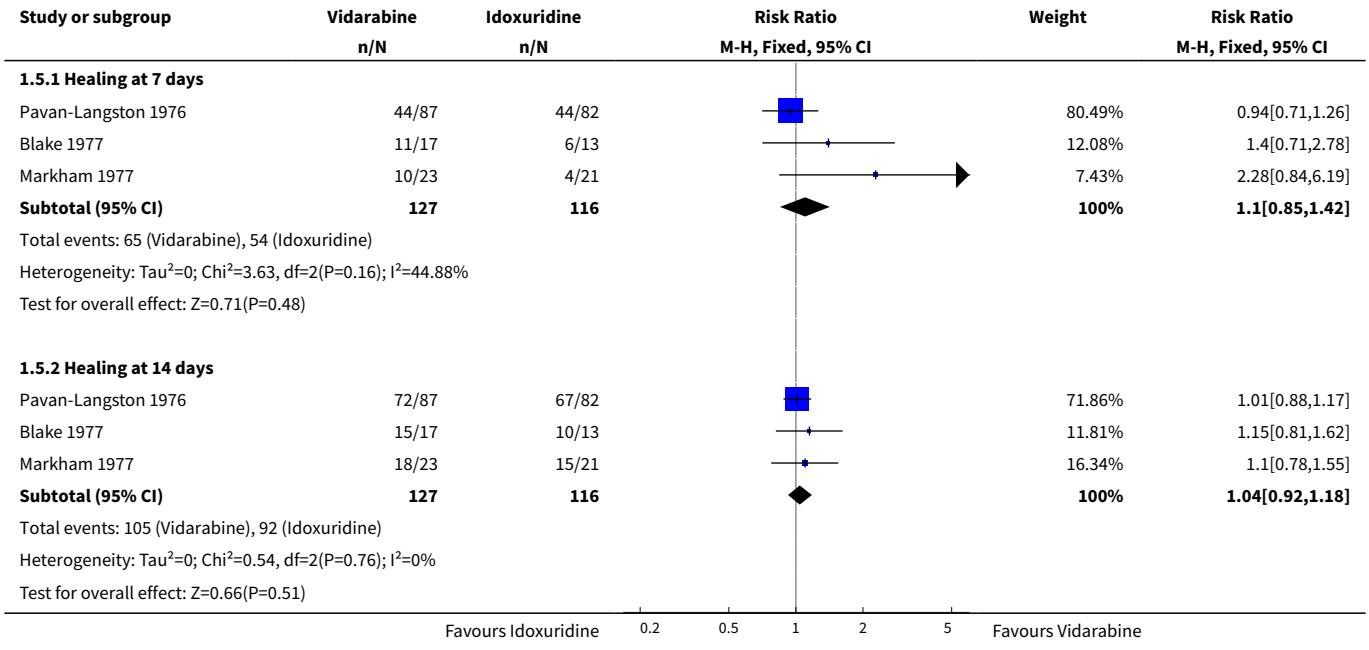
Analysis 1.3. Comparison 1 Topical antiviral agents, Outcome 3 Vidarabine *versus* inactive control: 7-day & 14-day healing.



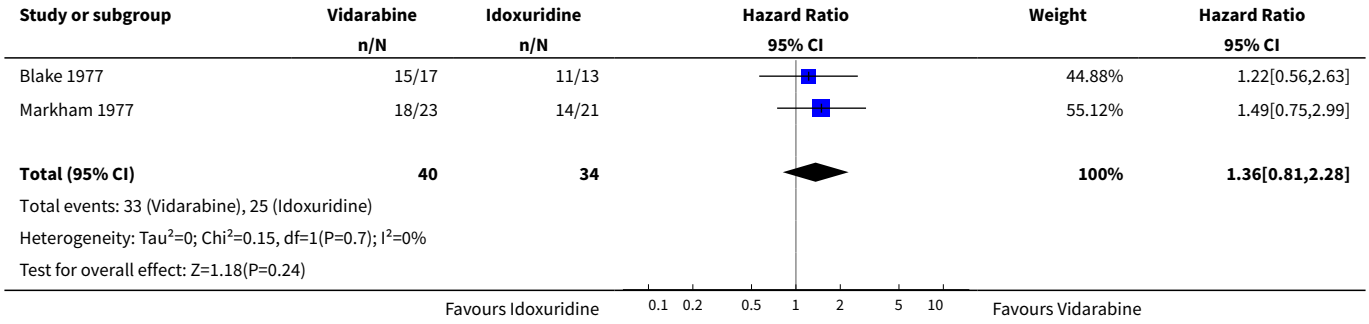
Analysis 1.4. Comparison 1 Topical antiviral agents, Outcome 4 Vidarabine *versus* inactive control: healing rate.



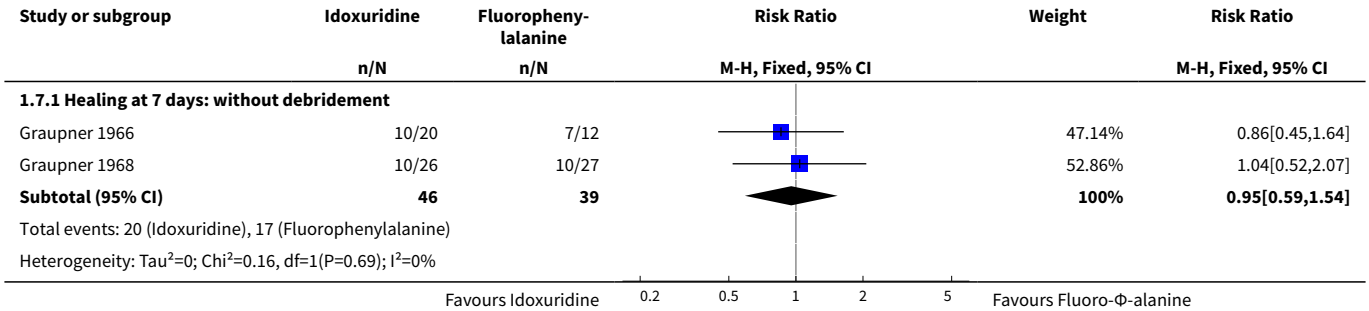
Analysis 1.5. Comparison 1 Topical antiviral agents, Outcome 5 Vidarabine *versus* idoxuridine: 7-day & 14-day healing.

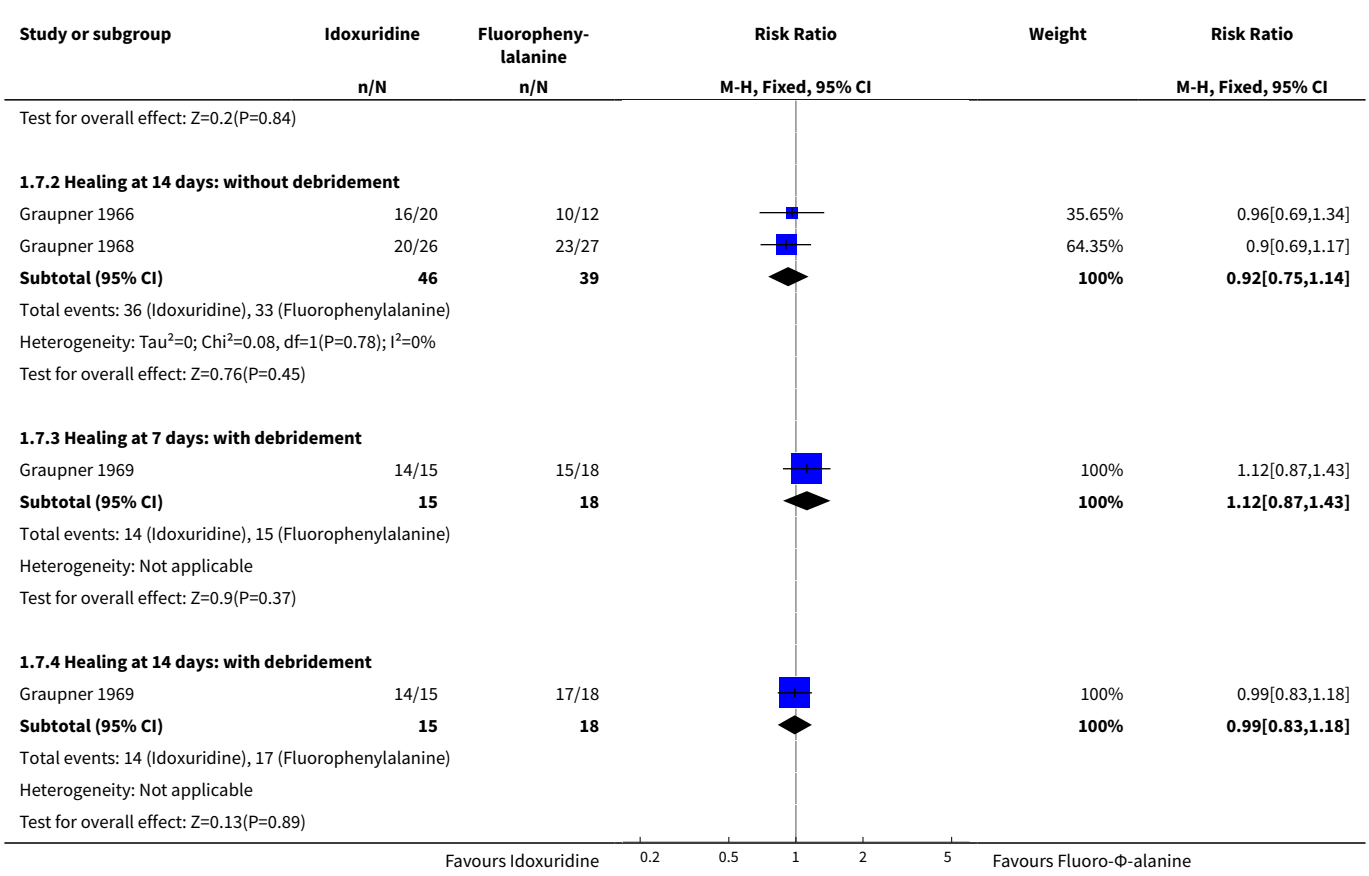


Analysis 1.6. Comparison 1 Topical antiviral agents, Outcome 6 Vidarabine *versus* idoxuridine: healing rate.

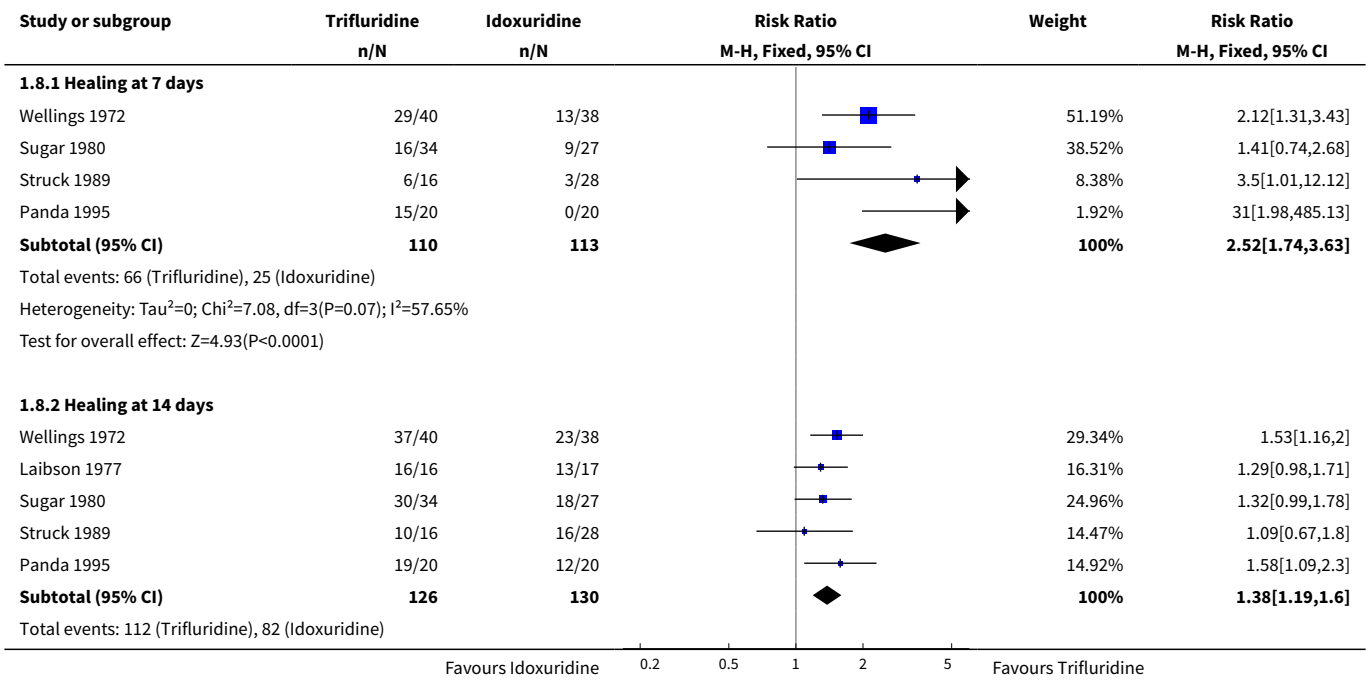


Analysis 1.7. Comparison 1 Topical antiviral agents, Outcome 7 *para*-Fluorophenylalanine *versus* idoxuridine: 7-day & 14-day healing.





Analysis 1.8. Comparison 1 Topical antiviral agents, Outcome 8 Trifluridine *versus* idoxuridine: 7-day & 14-day healing.



Study or subgroup	Trifluridine n/N	Idoxuridine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=2.19, df=4(P=0.7); I²=0%					
Test for overall effect: Z=4.33(P<0.0001)					

Favours Idoxuridine — Favours Trifluridine

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

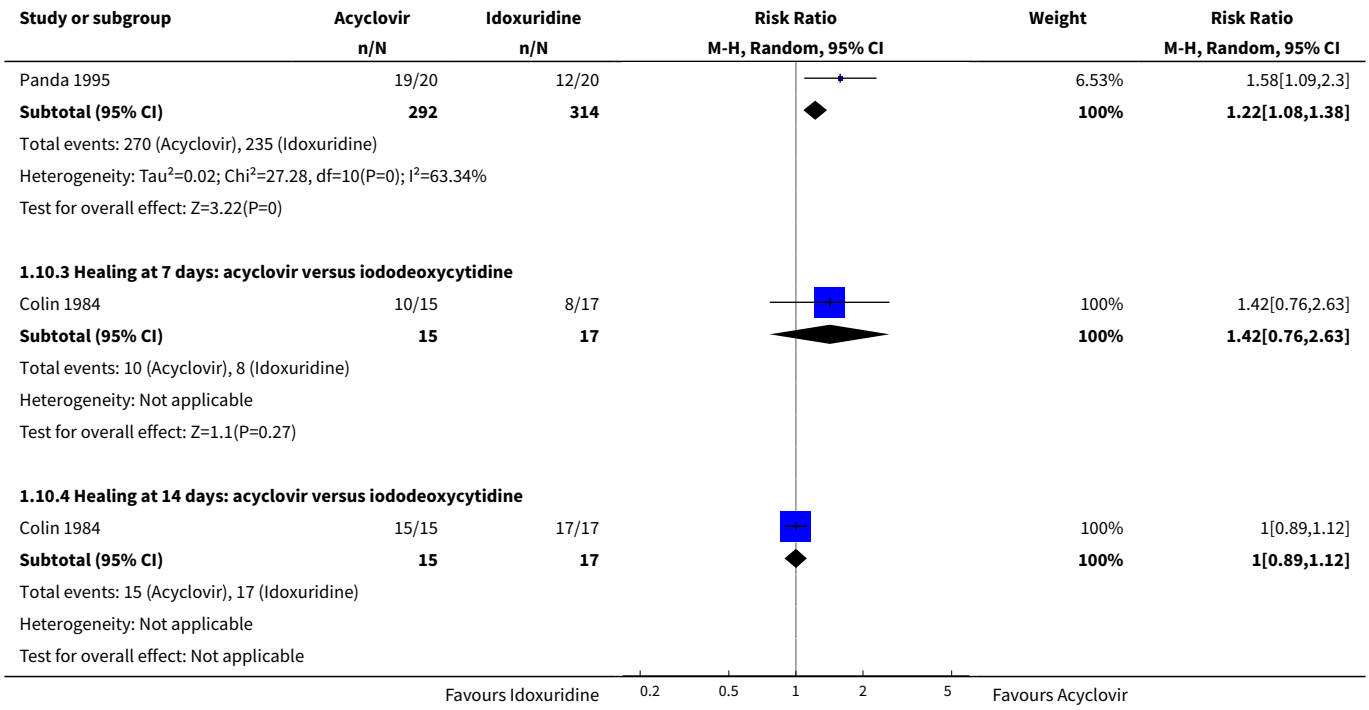
Study or subgroup	Trifluridine n/N	Idoxuridine n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
Wellings 1972	37/40	23/38		100%	2.29[1.37,3.83]
Total (95% CI)	**40**	**38**		**100%**	**2.29[1.37,3.83]**
Total events: 37 (Trifluridine), 23 (Idoxuridine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.16(P=0)					

Favours Idoxuridine — Favours Trifluridine

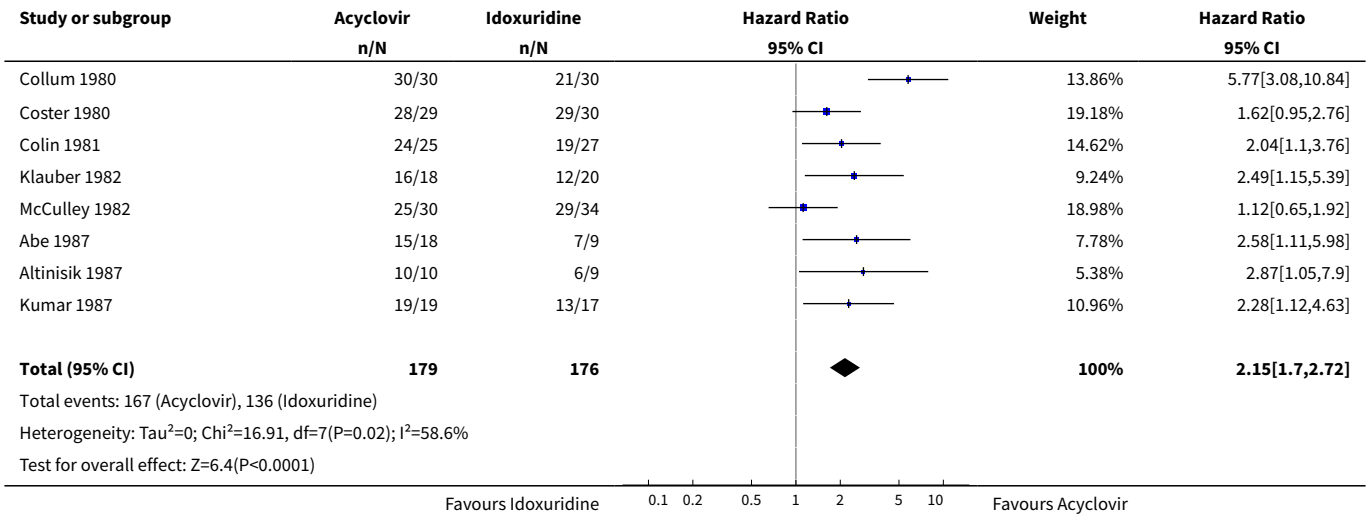
Analysis 1.10. Comparison 1 Topical antiviral agents, Outcome 10 Acyclovir *versus* idoxuridine: 7-day & 14-day healing.

Study or subgroup	Acyclovir n/N	Idoxuridine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Healing at 7 days: acyclovir versus idoxuridine					
Collum 1980	29/30	6/30		11.65%	4.83[2.36,9.92]
Coster 1980	25/29	21/30		17.88%	1.23[0.93,1.62]
Colin 1981	19/25	11/27		14.68%	1.87[1.13,3.09]
Klauber 1982	12/18	6/20		11.3%	2.22[1.06,4.68]
McCulley 1982	19/30	18/34		15.97%	1.2[0.79,1.82]
Kitano 1985	40/54	26/55		17.32%	1.57[1.14,2.16]
Abe 1987	11/18	2/9		6.19%	2.75[0.77,9.86]
Altinisik 1987	5/10	1/9		3.24%	4.5[0.64,31.6]
Panda 1995	16/20	0/20		1.77%	33[2.11,515.02]
Subtotal (95% CI)	**234**	**234**		**100%**	**1.98[1.35,2.9]**
Total events: 176 (Acyclovir), 91 (Idoxuridine)					
Heterogeneity: Tau²=0.19; Chi²=29.36, df=8(P=0); I²=72.75%					
Test for overall effect: Z=3.49(P=0)					
1.10.2 Healing at 14 days: acyclovir versus idoxuridine					
Collum 1980	30/30	21/30		10.15%	1.42[1.12,1.8]
Coster 1980	27/29	29/30		14.29%	0.96[0.85,1.09]
Colin 1981	23/25	22/27		10.98%	1.13[0.91,1.4]
Klauber 1982	15/18	12/20		5.71%	1.39[0.92,2.1]
McCulley 1982	25/30	29/34		11.03%	0.98[0.79,1.21]
Kitano 1985	50/54	43/55		12.93%	1.18[1.01,1.39]
Abe 1987	18/18	5/9		3.63%	1.77[1.01,3.12]
Altinisik 1987	9/10	6/9		4.3%	1.35[0.81,2.24]
Kumar 1987	19/19	13/17		8.97%	1.3[0.99,1.71]
Maichuk 1988	35/39	43/63		11.49%	1.31[1.08,1.6]

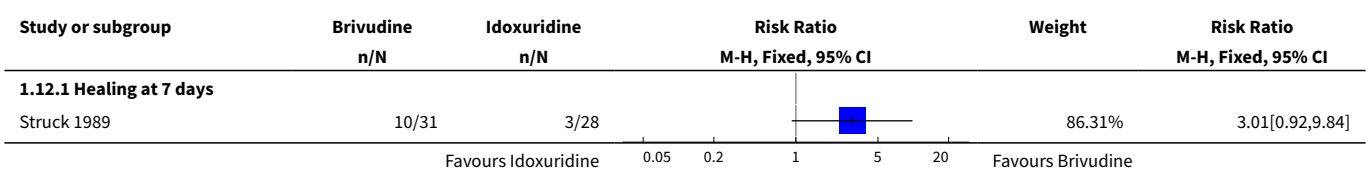
Favours Idoxuridine — Favours Acyclovir

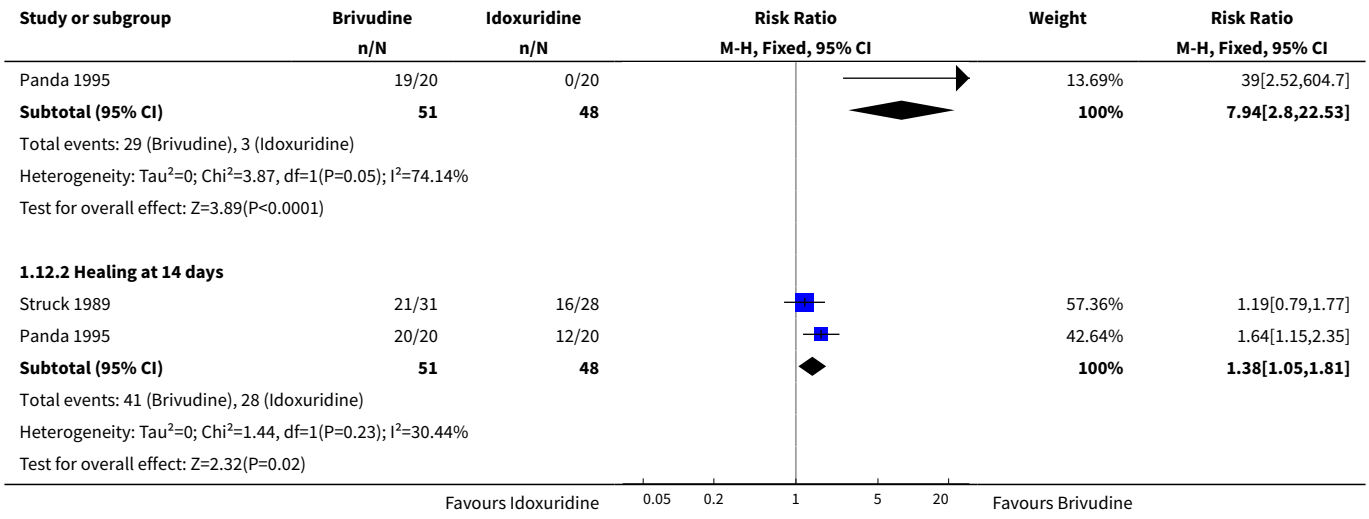


Analysis 1.11. Comparison 1 Topical antiviral agents, Outcome 11 Acyclovir *versus* idoxuridine: healing rate.

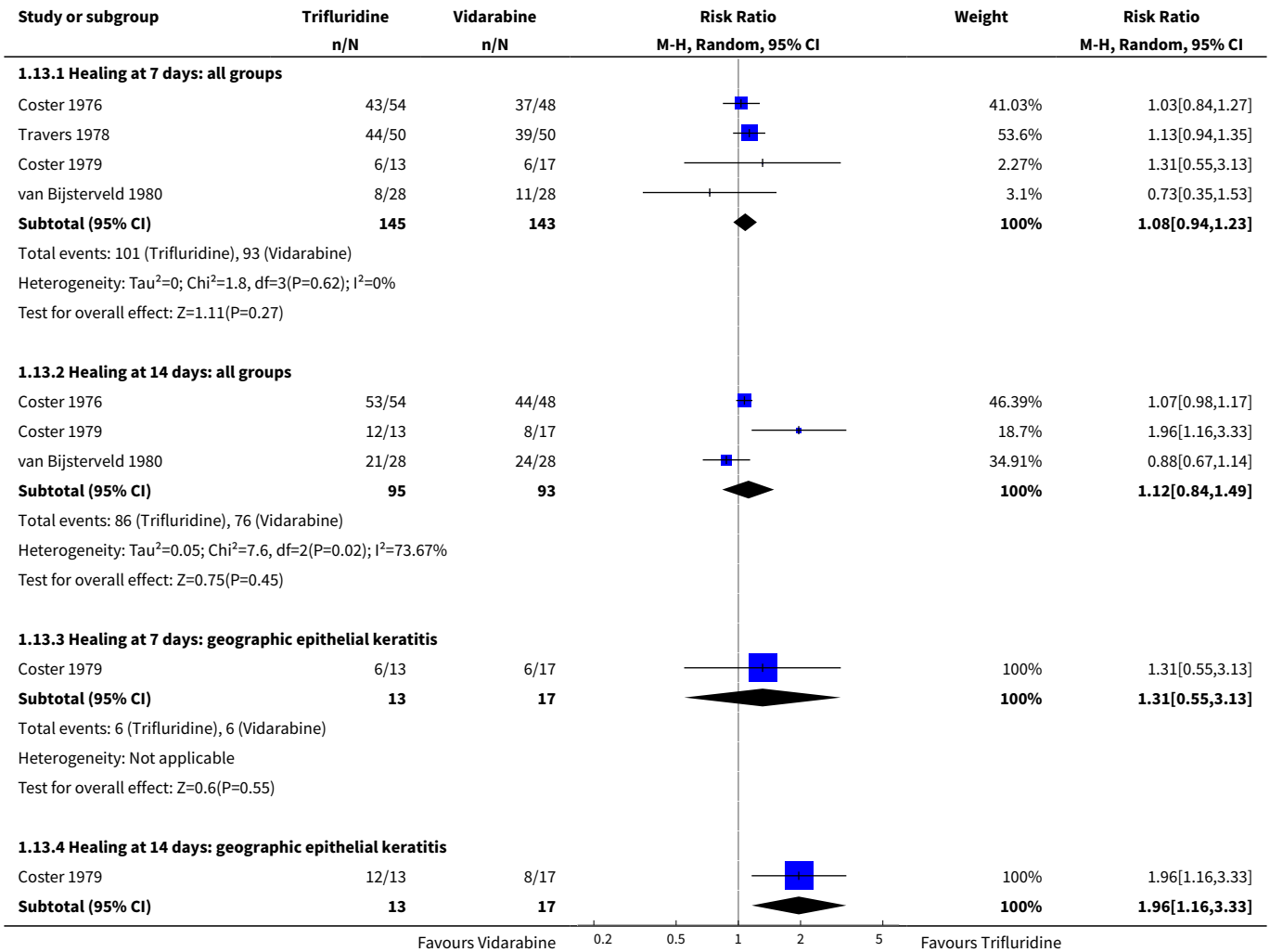


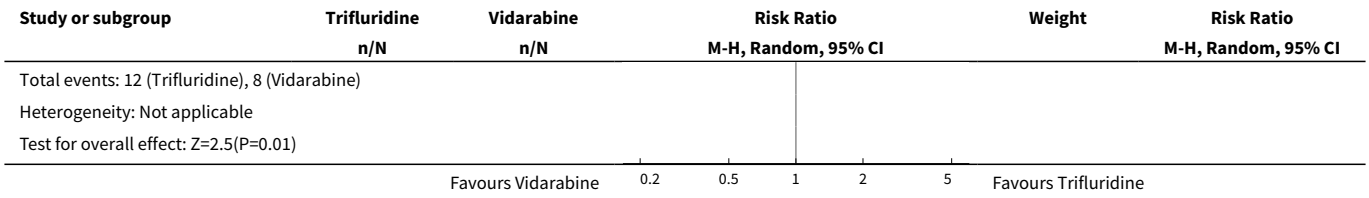
Analysis 1.12. Comparison 1 Topical antiviral agents, Outcome 12 Brivudine *versus* idoxuridine: 7-day & 14-day healing.



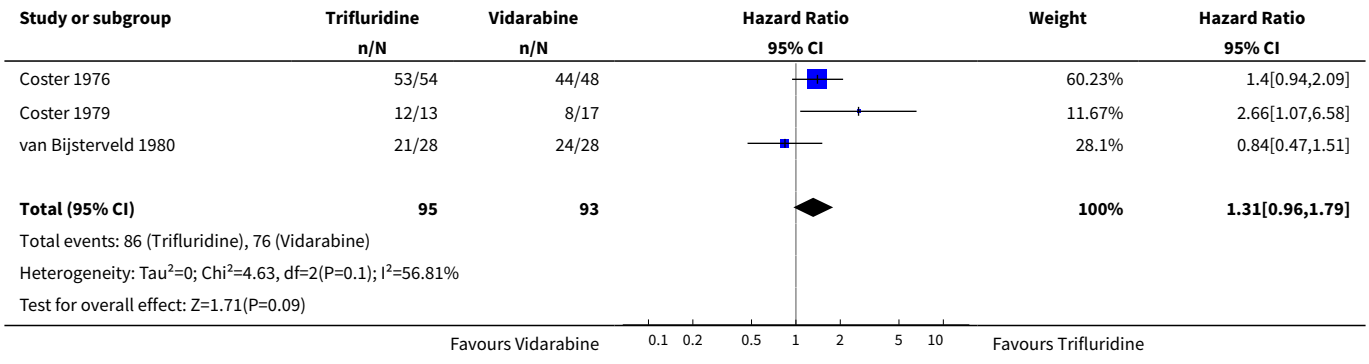


Analysis 1.13. Comparison 1 Topical antiviral agents, Outcome 13 Trifluridine *versus* vidarabine: 7-day & 14-day healing.

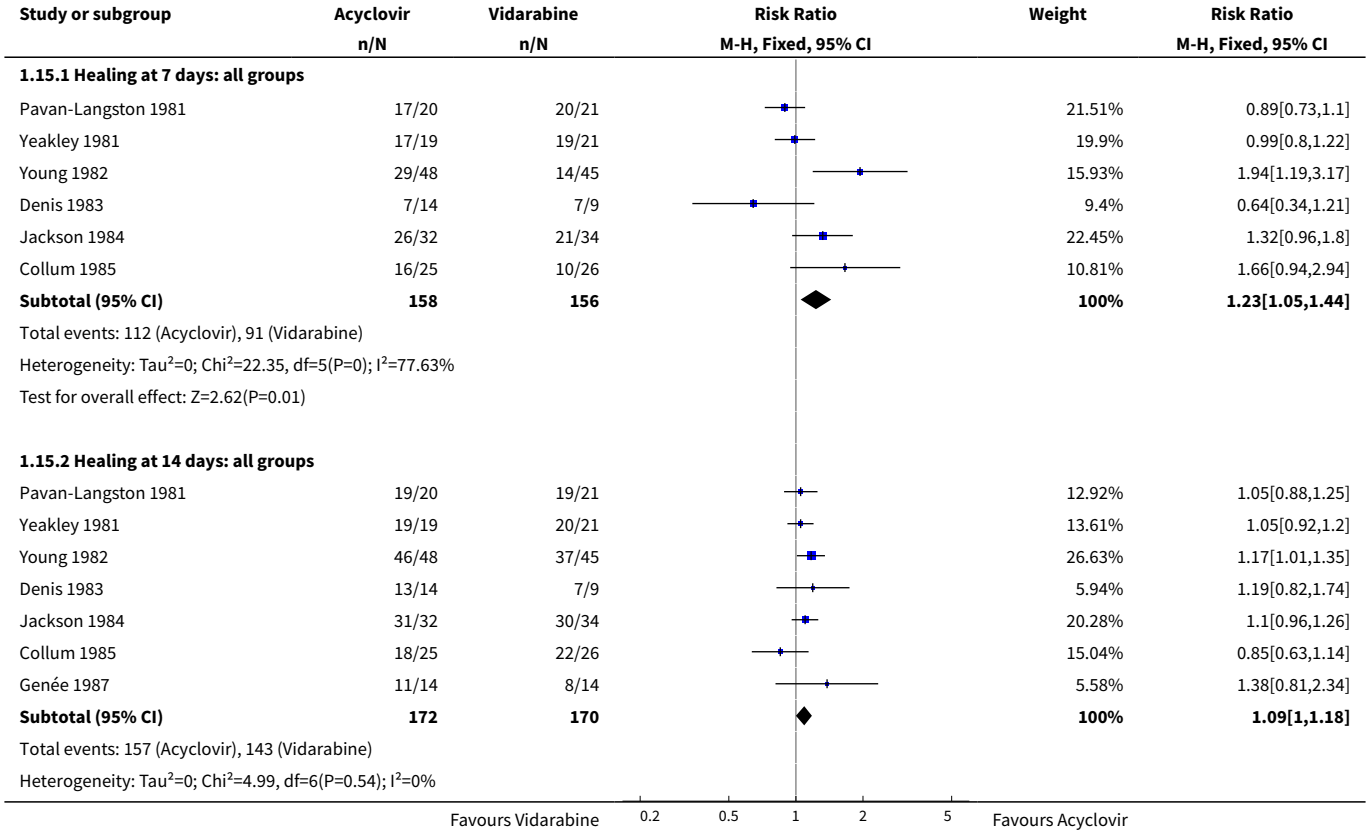


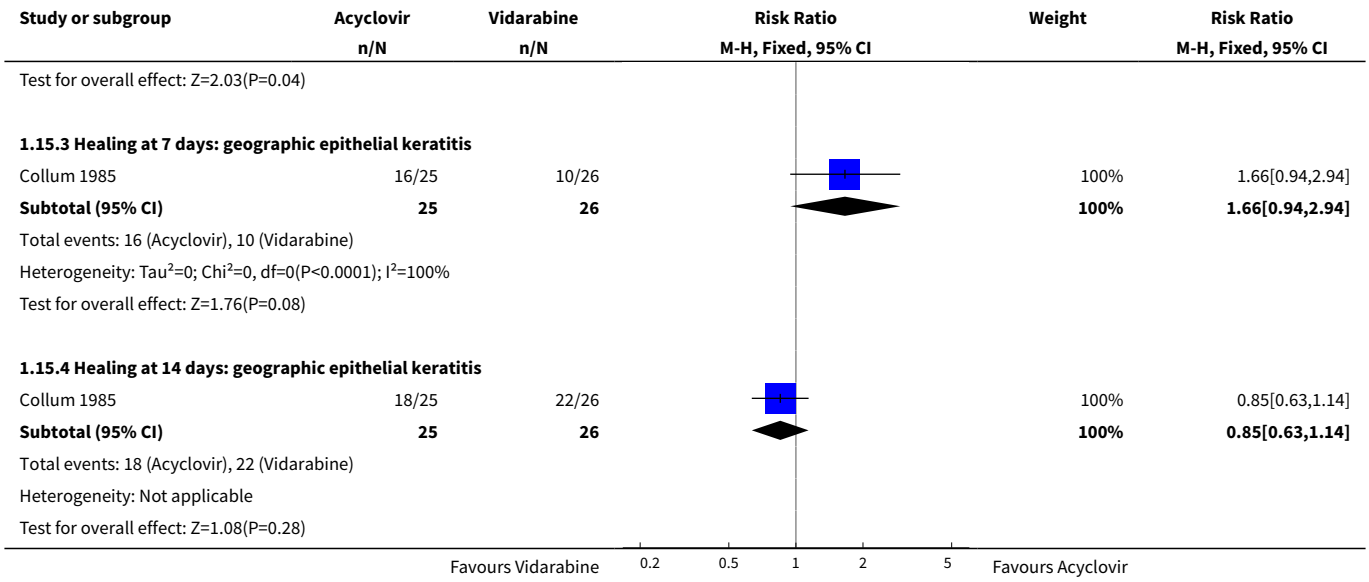


Analysis 1.14. Comparison 1 Topical antiviral agents, Outcome 14 Trifluridine *versus* vidarabine: healing rate.

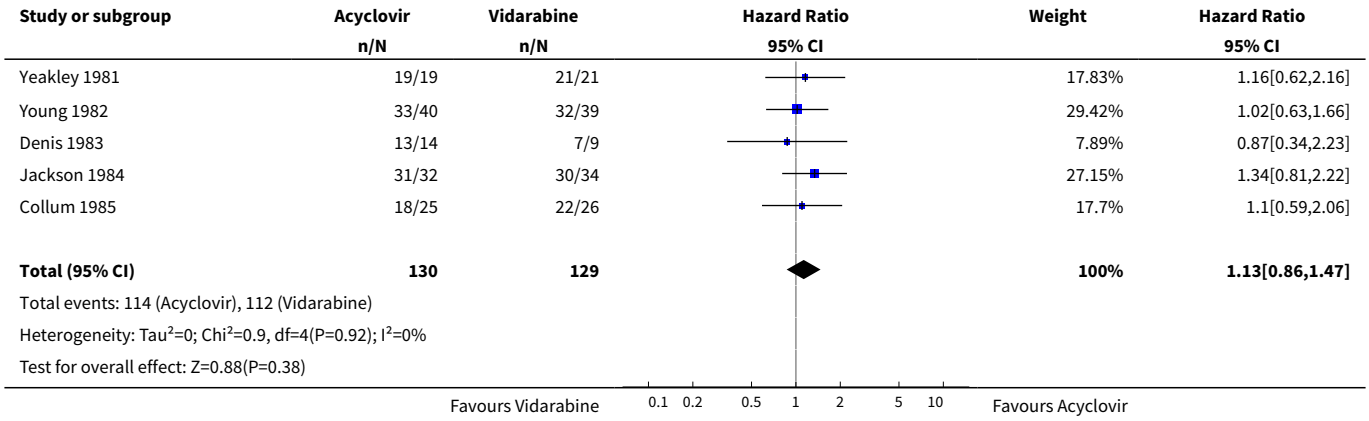


Analysis 1.15. Comparison 1 Topical antiviral agents, Outcome 15 Acyclovir *versus* vidarabine: 7-day & 14-day healing.

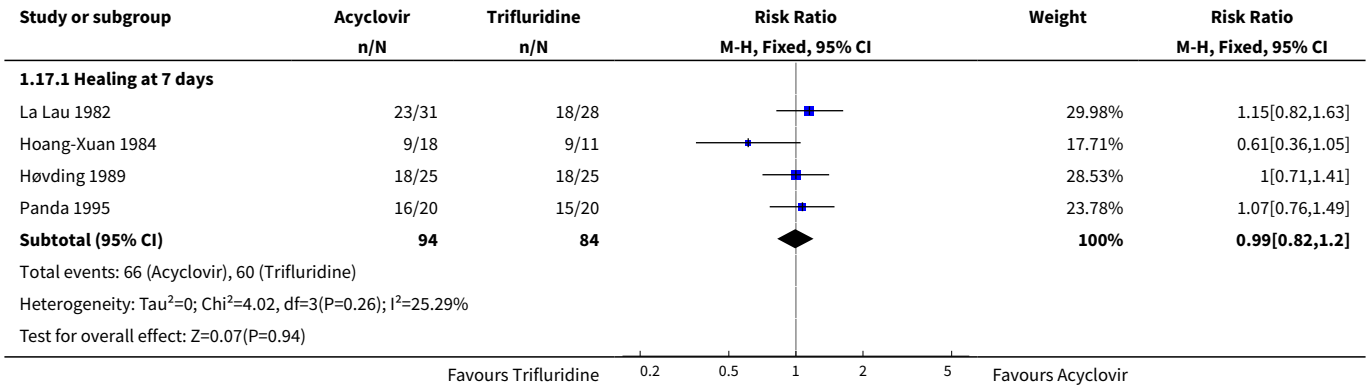


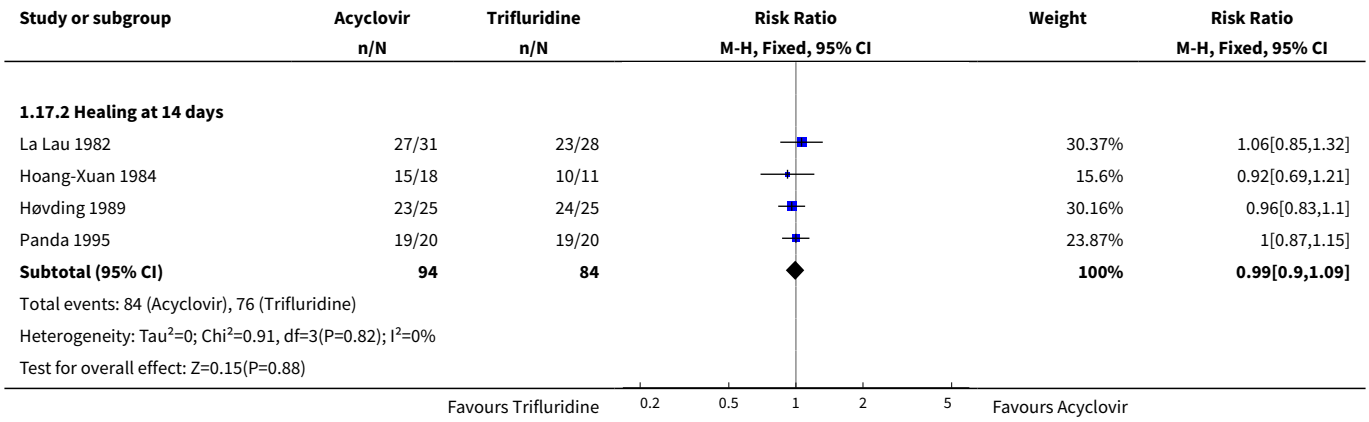


Analysis 1.16. Comparison 1 Topical antiviral agents, Outcome 16 Acyclovir *versus* vidarabine: healing rate.

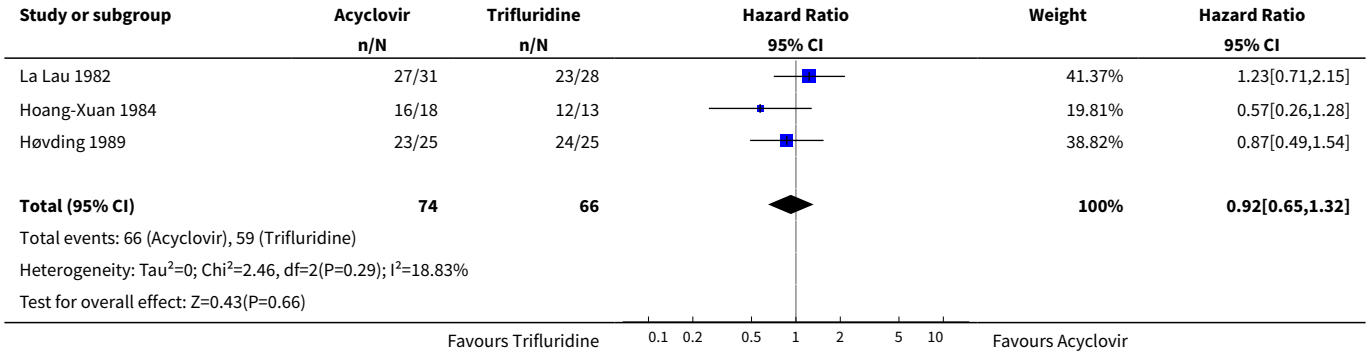


Analysis 1.17. Comparison 1 Topical antiviral agents, Outcome 17 Acyclovir *versus* trifluridine: 7-day & 14-day healing.

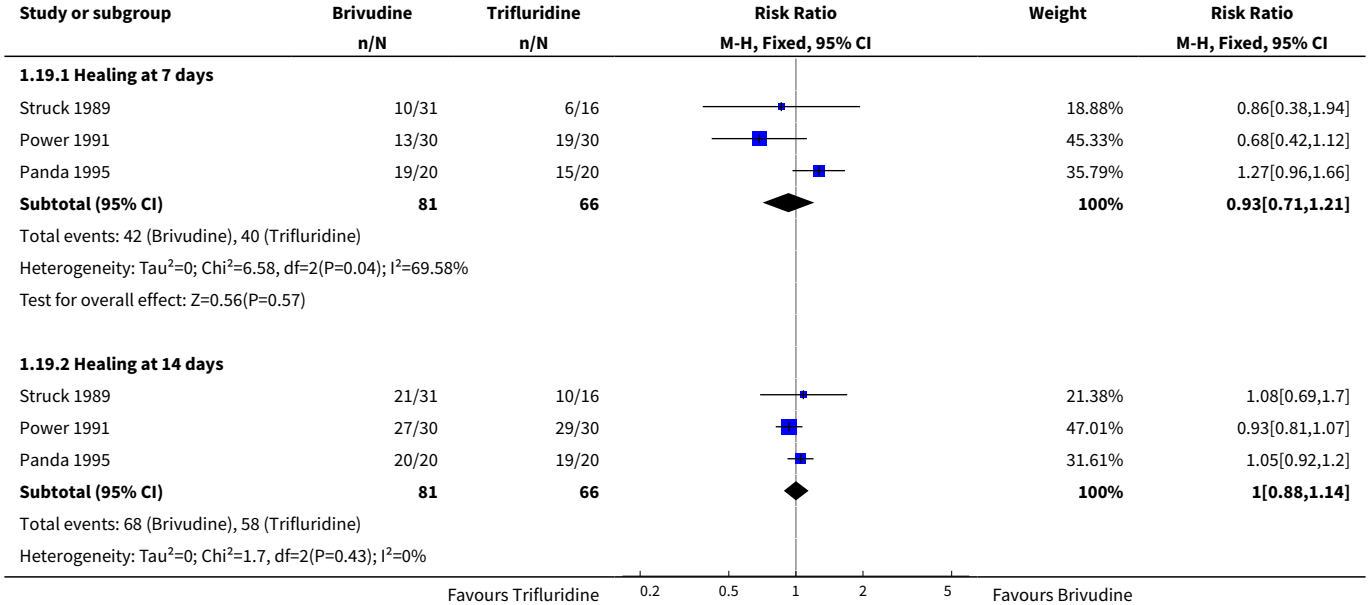


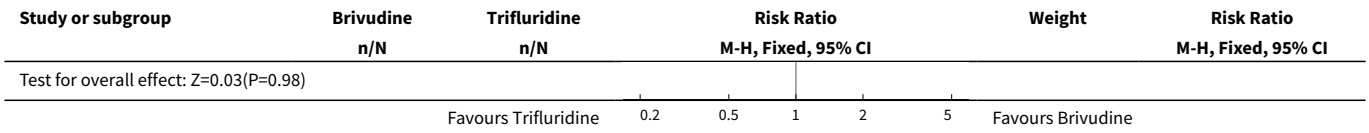


Analysis 1.18. Comparison 1 Topical antiviral agents, Outcome 18 Acyclovir *versus* trifluridine: healing rate.

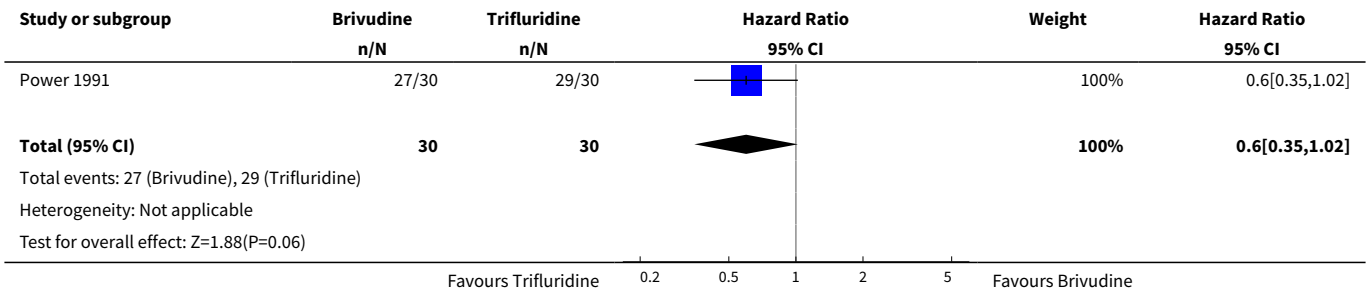


Analysis 1.19. Comparison 1 Topical antiviral agents, Outcome 19 Brivudine *versus* trifluridine: 7-day & 14-day healing.

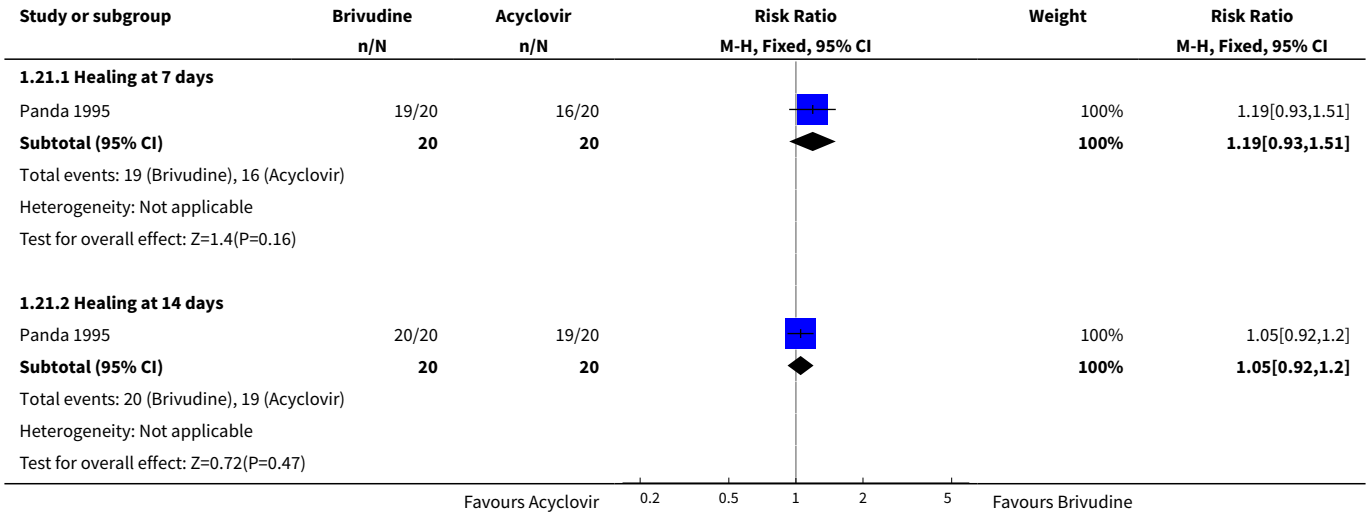




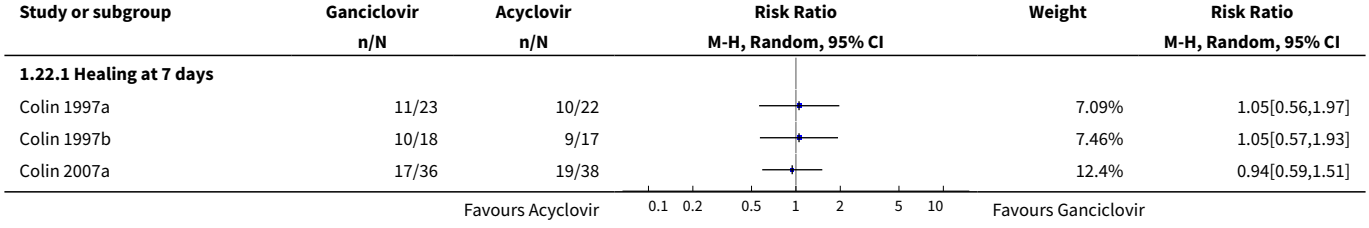
Analysis 1.20. Comparison 1 Topical antiviral agents, Outcome 20 Brivudine *versus* trifluridine: healing rate.

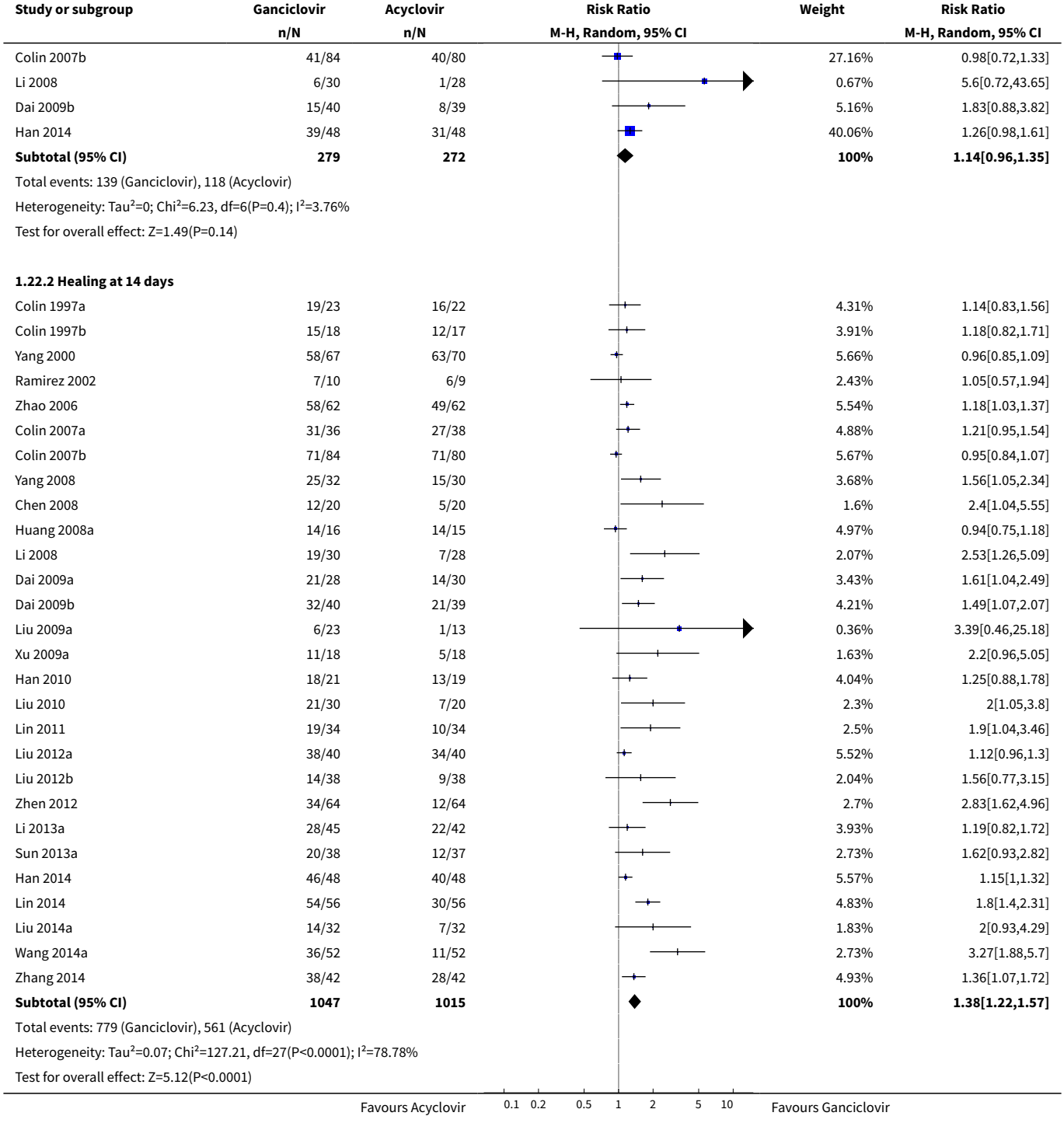


Analysis 1.21. Comparison 1 Topical antiviral agents, Outcome 21 Brivudine *versus* acyclovir: 7-day & 14-day healing.



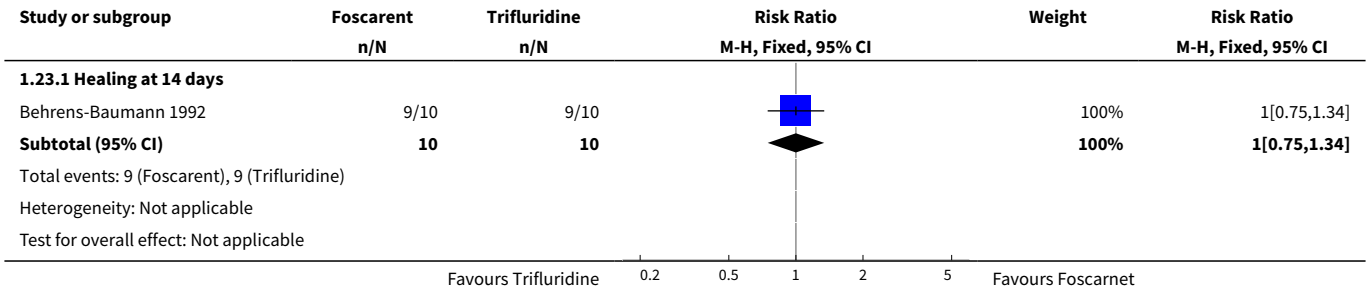
Analysis 1.22. Comparison 1 Topical antiviral agents, Outcome 22 Ganciclovir *versus* acyclovir: 7-day & 14-day healing.



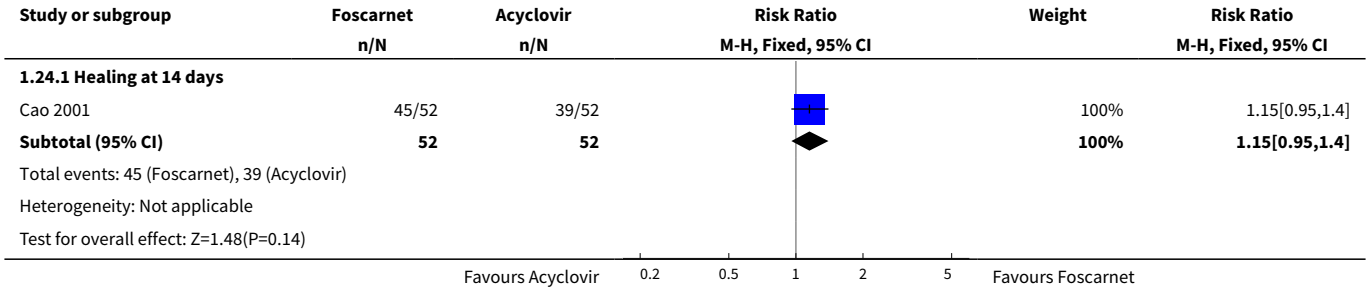


Study or subgroup	Ganciclovir n/N	Acyclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Colin 2007b	41/84	40/80		27.16%	0.98[0.72,1.33]
Li 2008	6/30	1/28		0.67%	5.6[0.72,43.65]
Dai 2009b	15/40	8/39		5.16%	1.83[0.88,3.82]
Han 2014	39/48	31/48		40.06%	1.26[0.98,1.61]
Subtotal (95% CI)	**279**	**272**		**100%**	**1.14[0.96,1.35]**
Total events: 139 (Ganciclovir), 118 (Acyclovir)					
Heterogeneity: Tau^2=0; Chi^2=6.23, df=6(P=0.4); I^2=3.76%					
Test for overall effect: Z=1.49(P=0.14)					
1.22.2 Healing at 14 days					
Colin 1997a	19/23	16/22		4.31%	1.14[0.83,1.56]
Colin 1997b	15/18	12/17		3.91%	1.18[0.82,1.71]
Yang 2000	58/67	63/70		5.66%	0.96[0.85,1.09]
Ramirez 2002	7/10	6/9		2.43%	1.05[0.57,1.94]
Zhao 2006	58/62	49/62		5.54%	1.18[1.03,1.37]
Colin 2007a	31/36	27/38		4.88%	1.21[0.95,1.54]
Colin 2007b	71/84	71/80		5.67%	0.95[0.84,1.07]
Yang 2008	25/32	15/30		3.68%	1.56[1.05,2.34]
Chen 2008	12/20	5/20		1.6%	2.4[1.04,5.55]
Huang 2008a	14/16	14/15		4.97%	0.94[0.75,1.18]
Li 2008	19/30	7/28		2.07%	2.53[1.26,5.09]
Dai 2009a	21/28	14/30		3.43%	1.61[1.04,2.49]
Dai 2009b	32/40	21/39		4.21%	1.49[1.07,2.07]
Liu 2009a	6/23	1/13		0.36%	3.39[0.46,25.18]
Xu 2009a	11/18	5/18		1.63%	2.2[0.96,5.05]
Han 2010	18/21	13/19		4.04%	1.25[0.88,1.78]
Liu 2010	21/30	7/20		2.3%	2[1.05,3.8]
Lin 2011	19/34	10/34		2.5%	1.9[1.04,3.46]
Liu 2012a	38/40	34/40		5.52%	1.12[0.96,1.3]
Liu 2012b	14/38	9/38		2.04%	1.56[0.77,3.15]
Zhen 2012	34/64	12/64		2.7%	2.83[1.62,4.96]
Li 2013a	28/45	22/42		3.93%	1.19[0.82,1.72]
Sun 2013a	20/38	12/37		2.73%	1.62[0.93,2.82]
Han 2014	46/48	40/48		5.57%	1.15[1,1.32]
Lin 2014	54/56	30/56		4.83%	1.8[1.4,2.31]
Liu 2014a	14/32	7/32		1.83%	2[0.93,4.29]
Wang 2014a	36/52	11/52		2.73%	3.27[1.88,5.7]
Zhang 2014	38/42	28/42		4.93%	1.36[1.07,1.72]
Subtotal (95% CI)	**1047**	**1015**		**100%**	**1.38[1.22,1.57]**
Total events: 779 (Ganciclovir), 561 (Acyclovir)					
Heterogeneity: Tau^2=0.07; Chi^2=127.21, df=27(P<0.0001); I^2=78.78%					
Test for overall effect: Z=5.12(P<0.0001)					

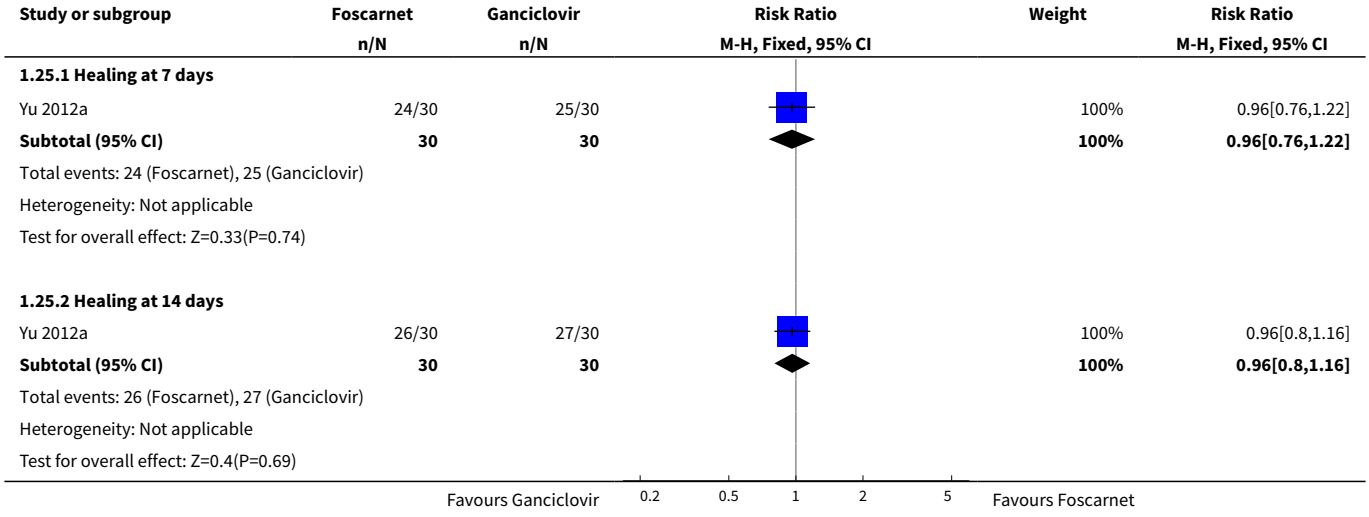
Analysis 1.23. Comparison 1 Topical antiviral agents, Outcome 23 Foscarnet *versus* trifluridine: 7-day & 14-day healing.



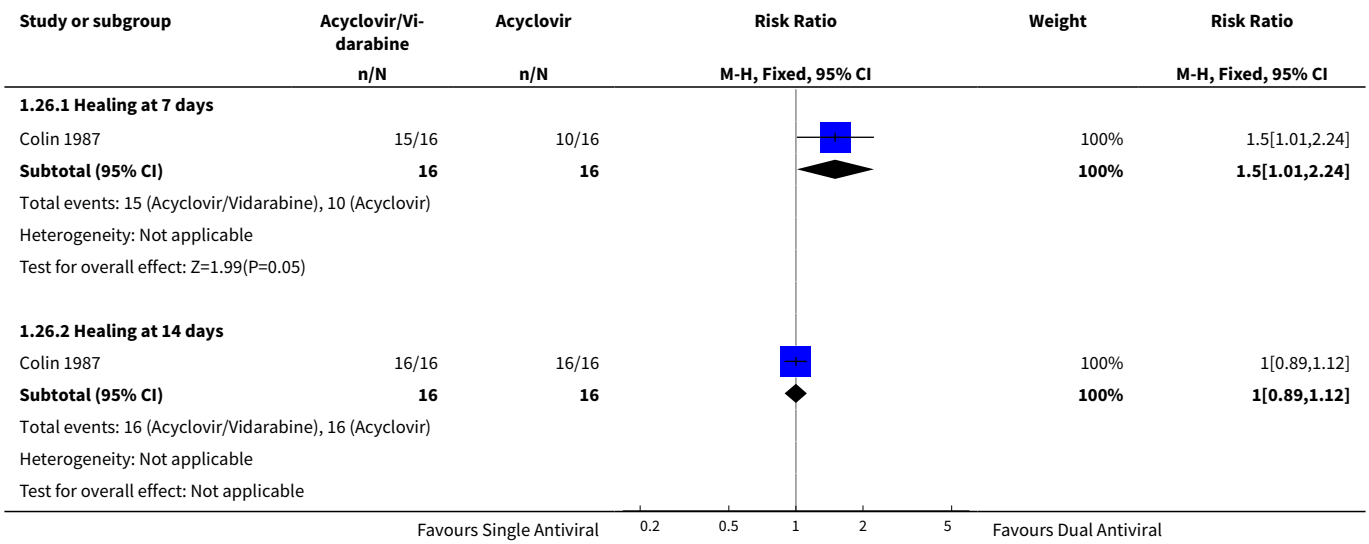
Analysis 1.24. Comparison 1 Topical antiviral agents, Outcome 24 Foscarnet *versus* acyclovir: 14-day healing.



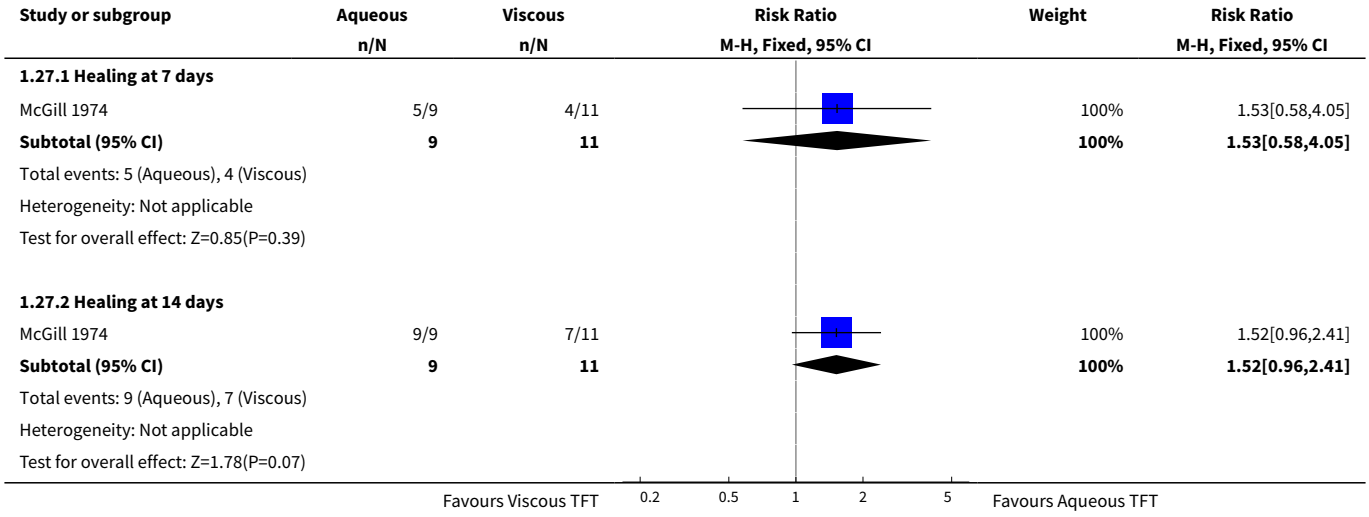
Analysis 1.25. Comparison 1 Topical antiviral agents, Outcome 25 Foscarnet *versus* ganciclovir: 7-day & 14-day healing.



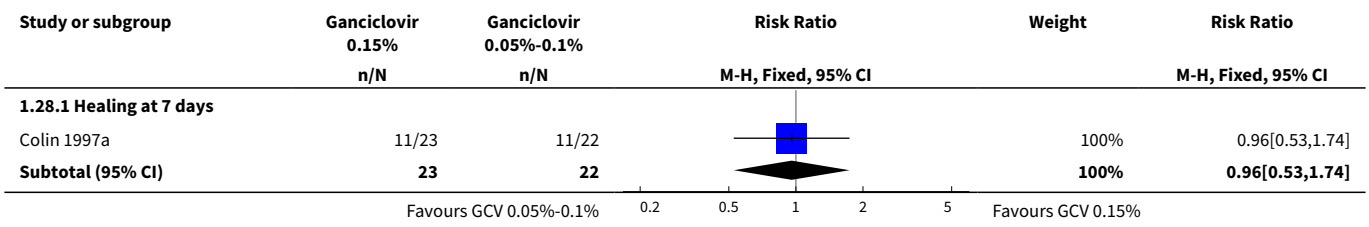
Analysis 1.26. Comparison 1 Topical antiviral agents, Outcome 26 Acyclovir/vidarabine *versus* acyclovir: 7-day & 14-day healing.

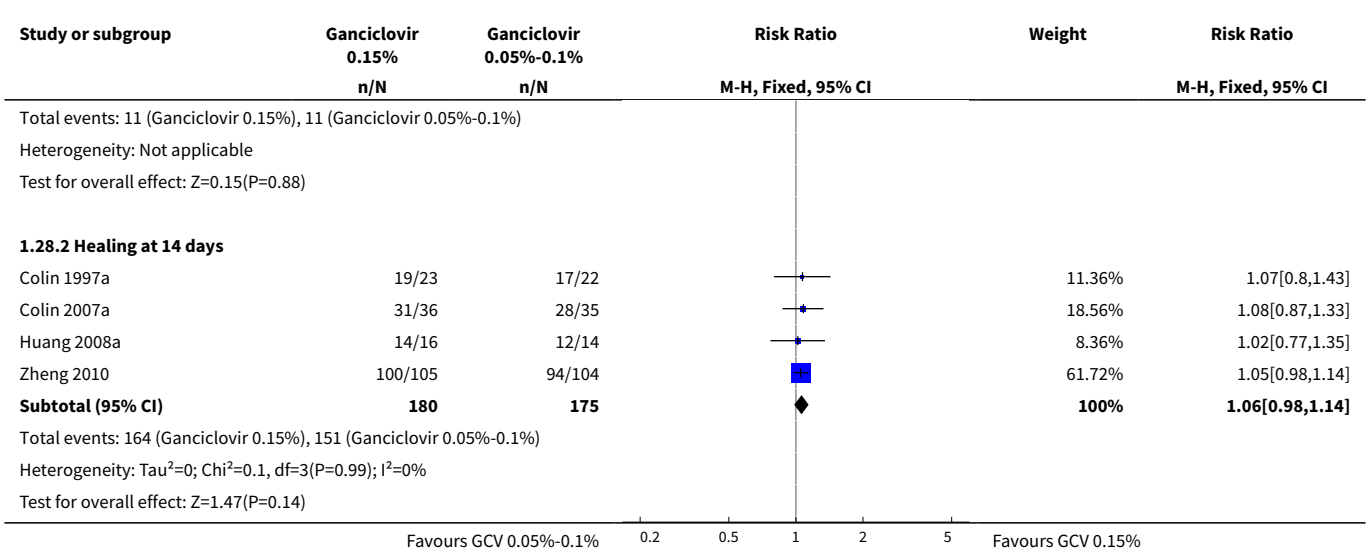


Analysis 1.27. Comparison 1 Topical antiviral agents, Outcome 27 Trifluridine (aqueous) *versus* trifluridine (viscous).



Analysis 1.28. Comparison 1 Topical antiviral agents, Outcome 28 Ganciclovir 0.15% gel *versus* ganciclovir 0.05% gel or 0.1% solution.

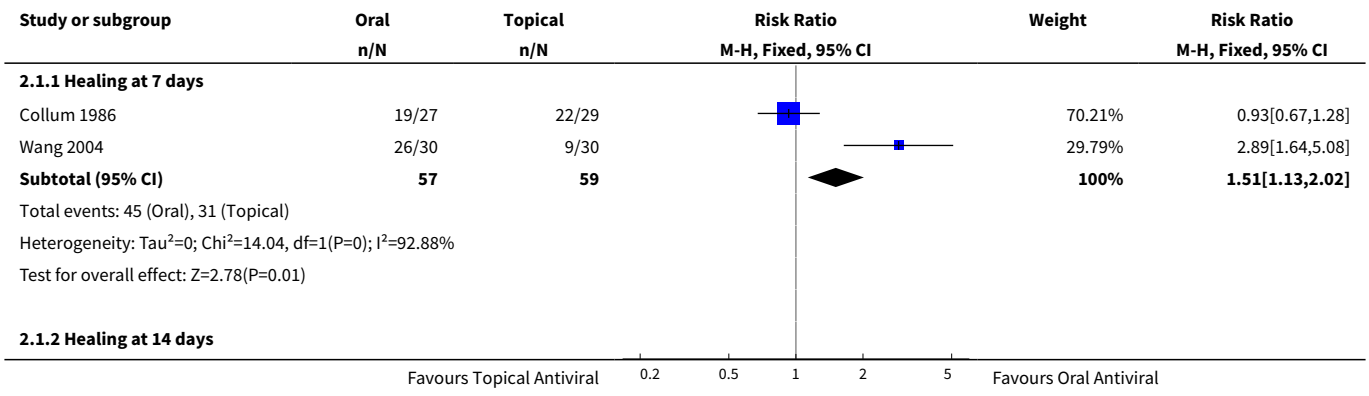


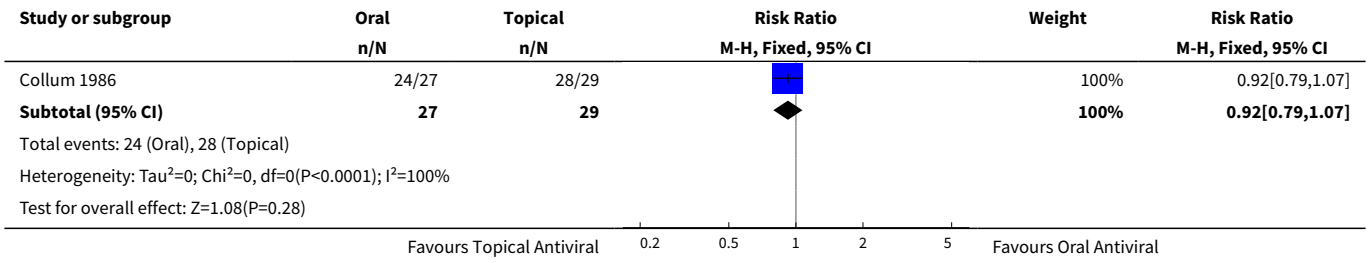


Comparison 2. Oral antiviral agents

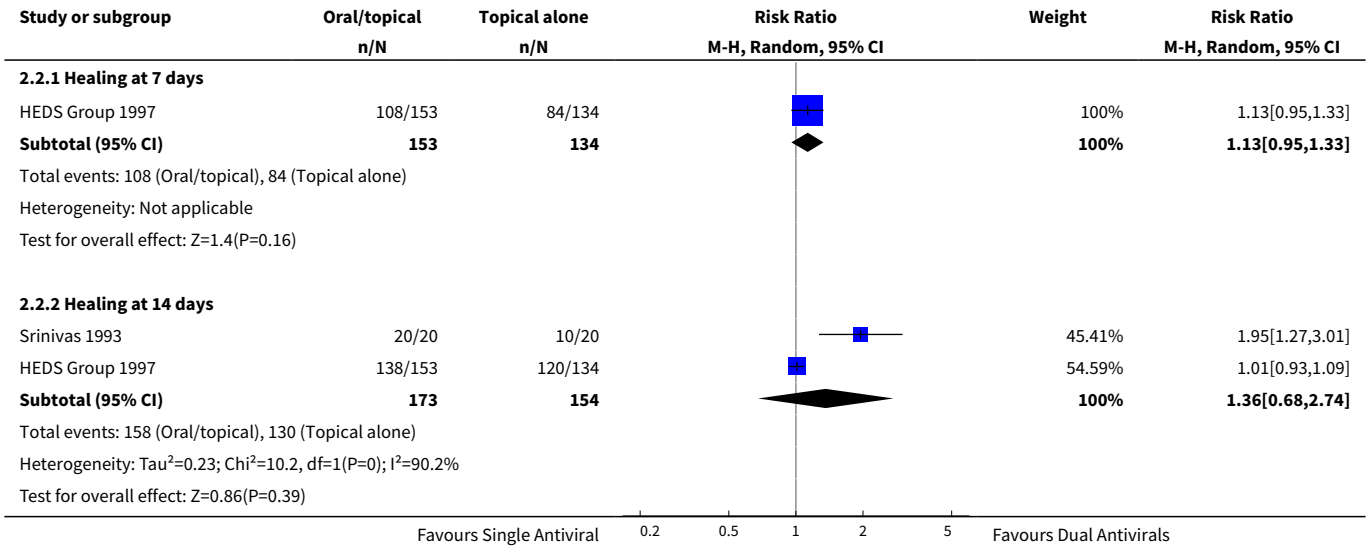
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral antiviral *versus* topical antiviral	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healing at 7 days	2	116	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.13, 2.02]
1.2 Healing at 14 days	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.07]
2 Oral/topical antivirals *versus* topical antiviral	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Healing at 7 days	1	287	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.95, 1.33]
2.2 Healing at 14 days	2	327	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.68, 2.74]

Analysis 2.1. Comparison 2 Oral antiviral agents, Outcome 1 Oral antiviral *versus* topical antiviral.





Analysis 2.2. Comparison 2 Oral antiviral agents, Outcome 2 Oral/topical antivirals *versus* topical antiviral.

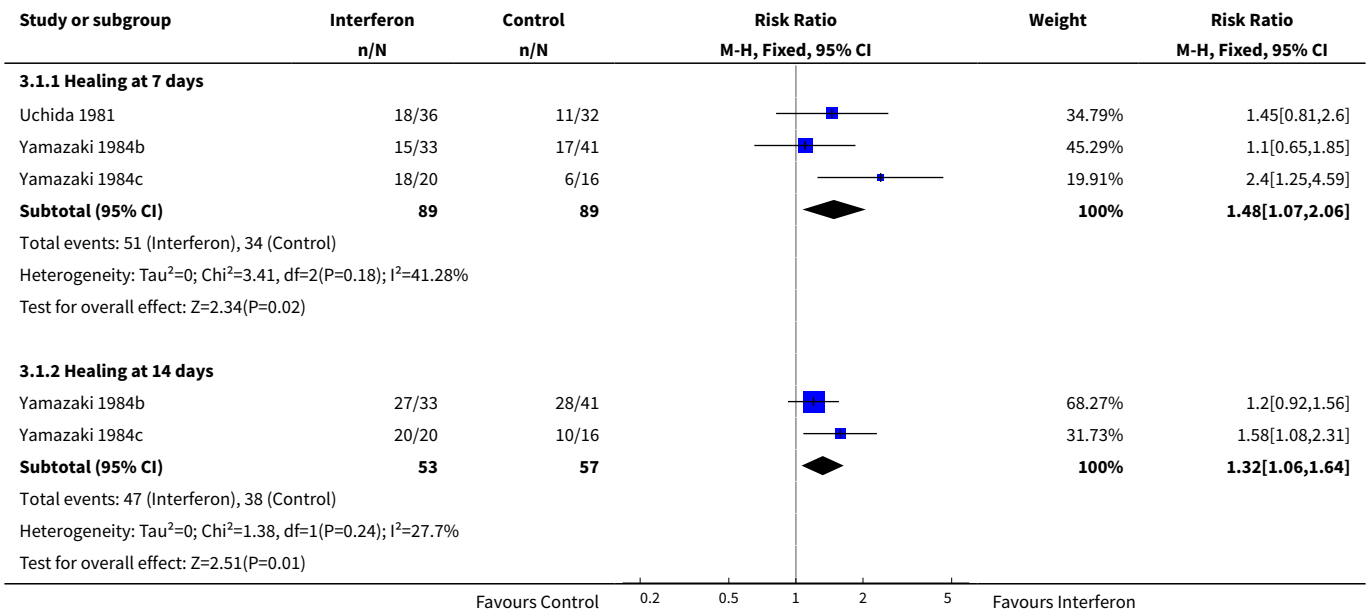


Comparison 3. Interferon

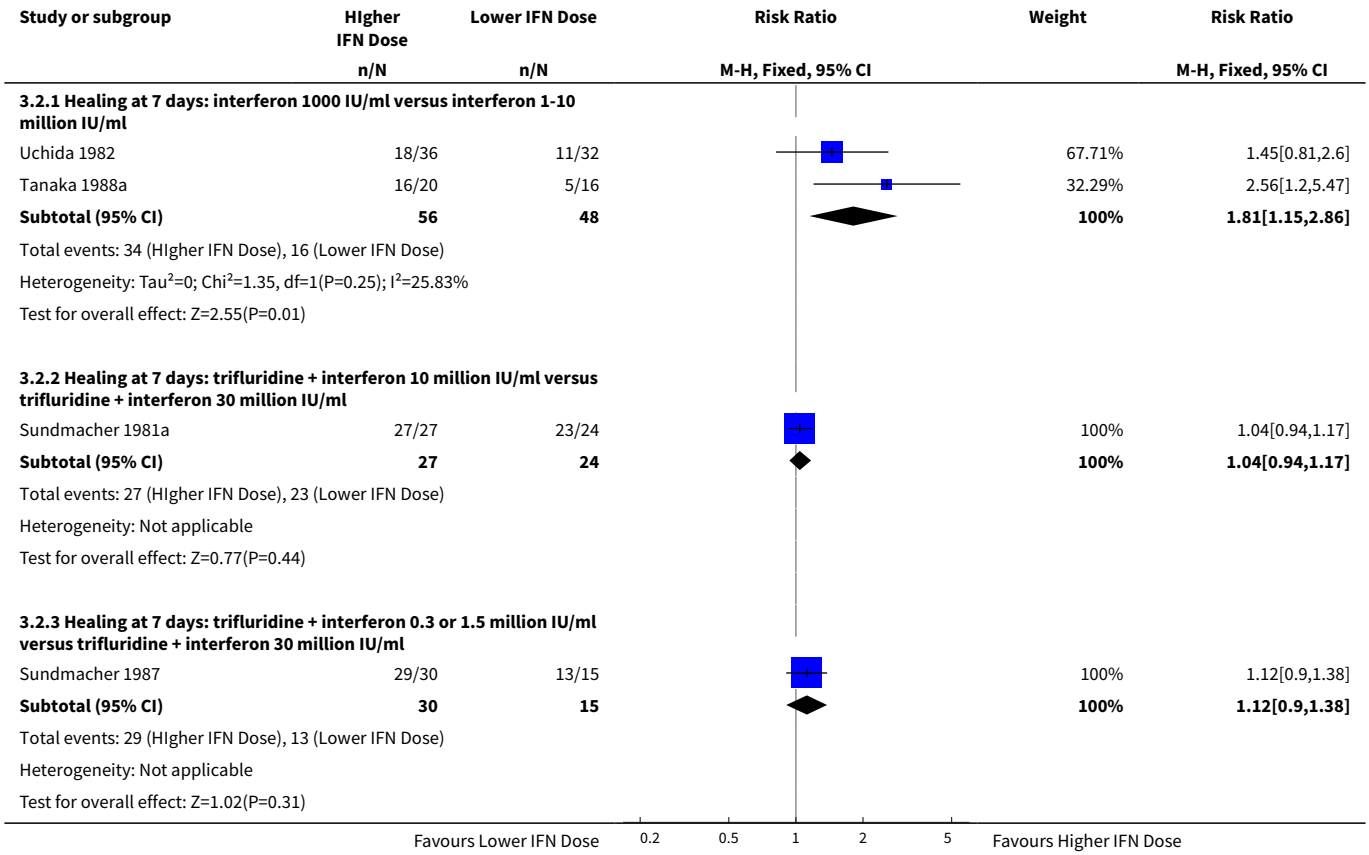
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Interferon *versus* inactive control, without or with debridement	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healing at 7 days	3	178	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.07, 2.06]
1.2 Healing at 14 days	2	110	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.06, 1.64]
2 Interferon dosages	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Healing at 7 days: interferon 1000 IU/ml *versus* interferon 1-10 million IU/ml	2	104	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.15, 2.86]

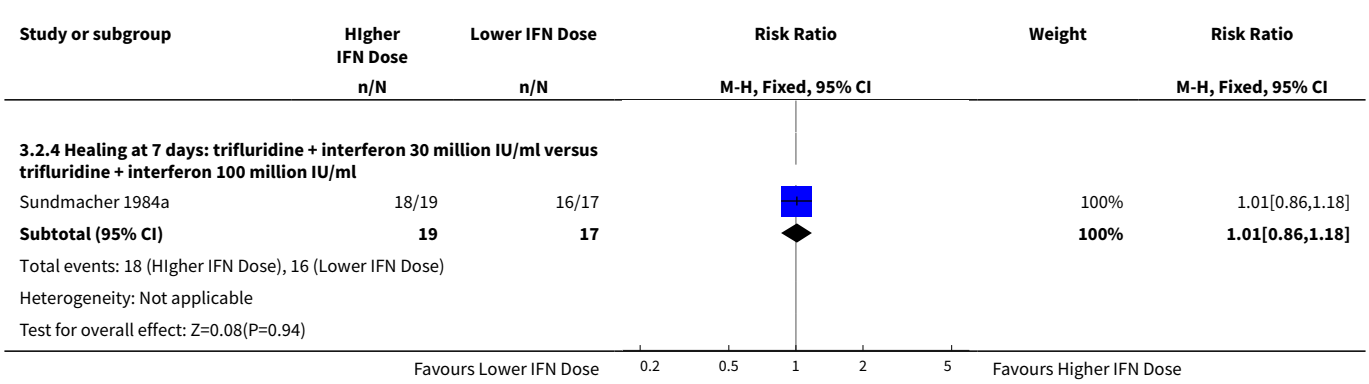
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Healing at 7 days: trifluridine + interferon 10 million IU/ml *versus* trifluridine + interferon 30 million IU/ml	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.94, 1.17]
2.3 Healing at 7 days: trifluridine + interferon 0.3 or 1.5 million IU/ml *versus* 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 *versus* 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 debridement *versus* interferon-β with debridement	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 *versus* 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 *versus* nucleoside antiviral	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Healing at 7 days	3	85	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.81, 1.21]
5.2 Healing at 14 days	4	222	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.91, 1.62]
6 Interferon inducer *versus* 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 *versus* nucleoside antiviral: 7-day & 14-day healing	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Healing at 7 days	9	475	Risk Ratio (M-H, Random, 95% CI)	1.85 [1.35, 2.55]
7.2 Healing at 14 days	12	718	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.99, 1.13]
8 Interferon/nucleoside antiviral *versus* nucleoside antiviral: healing rate	5	229	Hazard Ratio (95% CI)	2.84 [2.13, 3.79]

Analysis 3.1. Comparison 3 Interferon, Outcome 1 Interferon *versus* inactive control, without or with debridement.

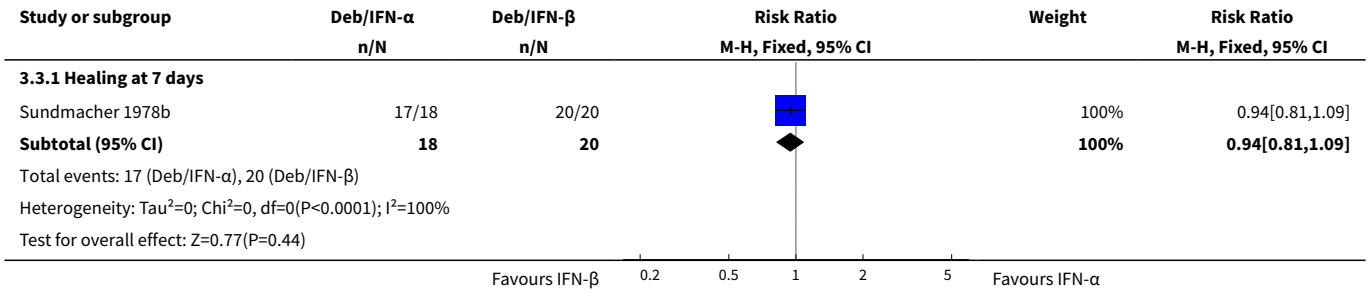


Analysis 3.2. Comparison 3 Interferon, Outcome 2 Interferon dosages.

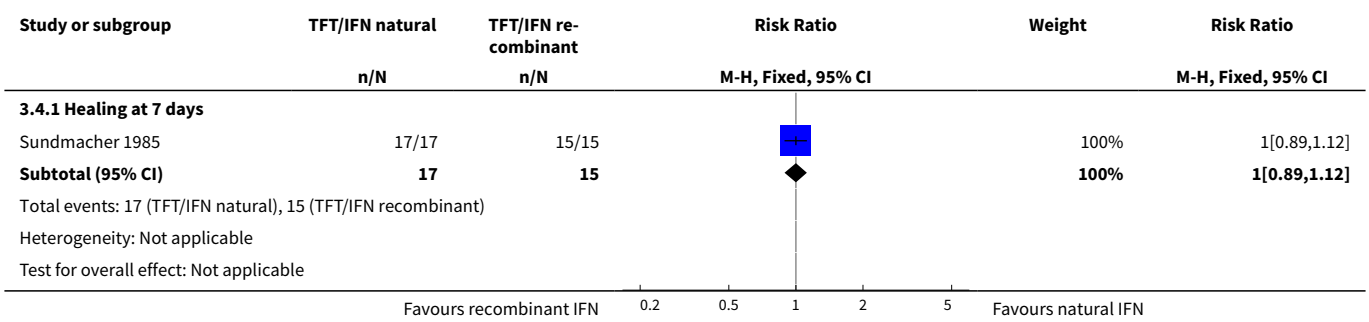




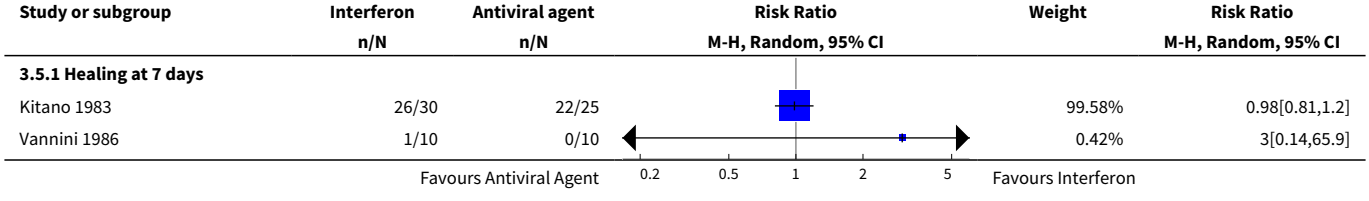
Analysis 3.3. Comparison 3 Interferon, Outcome 3 Interferon-α with debridement *versus* interferon-β with debridement.

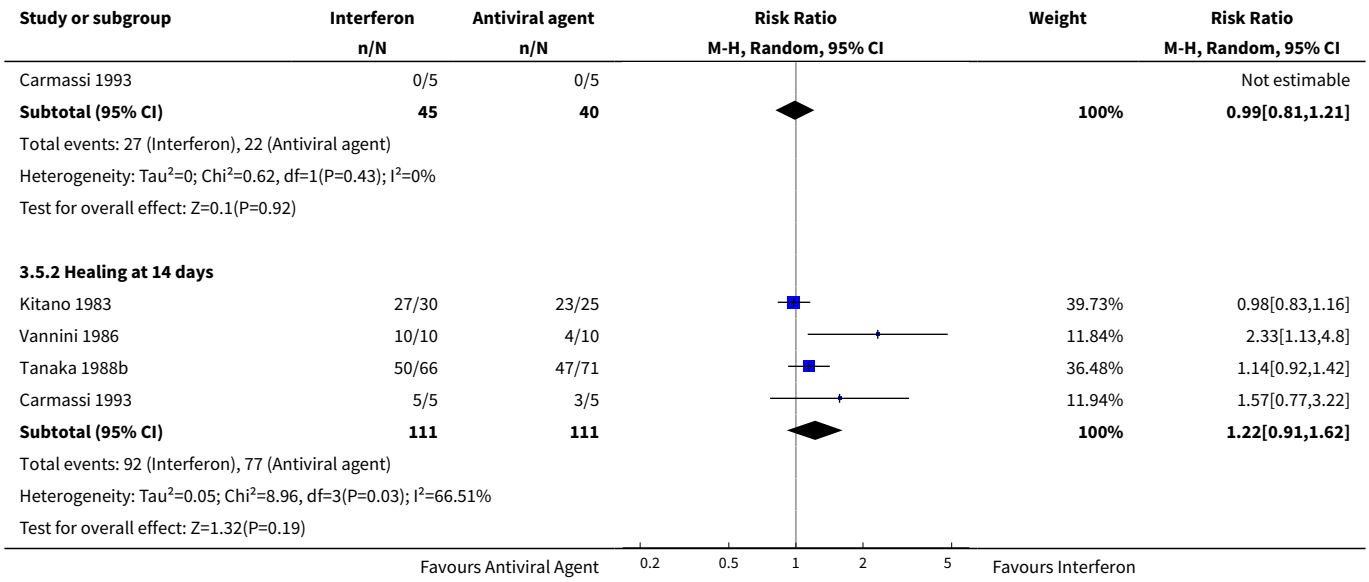


Analysis 3.4. Comparison 3 Interferon, Outcome 4 Natural interferon-α with trifluridine *versus* recombinant interferon-α with trifluridine.

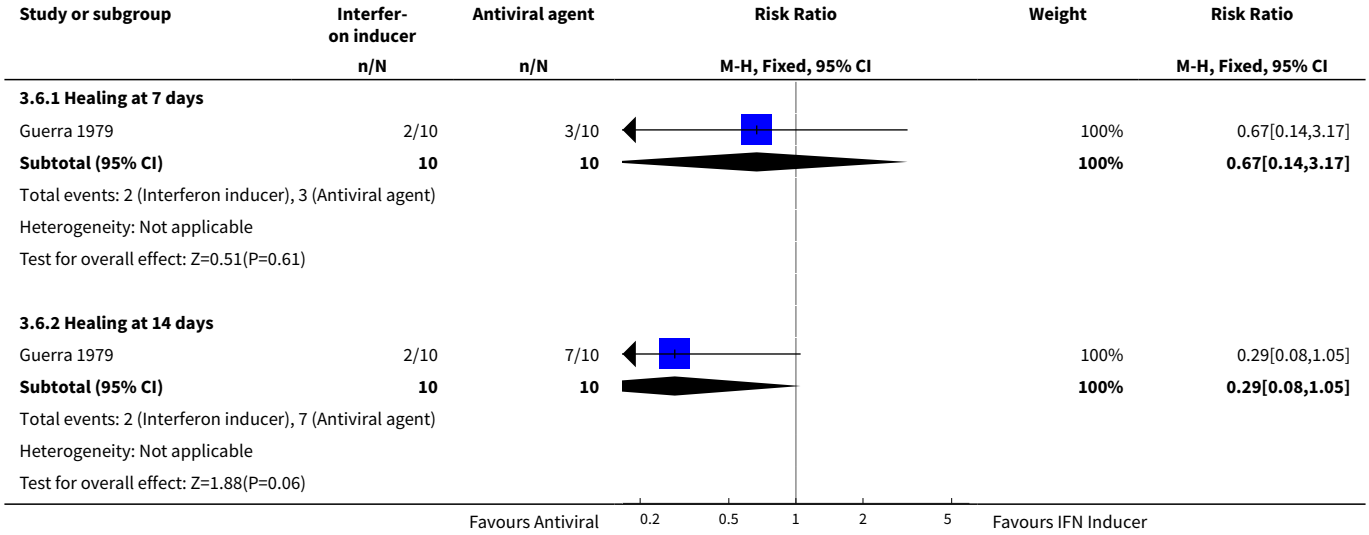


Analysis 3.5. Comparison 3 Interferon, Outcome 5 Interferon *versus* nucleoside antiviral.

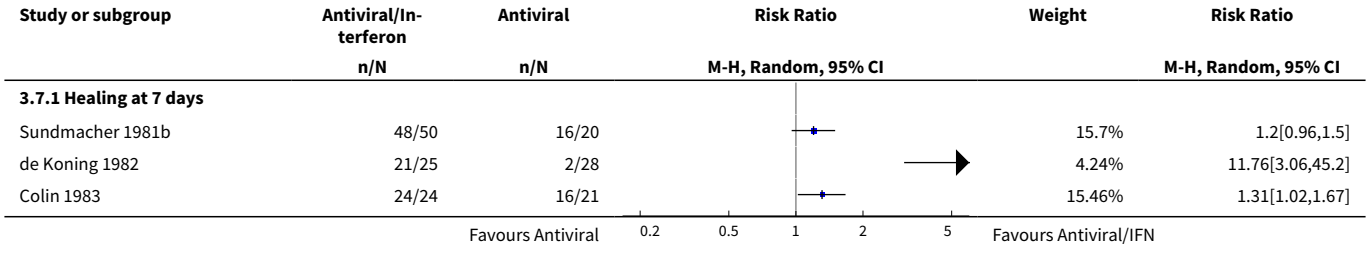


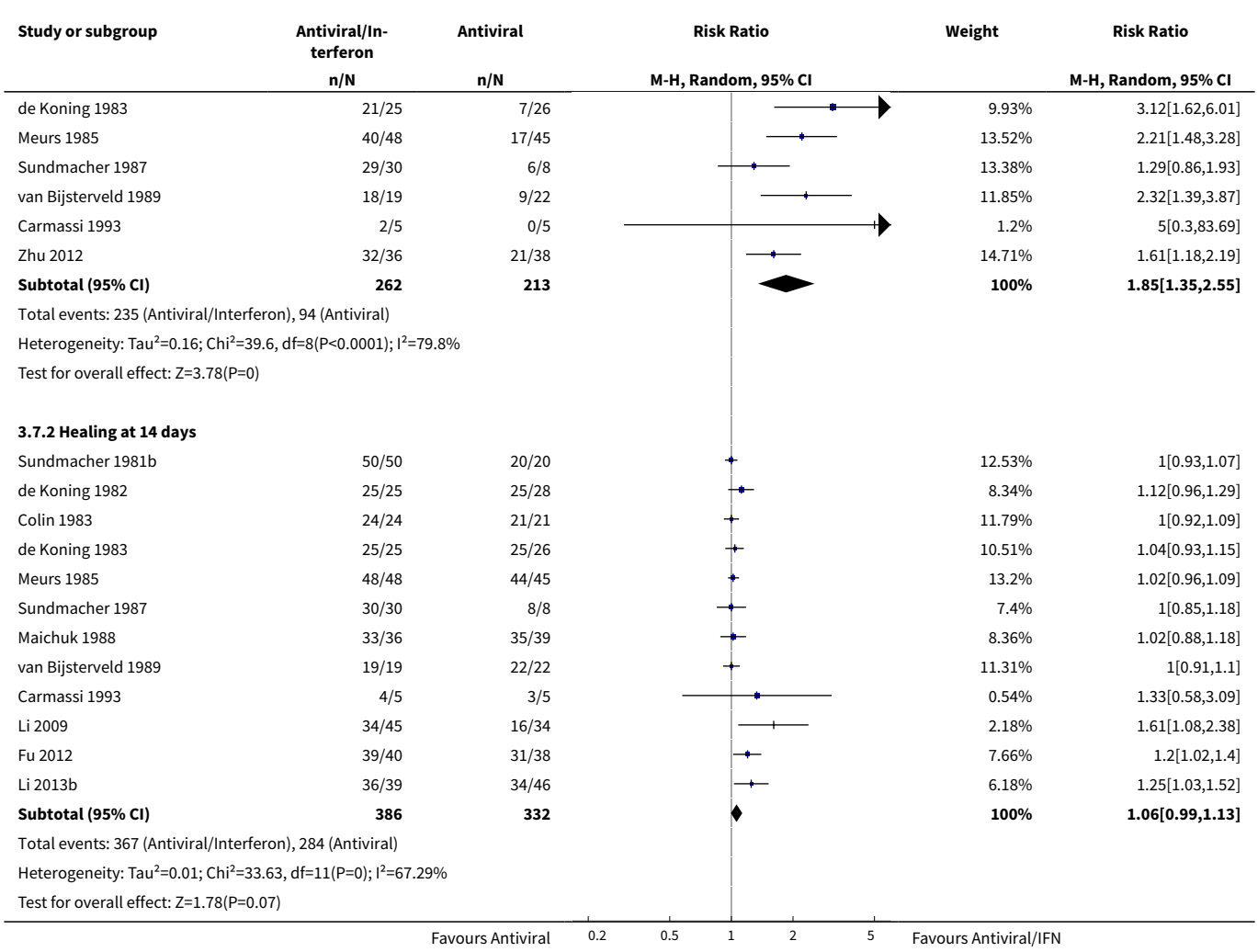


Analysis 3.6. Comparison 3 Interferon, Outcome 6 Interferon inducer *versus* nucleoside antiviral.

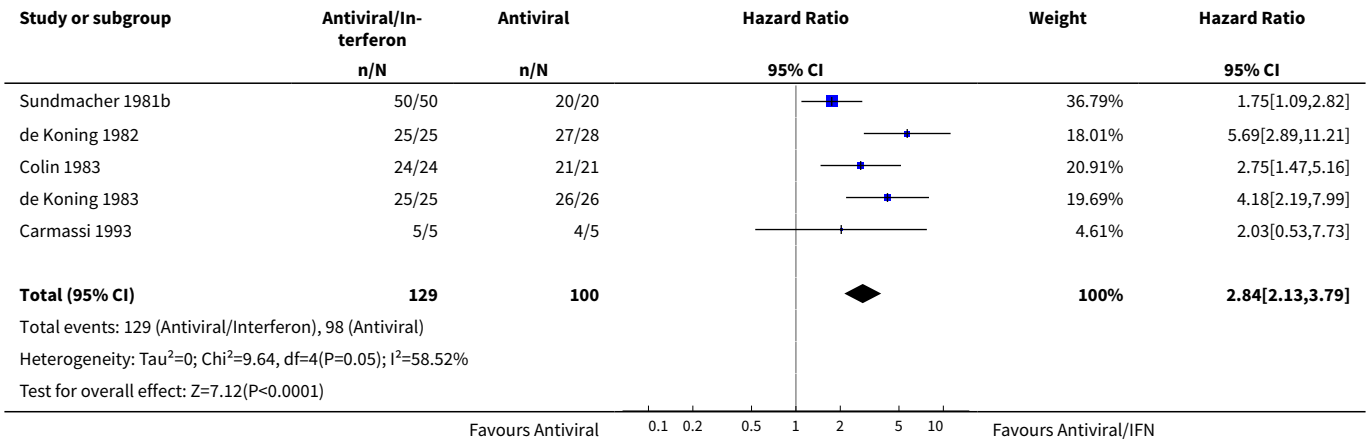


Analysis 3.7. Comparison 3 Interferon, Outcome 7 Interferon/ nucleoside antiviral *versus* nucleoside antiviral: 7-day & 14-day healing.





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

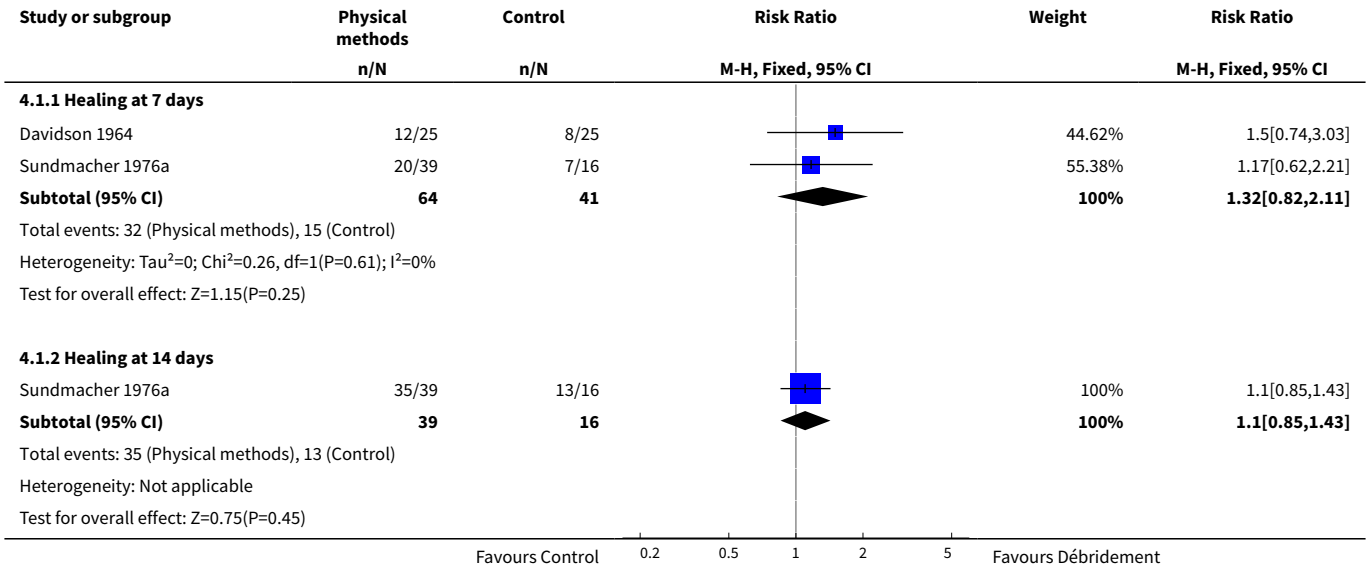


Comparison 4. Debridement

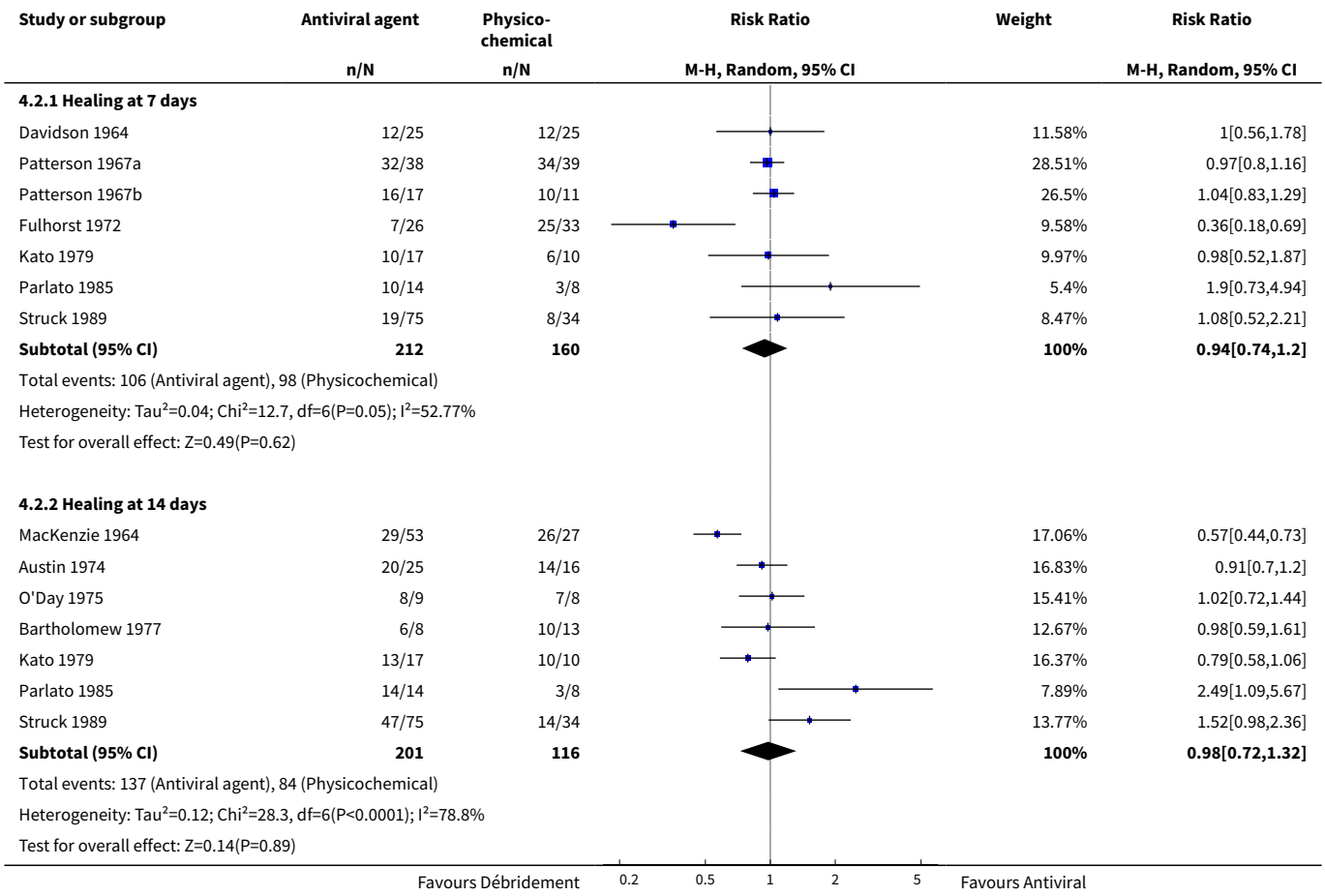
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Debridement *versus* control	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healing at 7 days	2	105	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.82, 2.11]
1.2 Healing at 14 days	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.85, 1.43]
2 Topical antiviral agent *versus* debridement	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Healing at 7 days	7	372	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.20]
2.2 Healing at 14 days	7	317	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.72, 1.32]
3 Different debridement methods	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Healing at 7 days: cryotherapy *versus* carbolisation	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.95, 2.31]
3.2 Healing at 7 days: cryotherapy/idoxuridine *versus* carbolisation/idoxuridine	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.99, 2.07]
3.3 Healing at 7 days: thermocautery/interferon *versus* wiping/interferon	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.13]
3.4 Healing at 7 days: iodinisation/panthenol *versus* cryotherapy/panthenol	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.66, 1.12]
3.5 Healing at 7 days: iodinisation/fluorophenylalanine *versus* cryotherapy/fluorophenylalanine	1	61	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.92, 1.46]
3.6 Healing at 14 days: thermocautery/interferon *versus* wiping/interferon	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.91, 1.10]
3.7 Healing at 14 days: iodinisation/panthenol *versus* cryotherapy/panthenol	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.73, 1.00]
3.8 Healing at 14 days: iodinisation/fluorophenylalanine *versus* cryotherapy/fluorophenylalanine	1	61	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.91, 1.14]
3.9 Healing at 14 days: photoinactivation *versus* carbolisation	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.41, 1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Debridement with antiviral or interferon *versus* debridement	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Healing at 7 days	8	347	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.94, 1.36]
4.2 Healing at 14 days	3	99	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.78, 2.00]
5 Debridement 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 Debridement with antiviral *versus* antiviral: 7-day & 14-day healing	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Healing at 7 days	7	305	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.84, 1.79]
6.2 Healing at 14 days	7	334	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.94, 1.17]
7 Debridement with antiviral *versus* antiviral: healing rate	6	248	Hazard Ratio (95% CI)	1.76 [1.32, 2.35]

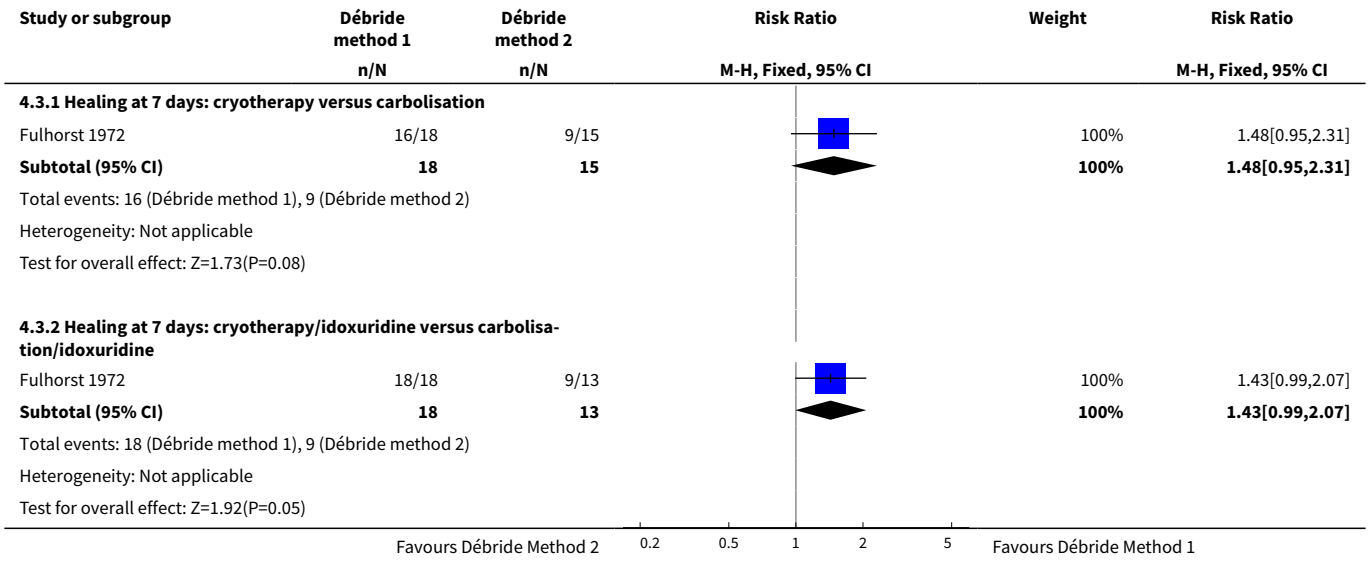
Analysis 4.1. Comparison 4 Debridement, Outcome 1 Debridement *versus* control.

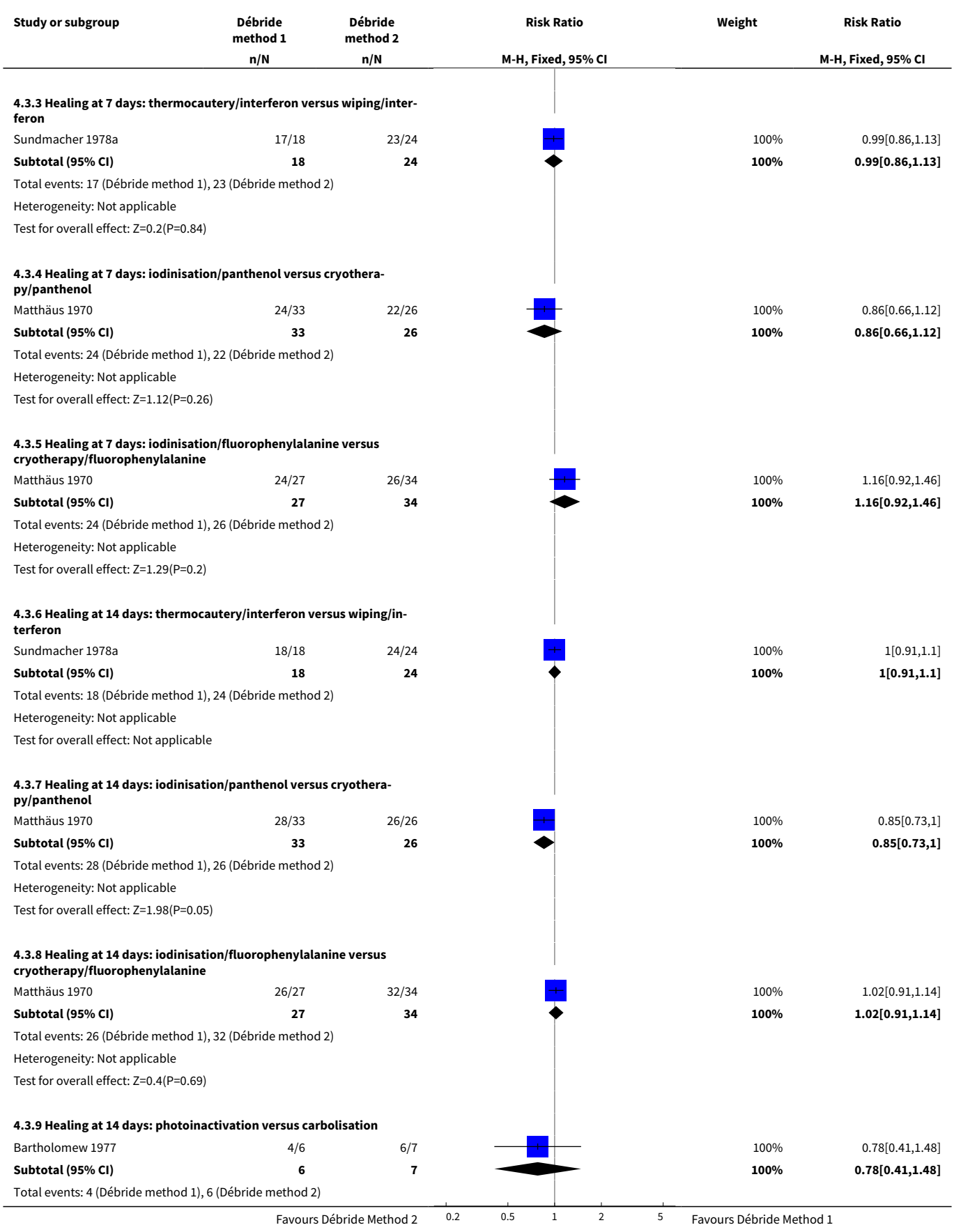


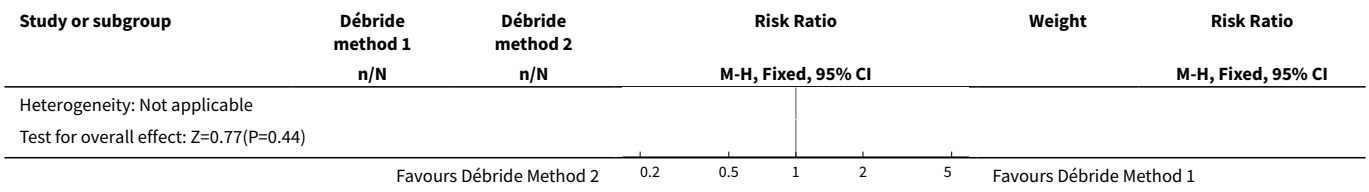
Analysis 4.2. Comparison 4 Debridement, Outcome 2 Topical antiviral agent *versus* debridement.



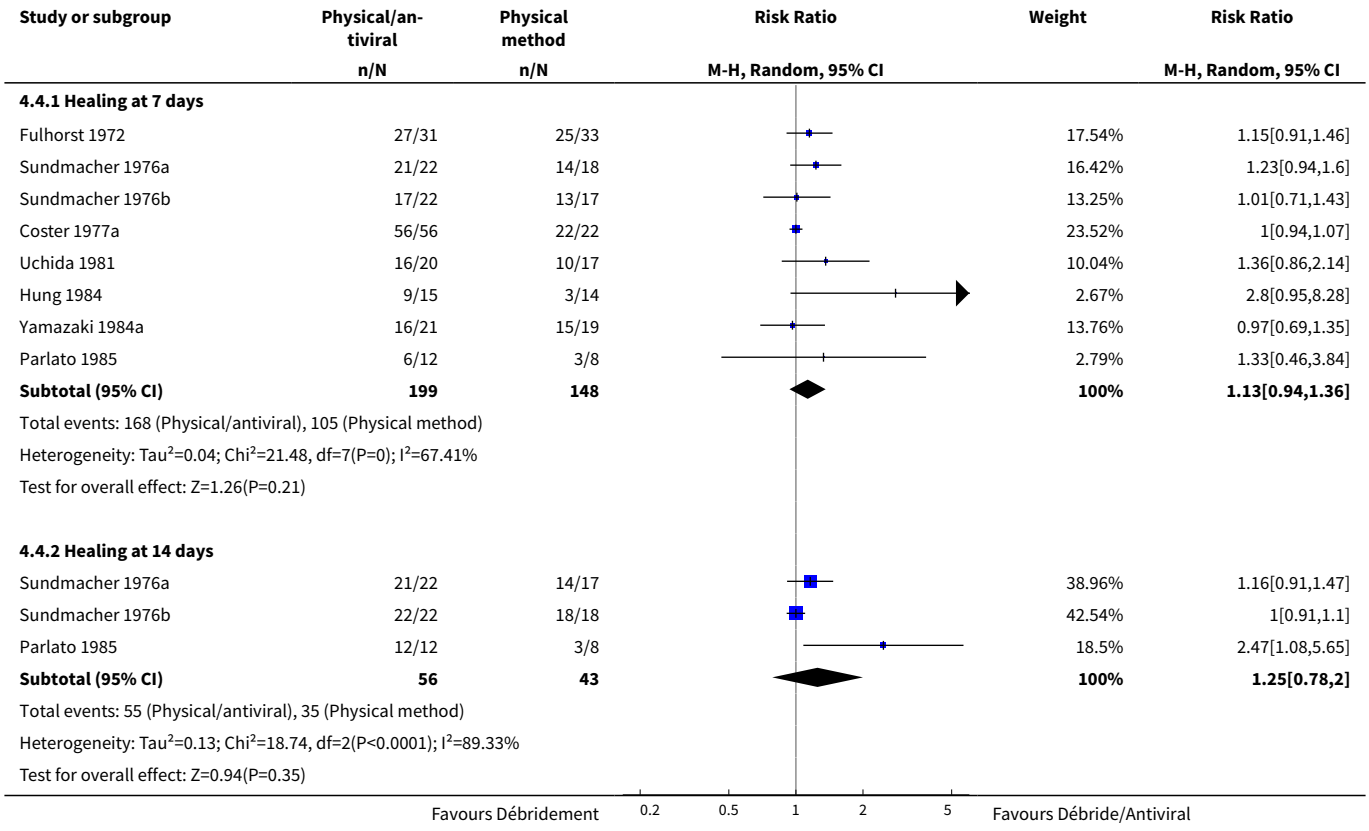
Analysis 4.3. Comparison 4 Debridement, Outcome 3 Different debridement methods.



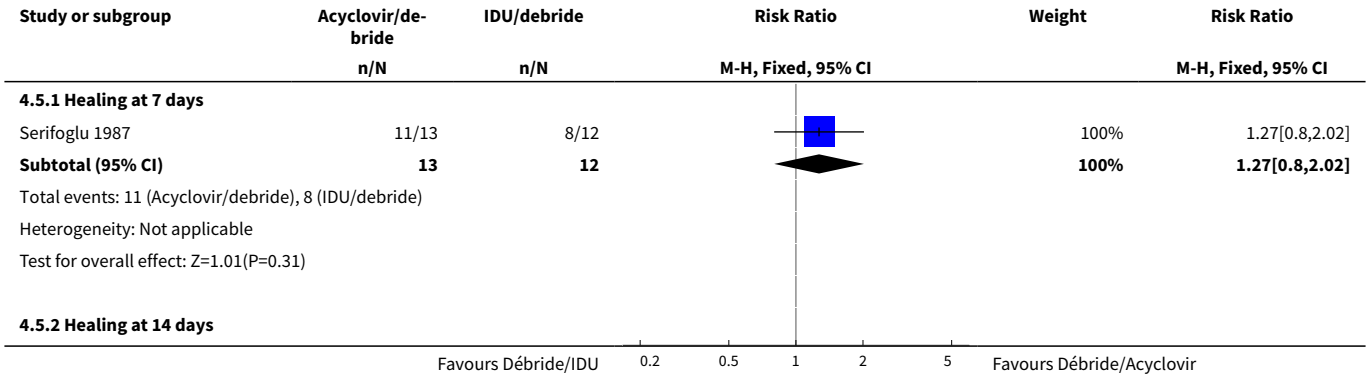


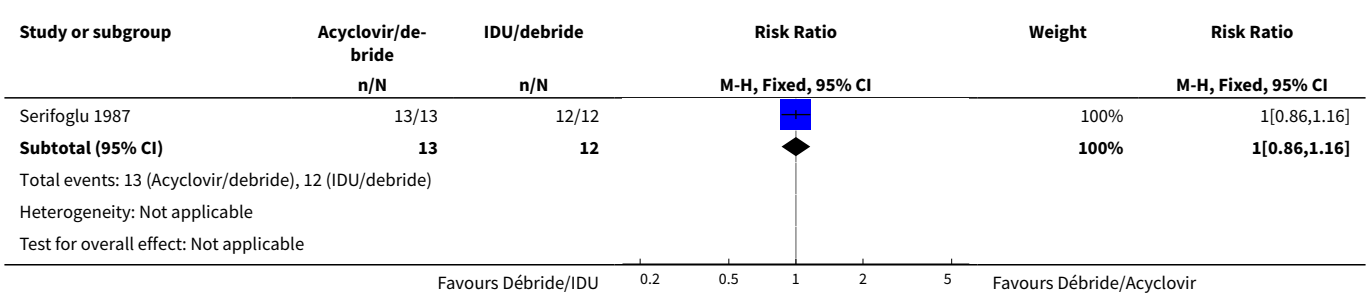


Analysis 4.4. Comparison 4 Debridement, Outcome 4 Debridement with antiviral or interferon *versus* debridement.

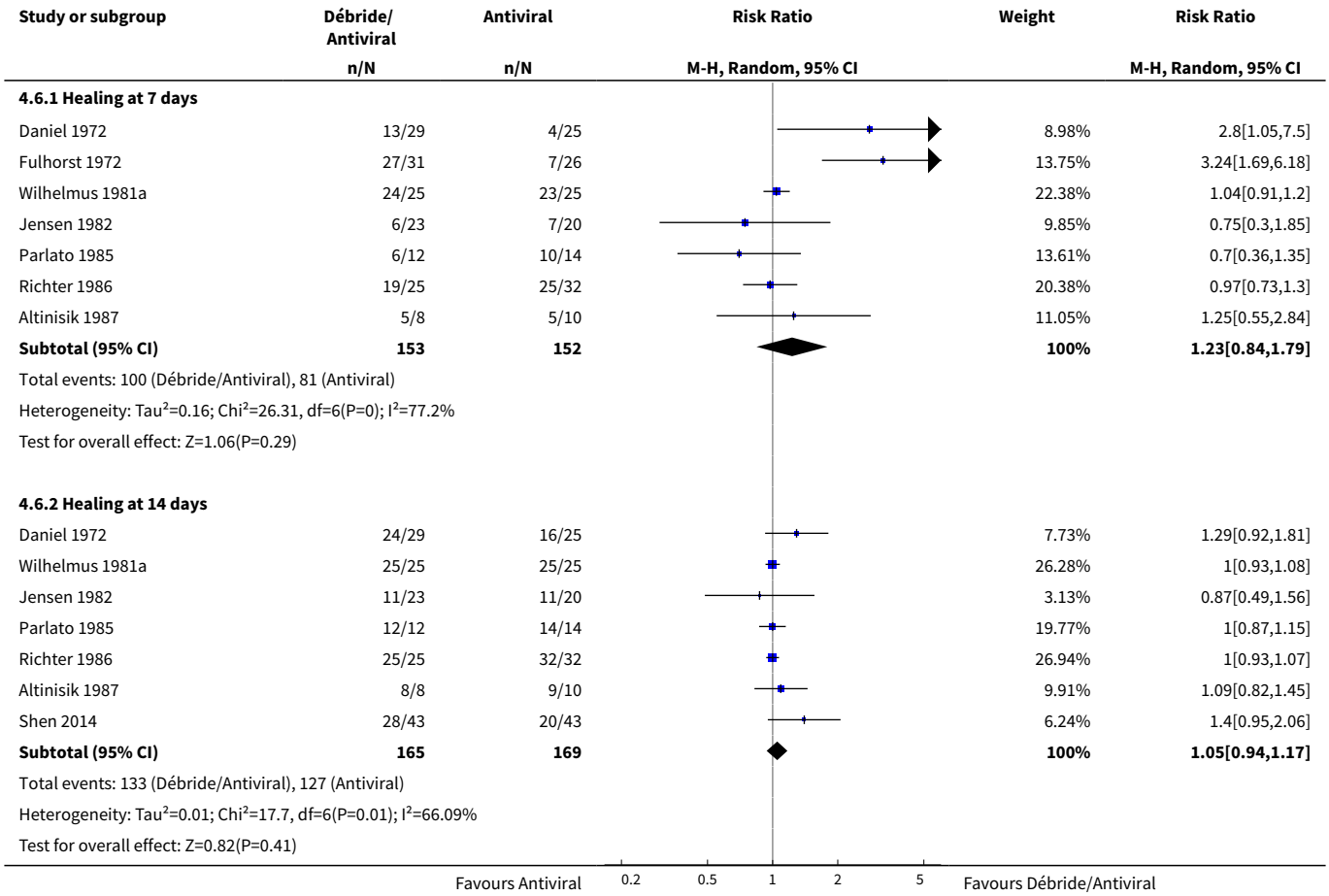


Analysis 4.5. Comparison 4 Debridement, Outcome 5 Debridement with different antivirals.

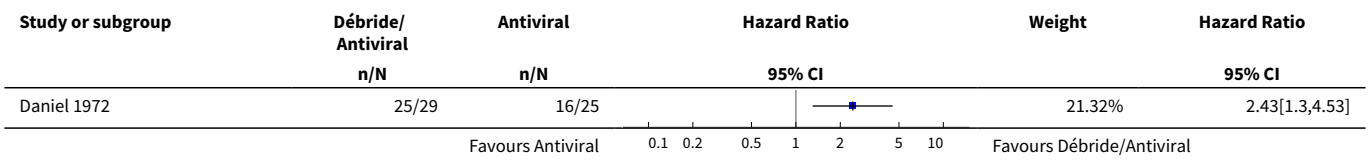


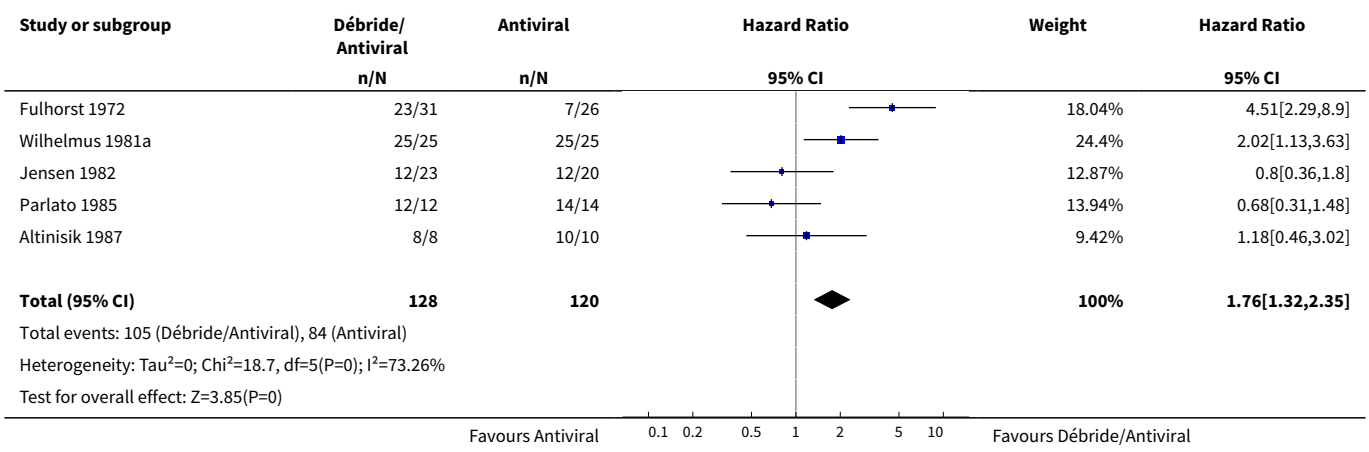


Analysis 4.6. Comparison 4 Debridement, Outcome 6 Debridement with antiviral *versus* antiviral: 7-day & 14-day healing.



Analysis 4.7. Comparison 4 Debridement, Outcome 7 Debridement with antiviral *versus* antiviral: healing rate.



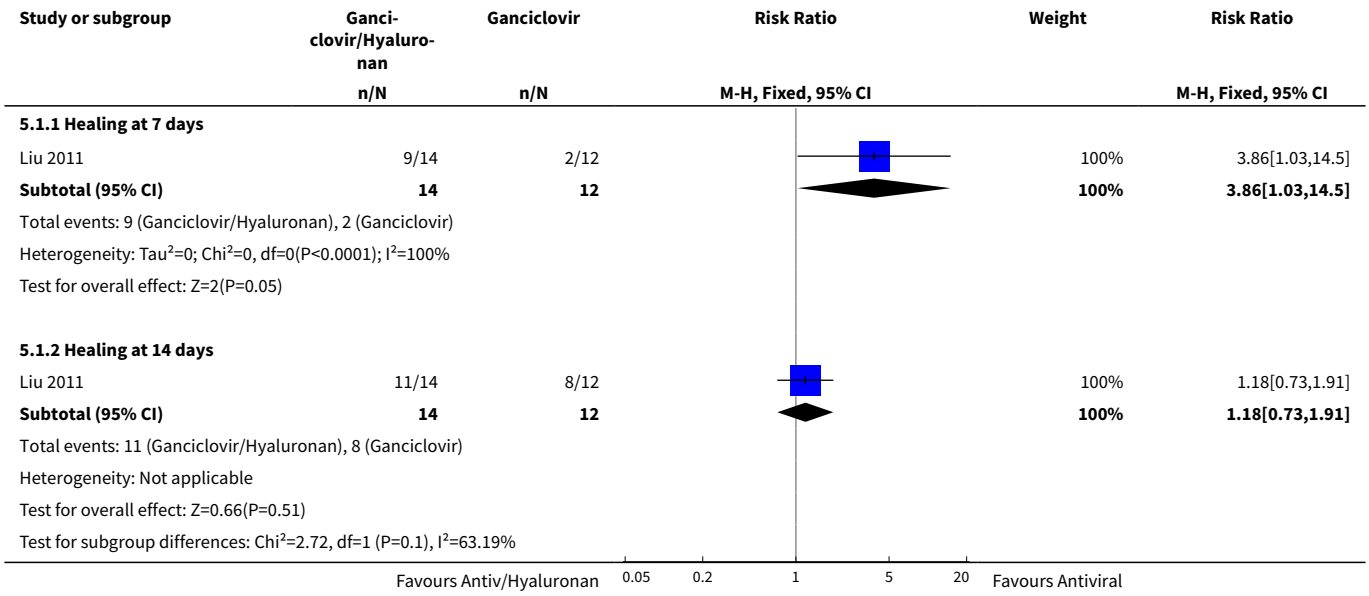


Comparison 5. Adjunctive and alternative agents: lubricant, growth factor, nonsteroidal anti-inflammatory drug, immunomodulator

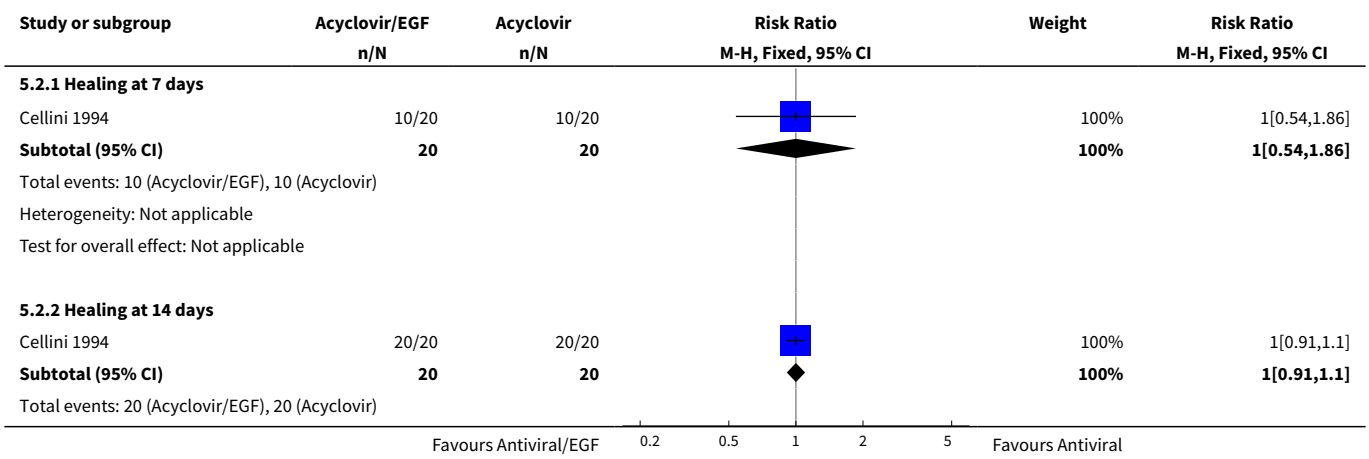
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antiviral/lubricant *versus* antiviral	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healing at 7 days	1	26	Risk Ratio (M-H, Fixed, 95% CI)	3.86 [1.03, 14.50]
1.2 Healing at 14 days	1	26	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.73, 1.91]
2 Antiviral/epidermal growth factor *versus* antiviral	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Healing at 7 days	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.54, 1.86]
2.2 Healing at 14 days	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.91, 1.10]
3 Panthenol *versus para*-fluorophenylalanine, with debridement	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Healing at 7 days	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.79, 1.14]
3.2 Healing at 14 days	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.88, 1.08]
4 Interferon/methyl uracil *versus* interferon	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Healing at 7 days	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.27, 2.67]
4.2 Healing at 14 days	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.79, 1.41]
5 Antiviral/oxyphenbutazone *versus* antiviral	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Healing at 7 days	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.56, 1.11]

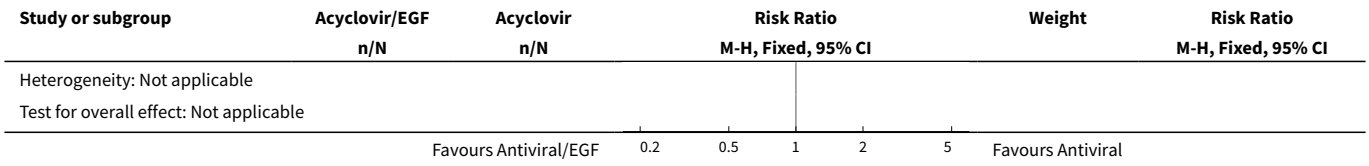
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Oral inosine pranobex *versus* inactive control, with or without antiviral	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Healing at 7 days	2	50	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.07, 3.47]
6.2 Healing at 14 days	2	50	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.91, 1.62]

Analysis 5.1. Comparison 5 Adjunctive and alternative agents: lubricant, growth factor, nonsteroidal anti-inflammatory drug, immunomodulator, Outcome 1 Antiviral/lubricant *versus* antiviral.

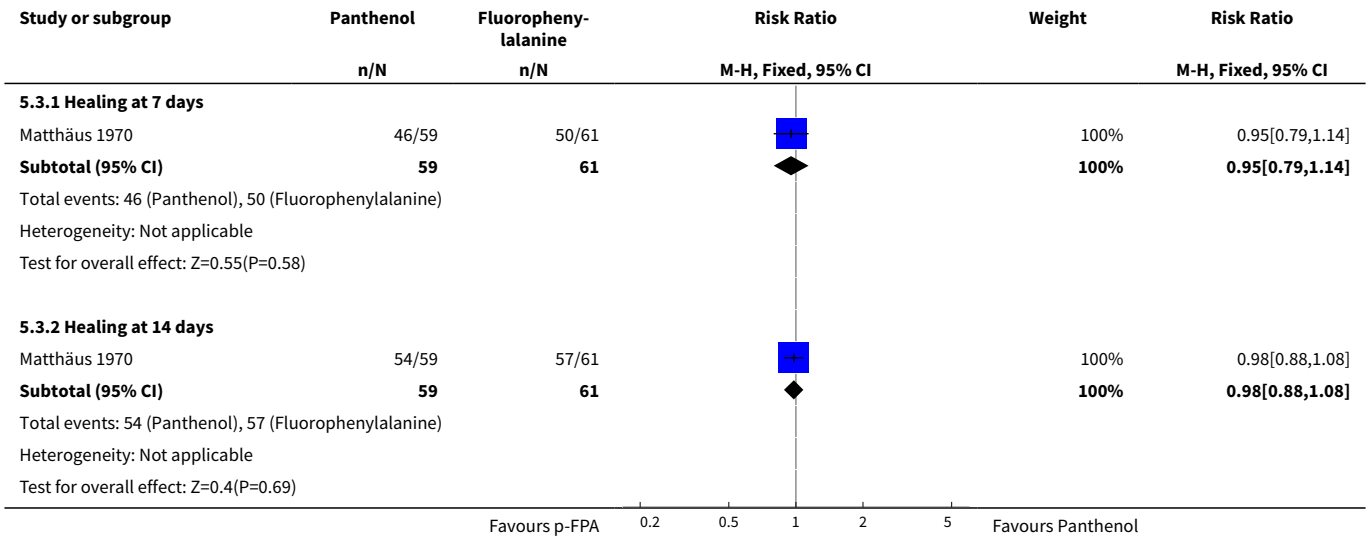


Analysis 5.2. Comparison 5 Adjunctive and alternative agents: lubricant, growth factor, nonsteroidal anti-inflammatory drug, immunomodulator, Outcome 2 Antiviral/epidermal growth factor *versus* antiviral.

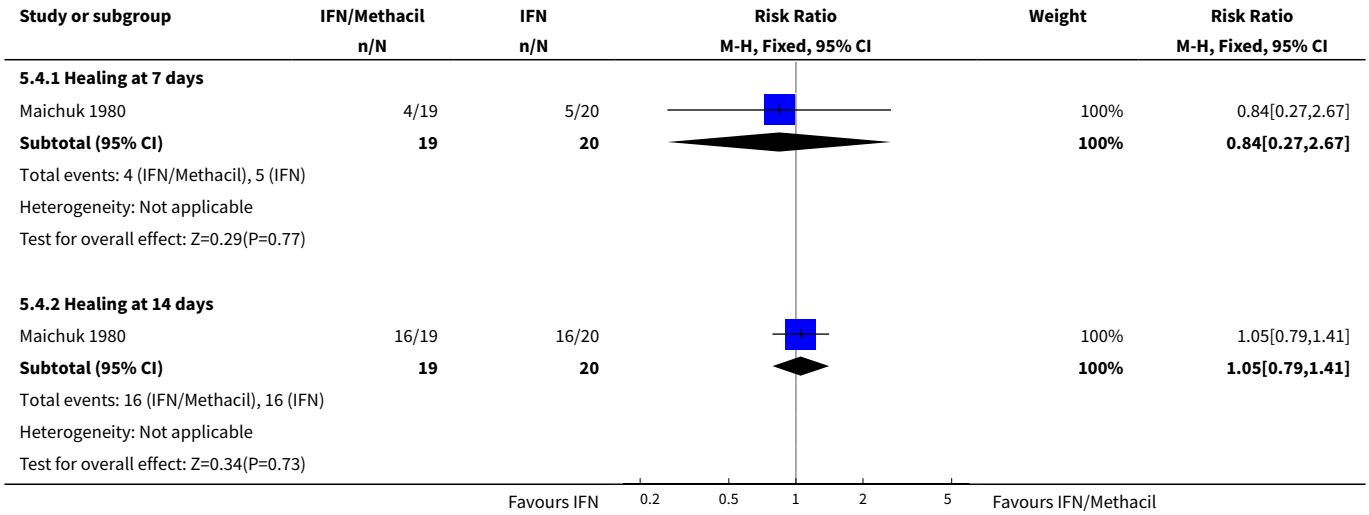




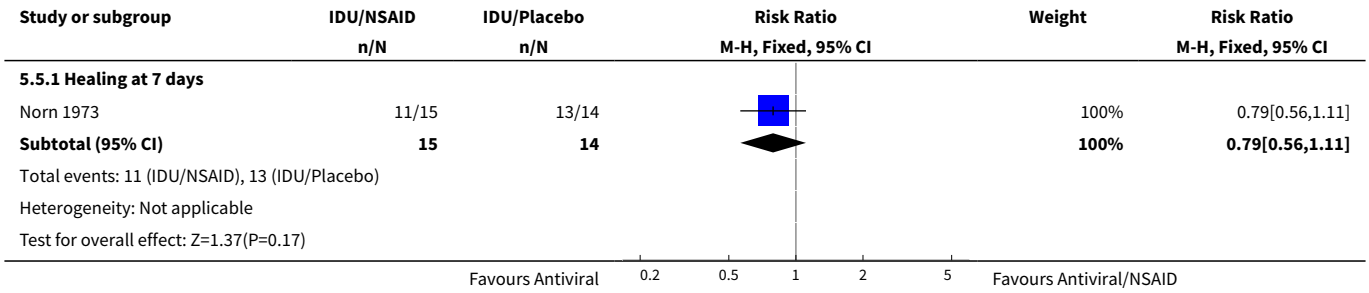
Analysis 5.3. Comparison 5 Adjunctive and alternative agents: lubricant, growth factor, nonsteroidal anti-inflammatory drug, immunomodulator, Outcome 3 Panthenol *versus para*-fluorophenylalanine, with debridement.



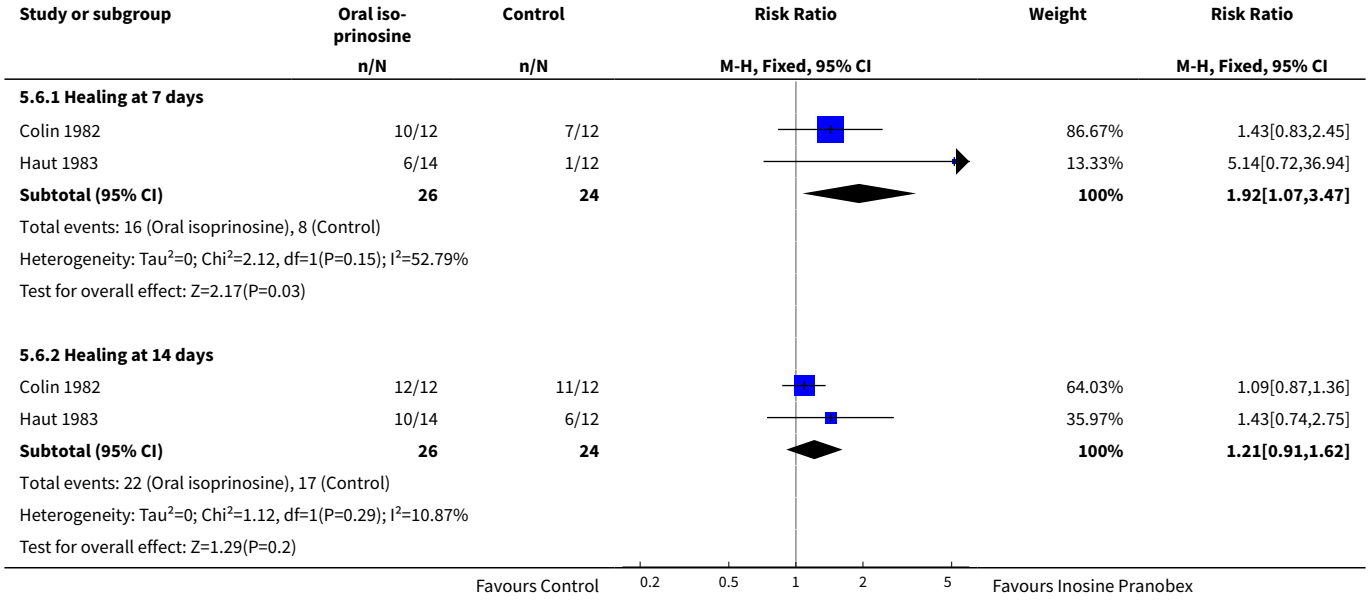
Analysis 5.4. Comparison 5 Adjunctive and alternative agents: lubricant, growth factor, nonsteroidal anti-inflammatory drug, immunomodulator, Outcome 4 Interferon/methyl uracil *versus* interferon.



Analysis 5.5. Comparison 5 Adjunctive and alternative agents: lubricant, growth factor, nonsteroidal anti-inflammatory drug, immunomodulator, Outcome 5 Antiviral/oxyphenbutazone *versus* antiviral.



Analysis 5.6. Comparison 5 Adjunctive and alternative agents: lubricant, growth factor, nonsteroidal anti-inflammatory drug, immunomodulator, Outcome 6 Oral inosine pranobex *versus* inactive control, with or without antiviral.



ADDITIONAL TABLES

Table 1. 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[1]	Risk ratio (95% CI)	Combined risk ratio (95% CI)[2]
Idoxuridine versus placebo	Direct	2	1.31 (0.45-3.84)*	1.74 (1.03-2.91)
	Indirect (vidarabine)	3, 1	1.89 (1.04-3.40)	
Vidarabine versus placebo	Direct	1	1.96 (1.10-3.49)	1.81 (1.09-3.01)

Table 1. Combined direct and indirect comparisons: relative healing of HSV epithelial keratitis at 14 days between topical antiviral agents *(Continued)*

	Indirect (idoxuridine)	3, 2	1.36 (0.46-4.01)*	
Vidarabine versus idoxuridine	Direct	3	1.04 (0.92-1.18)	1.13 (1.02-1.25)
	Indirect (inactive control)	1, 2	1.67 (0.55-5.12)	
	Indirect (trifluridine)	3, 5	1.23 (0.89-1.70)*	
	Indirect (acyclovir)	7, 11	1.12 (0.96-1.30)	
Trifluridine versus idoxuridine	Direct	5	1.38 (1.19-1.60)	1.30 (1.18-1.43)
	Indirect (vidarabine)	3, 3	1.17 (0.85-1.59)*	
	Indirect (acyclovir)	4, 11	1.23 (1.06-1.44)*	
	Indirect (brivudine)	3, 2	1.38 (1.02-1.87)	
Acyclovir versus idoxuridine	Direct	11	1.22 (1.08-1.38)*	1.23 (1.14-1.34)
	Indirect (vidarabine)	7, 3	1.13 (0.98-1.32)	
	Indirect (trifluridine)	4, 5	1.37 (1.15-1.63)	
	Indirect (brivudine)	1, 2	1.31 (0.97-1.78)	
Brivudine versus idoxuridine	Direct	2	1.38 (1.05-1.81)	1.34 (1.18-1.51)
	Indirect (trifluridine)	3, 5	1.38 (1.13-1.68)	
	Indirect (acyclovir)	1, 11	1.28 (1.07-1.54)*	
Trifluridine versus vidarabine	Direct	3	1.12 (0.84-1.49)*	1.17 (1.03-1.32)
	Indirect (idoxuridine)	5, 3	1.33 (1.09-1.61)	
	Indirect (acyclovir)	4, 7	1.10 (0.97-1.25)	
Acyclovir versus vidarabine	Direct	7	1.09 (1.00-1.18)	1.11 (1.03-1.19)
	Indirect (idoxuridine)	11, 3	1.17 (0.99-1.40)*	
	Indirect (trifluridine)	4, 3	1.11 (0.82-1.50)*	
Acyclovir versus trifluridine	Direct	4	0.99 (0.90-1.09)	0.96 (0.90-1.04)
	Indirect (idoxuridine)	11, 5	0.90 (0.76-1.06)*	
	Indirect (vidarabine)	7, 3	0.97 (0.72-1.31)*	
	Indirect (brivudine)	1, 3	0.95 (0.79-1.15)	
Brivudine versus trifluridine	Direct	3	1.00 (0.88-1.14)	1.01 (0.92-1.12)

Table 1. Combined direct and indirect comparisons: relative healing of HSV epithelial keratitis at 14 days between topical antiviral agents *(Continued)*

	Indirect (idoxuridine)	2, 5	1.00 (0.73-1.36)	
	Indirect (acyclovir)	1, 4	1.04 (0.88-1.22)	
Brivudine versus acyclovir	Direct	1	1.05 (0.92-1.20)	1.04 (0.95-1.15)
	Indirect (idoxuridine)	2, 11	1.13 (0.84-1.53)	
	Indirect (trifluridine)	4, 3	1.01 (0.86-1.19)	
Ganciclovir versus acyclovir	Direct	28	1.38 (1.22-1.57)*	1.34 (1.20-1.51)
	Indirect (foscarnet)	1, 1	1.20 (0.92-1.57)	
Foscarnet versus trifluridine	Direct	1	1.00 (0.75-1.34)	1.09 (0.92-1.29)
	Indirect (acyclovir)	1, 4	1.14 (0.92-1.41)	
Foscarnet versus acyclovir	Direct	1	1.15 (0.95-1.40)	1.15 (1.01-1.32)
	Indirect (trifluridine)	1, 4	1.01 (0.74-1.37)	
	Indirect (ganciclovir)	1, 17	1.27 (0.99-1.63)*	
Foscarnet versus ganciclovir	Direct	1	0.96 (0.80-1.16)	0.92 (0.75-1.13)
	Indirect (acyclovir)	1, 12	0.86 (0.62-1.20)*	

[1] Data derive from a network of antiviral treatment trials (Figure 3). Comparisons are based on reported outcomes at 14 days in which two antivirals were directly compared in at least one clinical trial. Indirect comparisons are limited to a linked network of trials having a single shared intermediate intervention since multiple intermediates were not considered for indirect adjustment. The number of trials indicate the number of direct comparisons made in either head-to-head trials or the number of trials between the first antiviral and the intermediate antiviral followed by the number of trials between the intermediate antiviral and the second antiviral.
[2] While $I^2 < 25\%$ for all combined direct and indirect comparisons estimated by the DerSimonian-Laird random-effects model method, networks that had at least one heterogeneous head-to-head comparison are identified (*).
CI: confidence interval; NA: not applicable (only direct or indirect comparison available)

Table 2. Sensitivity analysis including only higher-quality studies: relative healing at 14 days using only randomised, double-masked trials

Treatment comparisons	Randomised, double-masked studies[1]	Risk ratio (95% CI) all studies	I^2 (with all studies)	Risk ratio (95% CI) - only randomised, double-masked studies	I^2 (with only randomised, double-masked studies)
Idoxuridine versus inactive control	Markham 1977	1.31 (0.45-3.84)	92%	1.79 (0.98-3.26)	NA
Vidarabine versus idoxuridine	Markham 1977; Pavan-Langston 1976	1.04 (0.92-1.18)	0%	1.03 (0.90-1.17)	0%
Trifluridine versus idoxuridine	Panda 1995; Sugar 1980; Wellings 1972	1.38 (1.19-1.60)	0%	1.47 (1.23-1.75)	0%

Table 2. Sensitivity analysis including only higher-quality studies: relative healing at 14 days using only randomised, double-masked trials *(Continued)*

Acyclovir versus idoxuridine	Colin 1981; Collum 1980; Coster 1980; Kitano 1985; Kumar 1987; McCulley 1982; Panda 1995	1.22 (1.08-1.38)	63%	1.17 (1.02-1.34)	69%
Brivudine versus idoxuridine	Panda 1995	1.38 (1.05-1.81)	30%	1.64 (1.15-2.35)	NA
Trifluridine versus vidarabine	Coster 1976	1.12 (0.84-1.49)	74%	1.07 (0.98-1.17)	NA
Acyclovir versus vidarabine	Collum 1985; Denis 1983; Genée 1987; Pavan-Langston 1981; Yeakley 1981; Young 1982	1.09 (1.00-1.18)	0%	1.07 (0.98-1.18)	0%
Acyclovir versus trifluridine	Høvding 1989; La Lau 1982; Panda 1995	0.99 (0.90-1.09)	0%	1.01 (0.91-1.12)	0%
Brivudine versus trifluridine	Panda 1995; Power 1991	1.00 (0.88-1.14)	0%	0.98 (0.89-1.08)	0%
Brivudine versus acyclovir	Panda 1995	1.05 (0.92-1.20)	NA	NA	NA
Ganciclovir versus acyclovir	Colin 2007a	1.38 (1.22-1.57)	79%	1.21 (0.95-1.54)	NA
Foscarnet versus trifluridine	Behrens-Baumann 1992	1.00 (0.75-1.34)	NA	NA	NA
Acyclovir, vidarabine versus acyclovir	Colin 1987	1.00 (0.89-1.12)	NA	NA	NA
Oral versus topical antiviral	Collum 1986	0.92 (0.79-1.07)	NA	NA	NA
Oral + topical antivirals versus topical antiviral	HEDS Group 1997	1.36 (0.68-2.74)	90%	1.01 (0.93-1.09)	NA
Interferon + antiviral versus antiviral	Colin 1983; de Koning 1982; de Koning 1983; Meurs 1985; Sundmacher 1987; van Bijsterveld 1989	1.06 (0.99-1.13)	67%	1.02 (0.98-1.06)	0%

[1] 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 3. Overview of trial and participant characteristics among included studies

Study characteristics	Categories	No. (%) trials (n=137)
No. centres	One	118 (86%)

Table 3. Overview of trial and participant characteristics among included studies *(Continued)*

	Two or more	19 (14%)
No. eyes per study	< 50	62 (45%)
	50 to 100	58 (42%)
	> 100	17 (12%)
Average age of participants	< 40 years	24 (18%)
	40 to 50 years	36 (26%)
	> 50 years	6 (4%)
	Not stated	71 (52%)
Gender of participants	Males exceed females	71 (52%)
	Females exceed males	7 (5%)
	Not stated	59 (43%)
Type of epithelial keratitis	Dendritic	74 (54%)
	Dendritic or geographic	59 (43%)
	Geographic	2 (1%)
	Not specified	2 (1%)
No. of intervention groups[1]	Two	116 (85%)
	Three	16 (12%)
	Four	4 (3%)
	Five	1 (1%)
Cycloplegic or mydriatic eye drops	Yes	51 (37%)
	None, variable, or not stated	86 (63%)
Antibacterial eye drops	Yes	19 (14%)
	None or not stated	118 (86%)

[1] Of 142 excluded studies, 121 had two intervention groups, ten had three groups, six had four groups, two had five groups, two had six groups, and one had eight groups.

Table 4. Outcomes reported in studies excluded due to insufficient healing data

Study (n=57)	Treatment group (no. eyes)[1]	Mean healing time ± SD, days; or P value[2]
Antiviral agents		
Babushkin 1993	Idoxuridine (60)	NS
	Acyclovir (24)	5.9 ± 1.2
Huang 2007	Acyclovir (62)	12
	Ganciclovir (62)	9.6
Inocencio 1982	Idoxuridine (9)	10.4
	Acyclovir (14)	7.0
Jing 2010	Acyclovir (22)	P = 0.005
	Ganciclovir (24)	

Table 4. Outcomes reported in studies excluded due to insufficient healing data *(Continued)*

Leopold 1965	Idoxuridine (5) Cytarabine (5)	NS NS
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
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
Wang 2009	Acyclovir (39) Ganciclovir (39)	P < 0.05
Debridement		
Assetto 1981	Debridement (8) Idoxuridine (16) Cytarabine (16) Trifluridine (8)	3 - 19 10 - 18 13 - 21 6 - 13
Fellinger 1980	Idoxuridine (13) Trifluridine (16) Debridement, idoxuridine (13) Debridement, 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	Iodinisation, idoxuridine (20) Cryotherapy, idoxuridine (20)	4.3 14.0
Koev 2007	Acyclovir (25) Acyclovir, pandavir (24) Debridement, acyclovir, pandavir (26)	9.3 ± 1.2 8.2 ± 1.1 6.2 ± 1.3
Mathur 1984	Iodinisation (50) Cryotherapy (20) Cryotherapy, autologous serum (24) Debridement (30) Debridement, idoxuridine (30)	11 9 7 9 6
Patterson 1967c	Debridement (9) Idoxuridine (15)	P < 0.01
Shimomura 1987	Debridement, idoxuridine (16) Idoxuridine (15)	P > 0.05
Tarakji 1978	Cryotherapy (21)	2.4

Table 4. Outcomes reported in studies excluded due to insufficient healing data *(Continued)*

	Idoxuridine (14)	6.2
Whitcher 1976	Debridement (20) Idoxuridine (31)	5 13
Interferon and interferon/antiviral combinations		
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
Lin 2013b	Ganciclovir (33) Ganciclovir, interferon (33)	P < 0.05
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
Su 2010	Ganciclovir (40) Ganciclovir, interferon (38)	P < 0.05
Tamburi 1990	Acyclovir (8) Interferon (8) Acyclovir, interferon (8)	5.2 9.0 5.0
Wan 2014	Ganciclovir (24) Ganciclovir, interferon (26)	6.5 ± 2.1 4.2 ± 1.1
Weng 2014	Acyclovir (35) Acyclovir, interferon (35)	P < 0.05
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

Table 4. Outcomes reported in studies excluded due to insufficient healing data *(Continued)*

Interferon inducers		
Galin 1976	Idoxuridine (20) Poly I:C (19)	NS NS
Kasparov 1972	Idoxuridine (16) Poly A:U (43) Immunomodulators (167) Debridement, 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
Liu 2014b	Acyclovir (NS) Poly I:C (NS) Acyclovir, poly I:C (NS)	NS
Wei 2012	Ganciclovir (24) Poly I:C (24)	22.75 ± 5.09 13.54 ± 4.06
Cytokines, growth factors, and immunomodulators		
He 2014	Antiviral (34) Autologous serum (34)	P = 0.015
Kolomiets 1986	Control (10) HSV-immunoglobulin (14)	28.6 16.8
Liu 2007	Acyclovir (50) Acyclovir, fibroblast growth factor (46)	P < 0.05
Li 2014c	Ganciclovir, acyclovir (21) Ganciclovir, fibroblast growth factor (21)	P < 0.05
Pivetti-Pezzi 1985	Placebo (13) Thymic extract (11)	23 ± 13 23 ± 9
Prost 1986	Cryotherapy (20) Cryotherapy, oral inosine pranobex (19)	6.8 ± 3.9 6.5 ± 3.8
Salcedo Hernandez 2007	Autologous serum (9) Acyclovir (8)	10 7
Sellitti 1982	Topical/oral inosine pranobex (20)	13.3

Table 4. Outcomes reported in studies excluded due to insufficient healing data *(Continued)*

	Oral inosine pranobex (20)	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
Yu 2012b	Ganciclovir (30) Ganciclovir, measles vaccine (30)	P < 0.05
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; interventions are tabulated in Characteristics of excluded studies.
[2] A range of average healing times indicates that mean estimates were provided for subcategories (e.g., dendritic *vs*. geographic epithelial keratitis) without summary estimation. For studies not reporting mean healing times, P values are given that either compare the proportion healed in study groups at a time other than 14 days or compare clinical scores of symptoms and signs between study groups.
NS, not stated; SD, standard deviation (when reported)

Table 5. Sensitivity analysis omitting potentially biased studies: relative healing at 14 days after omitting trials with incomplete randomisation, concealment, or masking

Treatment comparisons[1]	Studies under investigation[2]	Risk ratio (95% CI) with studies included	I^2 (with studies included)	Risk ratio (95% CI) with studies omitted	I^2 (with studies omitted)
Idoxuridine versus inactive control	Luntz 1963	1.31 (0.45-3.84)	92%	1.79 (0.98-3.26)	NA
Trifluridine versus idoxuridine	Struck 1989	1.38 (1.19-1.60)	32%	1.43 (1.23-1.67)	0%
Acyclovir versus idoxuridine	Abe 1987; Altinisik 1987; Maichuk 1988	1.22 (1.08-1.38)	63%	1.18 (1.03-1.35)	66%
Brivudine versus idoxuridine	Struck 1989	1.38 (1.05-1.81)	30%	1.64 (1.15-2.35)	NA
Trifluridine versus vidarabine	Coster 1979	1.12 (0.84-1.49)	74%	0.99 (0.79-1.25)	65%
Brivudine versus trifluridine	Struck 1989	1.00 (0.88-1.14)	0%	0.98 (0.89-1.08)	36%
Ganciclovir versus acyclovir	Colin 1997a; Colin 1997b; Colin 2007b; Chen 2008; Dai 2009a; Dai 2009b; Han 2010; Han 2014; Huang 2008a; Li 2008; Li 2013a; Lin 2011; Lin 2014; Liu 2009a; Liu 2010; Liu 2012a; Liu 2012b; Liu 2014a; Ramirez 2002; Sun	1.38 (1.22-1.57)	79%	1.21 (0.95-1.54)	NA

Table 5. Sensitivity analysis omitting potentially biased studies: relative healing at 14 days after omitting trials with incomplete randomisation, concealment, or masking *(Continued)*

	2013a; Wang 2014a; Xu 2009a; Yang 2000; Yang 2008; Zhang 2014; Zhao 2006; Zhen 2012				
Oral + topical antivirals versus topical antiviral	Srinivas 1993	1.36 (0.68-2.74)	90%	1.01 (0.93-1.09)	NA
Interferon versus nucleoside antiviral	Kitano 1983; Tanaka 1988b; Vannini 1986	1.22 (0.91-1.62)	67%	1.57 (0.77-3.22)	NA
Interferon + antiviral versus antiviral	Fu 2012; Li 2009; Li 2013b; Maichuk 1988	1.06 (0.99-1.13)	67%	1.02 (0.98-1.05)	0%
Topical antiviral versus debridement	Bartholomew 1977; Kato 1979; MacKenzie 1964; O'Day 1975; Patterson 1967a; Struck 1989	0.98 (0.72-1.32)	79%	1.43 (0.44-4.67)	87%
Debridement + antiviral or interferon versus debridement	Sundmacher 1976a	1.25 (0.78-2.00)	89%	1.54 (0.21-11.5)	96%
Debridement + antiviral versus antiviral	Daniel 1972; Richter 1986; Shen 2014; Wilhelmus 1981a	1.05 (0.99-1.17)	66%	1.01 (0.89-1.15)	0%

[1] Three 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).
[2] Two 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 6. Safety assessment among antiviral treatment studies

Topical antiviral agent	No. studies reporting corneal toxicity prevalence	No. antiviral-treated participants assessed for corneal toxicity	Median prevalence of punctate epithelial erosions during antiviral use (interquartile range)
Idoxuridine	14[1]	430	10% (5%-20%)
Vidarabine	12[2]	395	11% (4%-17%)
Trifluridine	9[3]	220	4% (2%-7%)
Acyclovir	25[4]	667	10% (0%-17%)
Brivudine	3[5]	72	0%
Ganciclovir	4[6]	156	4% (0%-11%)
All of above	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 (omitting 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 (omitting 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

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

Appendix 2. PubMed search strategy

((randomized controlled trial [pt]) OR (controlled clinical trial [pt]) OR (clinical trial [pt]) OR (random allocation [mh]) OR (randomized controlled trials [mh])) AND ((herpes OR herpetic OR simplex) AND (cornea OR corneal OR keratitis OR ocular))

Appendix 3. EMBASE.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'herpes simplex keratitis'/exp
#34 ((herpe* OR simplex) NEAR/4 (cornea* OR kerati* OR dendr* OR ocular)):ab,ti
#35 #33 OR #34
#36 #32 AND #35

Appendix 4. LILACS search strategy

English Language Search Terms: (herpe$ or simplex) and (cornea$ or kerati$ or dendr$ or ocular)

Spanish Language Search Terms: (herpes simplex) and (dendrítica or queratitis)

Portuguese Language Search Terms (herpes simples) and (dendr$ or ceratite)

Appendix 5. OpenGrey search strategy

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

Appendix 6. BIOSIS search strategy

TS=(herpe* OR simplex) AND TS=(cornea* OR kerati* OR dendr* OR ocular) AND TS=(random* OR trial*)

Appendix 7. Scopus search strategy

Article Title, Abstract, Keywords=(herpe* OR simplex) AND (keratitis OR cornea*) AND (trial* OR RCT* OR random* OR blind*)

Appendix 8. J-Global search strategy

English Language Search Terms: (herpes OR simplex OR dendritic) AND (keratitis OR cornea)

Japanese Language Individual Search Terms: (ヘルペス OR 単純ヘルペス OR 樹枝状の OR 樹木状の) AND (角膜炎 OR 角膜)

Japanese Language Combined Search Terms: ヘルペス性角膜炎 OR 角膜ヘルペス OR 純ヘルペス性角膜炎 OR 樹枝状角膜炎

Appendix 9. CNKI search strategy

English Language Search Term (subject, precise): herpes simplex keratitis

Chinese Language Search Term (subject, precise): 单纯疱疹性角膜炎

Appendix 10. ZETOC search strategy

herpe* simplex kerati* random*

herpe* simplex kerati* trial*

Appendix 11. *meta*Register of Controlled Trials search strategy

herpe* simplex AND keratitis

Appendix 12. ClinicalTrials.gov search strategy

Condition: (herpes OR simplex) AND (corneal OR keratitis OR dendritic OR ocular)

Appendix 13. ICTRP search strategy

keratitis

Appendix 14. ChiCTR search strategy

Target disease=eye or cornea or keratitis

Appendix 15. U.S. Food and Drug Administration search strategy

"herpes simplex keratitis" and "dendritic keratitis"

Appendix 16. National Institute for Health and Clinical Excellence search strategy

"herpes simplex keratitis" and "dendritic keratitis"

Appendix 17. European Medicines Agency search strategy

"herpes simplex keratitis" and "dendritic keratitis"

WHAT'S NEW

Date	Event	Description
9 January 2015	New citation required and conclusions have changed	Issue 1, 2015: Studies using the antiviral drug foscarnet have been included in this update.
9 January 2015	New search has been performed	Issue 1, 2015: Updated searches found 31 trials to include in the analysis (Cao 2001; Colin 1982; Dai 2009a; Dai 2009b; Fu 2012; Han 2010; Han 2014; Li 2009; Li 2013a; Li 2013b; Lin 2011; Lin 2014; Liu 2010; Liu 2011; Liu 2012a; Liu 2012b; Liu 2014a; Maichuk 1980; Ramirez 2002; Shen 2014; Sun 2013a; Tanaka 1988a; Tanaka 1988b; Wang 2014a; Yang 2008; Yu 2012a; Zhang 2014; Zhao 2006; Zhen 2012; Zheng 2010; Zhu 2012); a secondary citation of an existing study (Sundmacher 1976a); an additional 46 excluded studies (Cao 2012; Cao 2013; Gong 2013; Gulinuer 2011; He 2014; Hu 2013; Huang 2007; Huang 2013; Jiang 2011; Jing 2010; Li 2012; Li 2013c; Li 2014a; Li 2014b; Li 2014c; Lin 2013a; Lin 2013b; Liu 2014b; Long 2011; Ma 2010; Ma 2011; Ma 2013; Rykun 1988; Su 2010; Sun 2012; Sun 2014; Wan 2014; Wang 2010a; Wang 2010b; Wang 2011; Wang 2014b; Wei 2012; Wen 2011; Weng 2014; Xu 2012; Yang 2012; Yi 2011; Yu 2012b; Yu 2014; Yuan 2011; Zhan 2011; Zhang 2010; Zhao 2010; Zhao 2013; Zheng 2014; Zhong 2003); and an unpublished registered trial (Ajanta Pharma 2013). A recent systematic review comparing acyclovir and ganciclovir was incorporated (Li 2014d).

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 1, 2001

Date	Event	Description
24 May 2011	Amended	Issue 7, 2011: The review was edited. While new searches were not done for this interim update, two citations (Croxtall 2011; Guess 2010) were added to the 'Background' section. Satpathy 2010 citation updated to Satpathy 2011.
9 November 2010	New search has been performed	Issue 12, 2010: This review was substantively updated with the following changes: • The original title of 'Therapeutic interventions for herpes simplex virus epithelial keratitis' was changed to 'Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis.' • Six new studies comparing ganciclovir and acyclovir were added (Chen 2008; Huang 2008a; Li 2008; Liu 2009a; Xu 2009a; Yang 2000). • Risk of bias tables were completed for all included studies. • Trials of botanicals and traditional Chinese medicines were added to excluded studies. • Data on adverse drug-related effects added (Table 6). • Hazard ratios from healing curves were incorporated into the results (Summary of findings for the main comparison). • Table 4 was added to describe studies excluded because of insufficient data. • A literature flow diagram was included (Figure 2).

Date	Event	Description
6 November 2008	Feedback has been incorporated	Converted to new review format.
29 October 2007	New citation required and conclusions have changed	Issue 1, 2008: two new studies (Colin 2007a and Colin 2007b) added.
29 August 2006	New citation required and minor changes	Issue 1, 2007: one new study (Kitano 1985) added.

CONTRIBUTIONS OF AUTHORS

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

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None known

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  The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

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: the original title of 'Therapeutic interventions for herpes simplex virus epithelial keratitis' was changed.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans