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# Ocular herpes simplex

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## ABSTRACT

INTRODUCTION: Ocular infection with herpes simplex virus (HSV) is usually acquired early in life, with 50% of people from higher and 80% from lower socioeconomic groups in the USA having antibodies by the age of 30 years. Attacks usually resolve spontaneously within 1−2 weeks, but 50% of people will experience a recurrence within 10 years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments in people with epithelial keratitis? What are the effects of treatments in people with stomal keratitis? What are the effects of interventions to prevent recurrence of ocular herpes simplex? What are the effects of interventions to prevent recurrence of ocular herpes simplex in people with corneal grafts? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2007 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found seven systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: adding oral aciclovir to topical corticosteroids plus topical antiviral treatment; adding topical corticosteroids to topical antiviral treatment; antiviral agents (topical); debridement; interferons (topical); and oral aciclovir.


## QUESTIONS



## INTERVENTIONS



## Key points

- Ocular infection with HSV can cause inflammation of the eyelids, conjunctivae, iris, retina, and cornea.

  Infection is common and usually acquired early in life, with 50% of people from higher and 80% from lower socioeconomic groups in the USA having antibodies by the age of 30 years.

  HSV epithelial keratitis tends to resolve spontaneously within 1–2 weeks, while stromal keratitis is more likely to result in corneal scarring and loss of vision. Stromal keratitis or iritis occurs in about 25% of people after epithelial keratitis.

  Recurrence of ocular herpes (epithelial or stromal) for people with one episode is 10% at 1 year, 23% at 2 years, and 50% at 10 years.

- Topical antiviral agents and topical interferons increase healing of epithelial keratitis compared with placebo.

  Physicochemical debridement or interferon may speed up healing if added to antiviral agents, but we don't know whether debridement is effective when used alone.

- When added to topical antiviral agents, topical corticosteroids reduce progression and shorten the duration of stromal keratitis compared with placebo.

Adding oral aciclovir to topical corticosteroids plus topical antiviral treatment may not increase healing compared with topical treatment alone.

- Long-term oral aciclovir treatment in people with previous ocular epithelial or stromal keratitis reduces recurrence after 1 year compared with placebo.

Short-term prophylaxis (for 3 weeks) with oral aciclovir does not seem to reduce the risk of recurrence.

- We don't know whether oral aciclovir reduces recurrence of ocular herpes simplex infection after corneal grafts.

**DEFINITION**

Ocular herpes simplex is usually caused by herpes simplex virus type 1 (HSV-1) but also occasionally by the type 2 virus (HSV-2). Ocular manifestations of HSV are varied and include blepharitis (inflammation of the eyelids), canalicular obstruction, conjunctivitis, corneal complications, iritis, and retinitis. Corneal complications are of two main types: **epithelial keratitis** is inflammation of the cells that form the surface layer of the cornea, and **stromal keratitis** is inflammation of the middle layer (stroma) of the cornea. HSV infections are classified as neonatal, primary (HSV in a person with no previous viral exposure), and recurrent (previous viral exposure with humoral and cellular immunity present).

**INCIDENCE/ PREVALENCE**

Infections with HSV are usually acquired in early life. A US study found antibodies against HSV-1 in about 50% of people with high socioeconomic status and 80% of people with low socioeconomic status by age 30 years. It quoted a report which suggested overcrowding as a causal factor. [1] However, only about 20–25% of people with HSV antibodies had any history of clinical manifestations of ocular or cutaneous herpetic disease. [2] Ocular HSV is the most common cause of corneal blindness in high-income countries, and is the most common cause of unilateral corneal blindness worldwide. [3] A 33-year study of the population of Rochester, Minnesota found that the annual incidence of new cases of ocular herpes simplex was 8.4/100,000 (95% CI 6.9/100,000 to 9.9/100,000), and the annual incidence of all episodes (new and recurrent) was 20.7/100,000 (95% CI 18.3/100,000 to 23.1/100,000). [4] The prevalence of ocular herpes was 149/100,000 population (95% CI 115/100,000 to 183/100,000). Twelve per cent of people had bilateral disease. [4]

**AETIOLOGY/ RISK FACTORS**

Epithelial keratitis results from productive, lytic viral infection of the corneal epithelial cells. Stromal keratitis and iritis are thought to result from a combination of viral infection and compromised immune mechanisms. Observational evidence (346 people with ocular HSV in the placebo arm of an RCT) showed that a previous history of stromal keratitis was a significant risk factor for the recurrence of stromal keratitis (proportion of people with recurrence: 6/174 [4%] without previous stromal keratitis *v* 53/172 [32%] with previous stromal keratitis; RR 10.0, 95% CI 4.3 to 23.0; P less than 0.001). [5] Age, sex, ethnicity, and previous history of non-ocular HSV disease were not associated with an increased risk of recurrence. [5]

**PROGNOSIS**

HSV epithelial keratitis tends to resolve spontaneously within 1–2 weeks, while stromal keratitis is more likely to result in corneal scarring and loss of vision. In a trial of 271 people treated with topical trifluorothymidine and randomly assigned to receive either oral aciclovir or placebo, the epithelial lesion had resolved completely or was at least less than 1 mm after 1 week of treatment with placebo in 89% of people, and after 2 weeks in 99% of people. [6] Stromal keratitis or iritis occurs in about 25% of people after epithelial keratitis. [7] The effects of HSV stromal keratitis include scarring, tissue destruction, neovascularisation, glaucoma, and persistent epithelial defects. The rate of recurrence of ocular herpes (epithelial or stromal) for people with one episode is 10% at 1 year, 23% at 2 years, and 50% at 10 years. [8] The risk of recurrent ocular HSV infection (epithelial or stromal) also increases with the number of previous episodes reported (2 or 3 previous episodes: RR 1.41, 95% CI 0.82 to 2.42; 4 or more previous episodes: RR 2.09, 95% CI 1.24 to 3.50). [5] Of penetrating corneal grafts performed in Australia over a 22-year period, 4% were in people with visual disability, with active corneal disease, or with actual or impending perforation after stromal ocular herpes simplex. [9] Of the penetrating corneal grafts reported by The Australian Corneal Graft Registry that failed, the ocular herpes simplex was a cause for failure in 4% of cases.

**AIMS OF INTERVENTION**

To reduce the morbidity of HSV keratitis and iritis; to reduce the risk of recurrent disease; and to improve corneal graft survival after penetrating keratoplasty, with minimal adverse effects of treatment.

**OUTCOMES**

Healing time; severity and duration of symptoms; severity of complications; rates of recurrence; corneal graft survival, adverse effects of treatment.

**METHODS**

*BMJ Clinical Evidence* search and appraisal July 2007. The following databases were used to identify studies for this review: Medline 1966 to July 2007, Embase 1980 to July 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical

Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We did not exclude studies described as "blinded", "open", "open label", or not blinded. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 10 ).

**QUESTION** **What are the effects of treatments in people with epithelial keratitis?**

**OPTION** **ANTIVIRAL AGENTS (TOPICAL)**

**Healing rates**

*Compared with placebo* Topical idoxuridine seems more effective at increasing the proportion of people with healing at 7 and 14 days. Topical vidarabine seems more effective at increasing the proportion of people with healing at 14 days, but not at 7 days (moderate-quality evidence).

*Compared with each other* Topical trifluridine or topical aciclovir seem more effective than topical idoxuridine at increasing the proportion of people with healing at 7 and 14 days. Topical vidarabine and topical idoxuridine seem equally effective at increasing the proportion of people with healing at 7 and 14 days (moderate-quality evidence).

*Antiviral agents (primarily topical) plus physicochemical debridement compared with physicochemical debridement alone* A topical antiviral agent plus physicochemical debridement may be more effective at increasing the proportion of people with healing at 7 and 14 days (moderate-quality evidence).

*Topical antiviral agents plus physicochemical debridement compared with topical antiviral agents alone* A topical antiviral agent plus physicochemical debridement may be more effective at increasing the proportion of people with healing at 7 days, but not at 14 days (low-quality evidence).

*Topical aciclovir plus physical debridement compared with topical idoxuridine plus physical debridement* We don't know whether topical aciclovir plus physical debridement is more effective at increasing the proportion of people with healing at 7 and 14 days (very low-quality evidence).

*Compared with topical interferons* Topical idoxuridine may be less effective than topical interferon beta at increasing the proportion of people with healing at 14 days, but not at 7 days (low-quality evidence).

*Topical antiviral agents plus topical interferons compared with topical antiviral agents alone* Topical antiviral agents plus topical interferon alfa seems more effective than topical antiviral agents alone (mainly trifluridine) at increasing the proportion of people with healing at 7 days, but not at 14 days (moderate-quality evidence)

**For GRADE evaluation of interventions for ocular herpes simplex, see table, p 10 .**

**Benefits:** We found one systematic review (search date 2006, see comment below). [10]

**Topical antiviral agents versus placebo:**
The review found that, compared with placebo, topical idoxuridine significantly increased healing after 7 and 14 days (7 days: 10 RCTs, 392 people; OR 4.05, 95% CI 2.60 to 6.30; see comment below; 14 days: 2 RCTs, 63 people; OR 4.17, 95% CI 1.33 to 13.04). [10] The review also compared topical vidarabine versus placebo, and found no significant difference in healing after 7 days, although it may have lacked power to detect a clinically important difference (1 RCT, 43 people; OR 3.08, 95% CI 0.78 to 12.12). However, it found that topical vidarabine significantly increased healing after 14 days (1 RCT, 43 people; OR 5.40, 95% CI 1.42 to 20.52).

**Topical antiviral agents versus each other:**
The review found that, compared with topical idoxuridine, topical trifluridine significantly increased healing after 7 and 14 days (7 days: 4 RCTs, 223 people; OR 4.77, 95% CI 2.66 to 8.58; 14 days: 5 RCTs, 256 people; OR 4.26, 95% CI 2.20 to 8.23). [10] The review also found that, compared with idoxuridine, topical aciclovir significantly increased healing after 7 and 14 days (7 days: 9 RCTs, 462 people; OR 4.69, 95% CI 3.13 to 7.02; 14 days: 11 RCTs, 600 people; OR 4.18, 95% CI 2.48 to 7.03). It found no significant difference between topical vidarabine and topical idoxuridine

in healing after 7 and 14 days (7 days: 3 RCTs, 243 people; OR 1.20, 95% CI 0.70 to 2.00; 14 days: 3 RCTs, 243 people; OR 1.24, 95% CI 0.65 to 2.37).

**Antiviral agents (primarily topical) plus debridement:**
See benefits of debridement, p 4 .

**Topical antiviral agents versus topical interferons:**
See benefits of topical interferons, p 5 .

**Topical antiviral agents plus topical interferons:**
See benefits of topical interferons, p 5 .

**Harms:** The review stated that harms were reported in too few trials to allow treatment comparisons. [10]

**Antiviral agents (primarily topical) plus debridement:**
See harms of debridement, p 4 .

**Topical antiviral agents versus topical interferons:**
See harms of topical interferons, p 5 .

**Topical antiviral agents plus topical interferons:**
See harms of topical interferons, p 5 .

**Comment:** Studies in the review used different methods to assess “healing”. In most, healing was assessed using fluorescein or rose-Bengal staining. In some studies, the assessment method was not reported. [10]

## OPTION DEBRIDEMENT

**Healing rates**
*Compared with placebo or no treatment* Physicochemical debridement may be no more effective than no treatment at increasing the proportion of people with healing at 7 and 14 days (very low-quality evidence).

*Physicochemical debridement plus antiviral agents (primarily topical) compared with physicochemical debridement alone* Physicochemical debridement plus a topical antiviral agent may be more effective at increasing the proportion of people with healing at 7 and 14 days (moderate-quality evidence).

*Physicochemical debridement plus topical antiviral agents compared with topical antiviral agents alone* Physicochemical debridement plus a topical antiviral agent may be more effective at increasing the proportion of people with healing at 7 days, but not at 14 days (low-quality evidence).

*Physical debridement plus topical aciclovir compared with physical debridement plus topical idoxuridine* We don't know whether physical debridement plus topical aciclovir is more effective at increasing the proportion of people with healing at 7 and 14 days (very low-quality evidence).

**For GRADE evaluation of interventions for ocular herpes simplex, see table, p 10 .**

**Benefits:** We found one systematic review (search date 2006; see comment below). [10]

**Physicochemical debridement versus placebo or no treatment:**
The review compared different types of physicochemical debridement versus no treatment, and found no significant difference in healing after 7 and 14 days (7 days: 2 RCTs, 105 people; OR 1.63, 95% CI 0.72 to 3.61; 14 days: 1 RCT, 55 people; OR 2.02, 95% CI 0.40 to 10.27). [10]

**Physicochemical debridement plus antiviral agents (primarily topical) versus physicochemical debridement alone:**
The review found that, compared with physicochemical debridement alone, physicochemical debridement plus an antiviral agent significantly increased healing after 7 and 14 days (7 days: 6 RCTs including topical antiviral treatment and 1 RCT including oral antiviral treatment, 269 people; OR 2.08, 95% CI 1.17 to 3.71; 14 days: 2 RCTs, 59 people; OR 10.81, 95% CI 1.81 to 64.50). [10]

**Physicochemical debridement plus topical antiviral agents versus topical antiviral agents alone:**
The review also found that physicochemical debridement plus a topical antiviral agent significantly increased healing after 7 days compared with topical antiviral agents alone (7 RCTs of topical antiviral agents, 305 people; OR 2.01, 95% CI 1.21 to 3.34). It found no significant difference in healing after 14 days (3 RCTs, 115 people; OR 1.45, 95% CI 0.64 to 3.29).

**Physical debridement plus topical aciclovir versus physical debridement plus topical idoxuridine:**
One RCT identified by the review compared physical debridement plus topical aciclovir versus physical debridement plus topical idoxuridine, and found no significant difference in healing after 7 and 14 days (7 days: 1 RCT, 25 people; OR 2.75, 95% CI 0.40 to 18.88; 14 days: CI not reported).

**Harms:** The review stated that harms were reported in too few trials to allow treatment comparisons. [10]

**Comment:** The review found that all methods of debriding the corneal epithelium produced similar rates of re-epithelialisation. [10] The variety of treatments used in the review limits the applicability of the summary results. Studies in the review used different methods to assess "healing". In most, healing was assessed using fluorescein or rose-Bengal staining. In some studies, the assessment method was not reported. [10]

## OPTION INTERFERONS (TOPICAL)

**Healing rates**
*Compared with placebo* Topical interferons (alfa or beta) seem more effective at increasing the proportion of people with healing at 7 and 14 days (moderate-quality evidence).

*Compared with topical antiviral agents* Topical interferon beta may be more effective than topical idoxuridine at increasing the proportion of people with healing at 14 days, but not at 7 days (low-quality evidence).

*Topical interferons plus topical antiviral agents compared with topical antiviral agents alone* Topical interferon alfa plus a topical antiviral agent seems more effective than a topical antiviral agent alone (mainly trifluridine) at increasing the proportion of people with healing at 7 days, but not at 14 days (moderate-quality evidence).

**For GRADE evaluation of interventions for ocular herpes simplex, see table, p 10 .**

**Benefits:** We found one systematic review (search date 2006; see comment below). [10]

**Topical interferons versus placebo:**
The review found that, compared with placebo, topical interferons (alfa or beta) significantly increased healing after 7 and 14 days (7 days: 3 RCTs, 178 people; OR 2.09, 95% CI 1.15 to 3.81; 14 days: 2 RCTs, 110 people; OR 3.43, 95% CI 1.30 to 9.02). [10]

**Topical interferons versus topical antiviral agents:**
The review found no significant difference in healing after 7 days between topical interferon beta and topical nucleoside antiviral agents (idoxuridine) (2 RCTs, 75 people; OR 1.18, 95% CI 0.29 to 4.75). It found that topical interferon beta significantly increased healing after 14 days compared with iduroxidine (3 RCTs, 85 people; OR 3.48, 95% CI 1.06 to 11.40). [10]

**Topical interferons plus topical antiviral agents versus topical antiviral agents alone:**
The review found that topical interferon alfa plus a topical antiviral agent significantly increased healing after 7 days compared with a topical antiviral agent alone (usually trifluridine) (8 RCTs, 401 people; OR 13.31, 95% CI 7.41 to 23.89). It found no significant difference in healing after 14 days (5 RCTs, 282 people; OR 2.62, 95% CI 0.91 to 7.57). [10]

**Harms:** The review stated that harms were reported in too few trials to allow treatment comparisons. [10]

**Comment:** Studies in the review used different methods to assess "healing". In most, healing was assessed using fluorescein or rose-Bengal staining. In some studies, the assessment method was not reported.

## QUESTION What are the effects of treatments in people with stromal keratitis?

## OPTION CORTICOSTEROIDS (TOPICAL)

**Healing rates**
*Adding topical corticosteroids to topical antiviral agents compared with adding placebo to topical antiviral agents* Adding topical prednisolone (in decreasing concentrations over 10 weeks) to topical trifluridine may be more effective than adding placebo to topical trifluridine at reducing the persistence or progression of stromal inflammation, and at reducing the duration of stromal keratitis in people with stromal keratitis (very low-quality evidence).

**For GRADE evaluation of interventions for ocular herpes simplex, see table, p 10 .**

**Benefits:**

**Adding topical corticosteroids to topical antiviral agents versus adding placebo to topical antiviral agents:**
We found one RCT (106 people all receiving topical trifluridine; see comment below) comparing topical prednisolone sodium phosphate (in decreasing concentrations over 10 weeks) versus placebo. [11] It found that, compared with placebo, topical trifluridine plus topical prednisolone significantly reduced the persistence or progression of stromal inflammation, and shortened the duration of stromal keratitis (median duration: 26 days with corticosteroid *v* 72 days with placebo; difference 46 days, 95% CI 14 days to 58 days).

**Harms:**

**Adding topical corticosteroids to topical antiviral agents versus adding placebo to topical antiviral agents:**
In the RCT, nine people in the corticosteroid group reported adverse effects. [11] Four people developed dendritic epithelial keratitis and were removed from the trial. Four people developed toxic responses to trifluridine after week 5. These people were not withdrawn, but the trifluridine was stopped. One person developed an epithelial defect and was withdrawn. Adverse events were reported in six people receiving placebo. All six were withdrawn from the study (1 person developed dendritic keratitis, 3 people developed an epithelial defect, and 2 people developed allergic conjunctivitis attributed to trifluridine within the first 9 days of the trial).

**Comment:**

The trial did not specify whether intention-to-treat analysis was performed. [11]

## OPTION ACICLOVIR (ORAL) TO TREAT STROMAL KERATITIS

**Treatment failure**
*Adding oral aciclovir to topical corticosteroids plus topical antiviral agents compared with adding placebo to topical corticosteroids plus topical antiviral agents* Adding oral aciclovir to topical corticosteroids plus topical trifluridine may be no more effective than adding placebo to topical corticosteroids plus topical trifluridine at reducing the median time to treatment failure (defined as worsening or no improvement of stromal keratitis or an adverse event) or at reducing the proportion of people with treatment failure at 16 weeks in people with HSV stromal keratitis (low-quality evidence).

**Note**
We found no direct information about oral aciclovir alone in the treatment of people with stromal keratitis.

**For GRADE evaluation of interventions for ocular herpes simplex, see table, p 10 .**

**Benefits:**

**Oral aciclovir alone:**
We found no systematic review or RCTs.

**Adding oral aciclovir to topical corticosteroids plus topical antiviral agents versus adding placebo to topical corticosteroids plus topical antiviral agents:**
We found one RCT of oral aciclovir (104 people with HSV stromal keratitis receiving concomitant topical corticosteroids and a topical antiviral agent [trifluridine]). [12] The primary outcome was time to treatment failure, defined as worsening or no improvement of stromal keratitis, or an adverse event. The RCT found no significant difference in median time to treatment failure between oral aciclovir and placebo (84 days with aciclovir *v* 62 days with placebo; P = 0.46), or in reported rates of treatment failure by week 16 (38/51 [75%] with aciclovir *v* 39/53 [74%] with placebo; RR 1.01, 95% CI 0.78 to 1.24). [12]

**Harms:**

**Oral aciclovir alone:**
We found no RCTs.

**Adding oral aciclovir to topical corticosteroids plus topical antiviral agents versus adding placebo to topical corticosteroids plus topical antiviral agents:**
The RCT found that two people in the placebo group developed adverse effects attributed to trifluridine (epithelial keratopathy in 1 person and an allergic reaction in 1 person). [12] Other adverse effects reported included pneumonia with possible pulmonary embolus (1 person), congestive heart failure (1 person), diarrhoea (1 person), oedema of the lower extremities (1 person), and anaemia (1 person). Adverse reactions reported in the aciclovir group included toxicity to trifluorothymidine (1 person), and headache (1 person).

**Comment:**

None.

**QUESTION** **What are the effects of interventions to prevent recurrence of epithelial or stromal ocular herpes simplex?**

## OPTION ACICLOVIR (ORAL) FOR 1 YEAR TO PREVENT RECURRENCE

***Recurrence rates***

*Long-term (1 year) oral aciclovir compared with placebo* In people who have had epithelial or stromal ocular HSV in the preceding 12 months, prophylactic oral aciclovir for 1 year may be more effective than placebo at reducing the the proportion of people with any type of recurrence at 1 year. Oral aciclovir may be more effective than placebo at reducing the risk of recurrence of stromal keratitis in people with previous stromal keratitis, but not in people who have not had stromal keratitis previously. In people with previous epithelial keratitis, aciclovir for 1 year may be more effective than placebo at reducing the proportion of people with recurrence of epithelial keratitis at 1 year (very low-quality evidence).

**For GRADE evaluation of interventions for ocular herpes simplex, see table, p 10 .**

**Benefits:**

**Long-term (1 year) oral aciclovir versus placebo:**
We found no systematic review, but found two RCTs. [13] [14] The first RCT (703 immunocompetent people aged at least 12 years who had epithelial or stromal ocular HSV in 1 or both eyes within the preceding 12 months) compared oral aciclovir (400 mg twice daily for 1 year) versus placebo. [13] It found that aciclovir treatment significantly reduced the risk of any type of recurrence after 1 year (19% with aciclovir *v* 32% with placebo; RR 0.55, 95% CI 0.41 to 0.75). Prespecified subgroup analysis in people with previous stromal keratitis (337 people) found that aciclovir significantly reduced the risk of recurrence of stromal keratitis compared with placebo (14% with aciclovir *v* 28% with placebo; RR 0.48, 95% CI 0.29 to 0.80). However, the risk of stromal keratitis was not reduced in people who had not had stromal keratitis previously. The RCT found no rebound in the rate of ocular HSV in the 6 months after stopping treatment. The second RCT (96 people aged 7–62 years, 79 with epithelial, 20 with stromal ocular HSV in one eye) compared topical plus oral aciclovir (200 mg twice daily for two weeks, and then 100 mg three times daily) versus placebo for 1 year. [14] Prespecified subgroup analysis in people with previous epithelial keratitis (76 people) found that aciclovir significantly reduced the proportion of people with recurrence of epithelial keratitis over 1 year (5/38 [13%] with aciclovir *v* 14/38 [37%] with placebo P less than 0.01). Three people with epithelial keratitis who stopped oral aciclovir spontaneously because of fevers (unclear after how long) experienced dendritic corneal ulcer relapse; with repeated treatment (unclear what treatment was given) there was no recurrence within the next 6 months. There were too few participants with stromal keratitis (20 people) to assess the significance of the difference in recurrence between groups (proportion with recurrence: 1/10 [1%] with aciclovir *v* 4/10 [4%] with placebo; significance not reported).

**Harms:**

The first RCT found that adverse effects (mostly gastrointestinal problems) were uncommon, and occurred with similar frequency in both groups. [13] Thirty-two people (15/357 [4%] with aciclovir *v* 17/346 [5%] with placebo; significance not assessed) stopped treatment because of adverse effects. The main adverse effect leading to discontinuation was gastrointestinal upset (7/15 [47%] with aciclovir *v* 9/17 [53%] with placebo; significance not assessed). The second RCT gave no information on adverse effects other than to state that three people taking oral aciclovir had stopped treatment because of fevers. [14]

**Comment:**

None.

## OPTION ACICLOVIR (ORAL) FOR 3 WEEKS TO PREVENT RECURRENCE

**Recurrence rates**

*Short-term (3 weeks) oral aciclovir compared with placebo* A 3-week course of oral aciclovir seems no more effective than placebo at reducing the proportion of people with stromal keratitis or iritis, or at reducing the cumulative risk of developing stromal keratitis or iritis at 1 year, in people with epithelial keratitis who had been treated with topical trifluridine (moderate-quality evidence).

**For GRADE evaluation of interventions for ocular herpes simplex, see table, p 10 .**

**Benefits:**

**Short-term (3 weeks) oral aciclovir versus placebo:**
We found no systematic review. We found one RCT (287 people with epithelial keratitis all treated with topical trifluridine), comparing a 3-week course of oral aciclovir versus placebo. [6] It found no significant difference between aciclovir and placebo in the rate of stromal keratitis or iritis (11% with aciclovir *v* 10% with placebo; RR 1.04, 95% CI 0.52 to 2.10), or in the cumulative risk of developing stromal keratitis or iritis at 1-year follow-up (12% with aciclovir *v* 11% with placebo; P = 0.92).

**Harms:** The RCT gave no information on adverse effects. [6]

**Comment:** None.

**QUESTION** **What are the effects of interventions to prevent recurrence of ocular herpes simplex in people with corneal grafts?**

**OPTION** **ACICLOVIR (ORAL) TO PREVENT RECURRENCE AFTER CORNEAL GRAFTS**

**Recurrence rates**
*Compared with placebo* Oral aciclovir started before surgery, or on the first day after surgery, may be more effective at reducing the number of recurrences of ocular herpes simplex at a mean follow up of 17–21 months in people who had received keratoplasty (very low-quality evidence).

**Graft failure**
*Compared with placebo* Oral aciclovir started before surgery, or on the first day after surgery, may be more effective at reducing the proportion of eyes with graft failure in people who had received keratoplasty (low-quality evidence).

**For GRADE evaluation of interventions for ocular herpes simplex, see table, p 10 .**

**Benefits:** **Oral aciclovir versus placebo:**
We found no systematic review. We found one small open label RCT (22 people [23 eyes] who had received keratoplasty), which compared oral aciclovir (800 or 1000 mg, 4 or 5 times daily, tapered during the first 12 months, for a maximum of 15 months) versus placebo. [15] Oral aciclovir was started before surgery or on the first day after surgery. The RCT found that, compared with placebo, oral aciclovir significantly reduced the number of recurrences of ocular herpes simplex after a mean follow-up of 17 months in people receiving aciclovir, and of 21 months in those receiving placebo (0% with aciclovir *v* 44% with placebo; P less than 0.01), and also that aciclovir significantly reduced the proportion of eyes with graft failure compared with usual care (14% with aciclovir-treated eyes *v* 56% with placebo-treated eyes; P less than 0.05).

**Harms:** The review gave no information on adverse effects associated with oral aciclovir. [15]

**Comment:** None.

## GLOSSARY

**Keratoplasty** A procedure in which diseased corneal tissue is removed and replaced by donor corneal material.

**Low-quality evidence** 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.

**Moderate-quality evidence** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Very low-quality evidence** Any estimate of effect is very uncertain.

## SUBSTANTIVE CHANGES

**Aciclovir (oral) for 1 year to prevent recurrence** One RCT added that confirmed previous conclusions that aciclovir given prophylactically for 1 year reduces recurrence of ocular herpes simplex. [14] Categorisation unchanged (Beneficial).

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## Disclaimer

**TABLE** **GRADE evaluation of interventions for ocular herpes simplex**

| **Important outcomes** | **Healing rates, recurrence rates, treatment failure, graft failure.** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Number of studies (participants)** | **Outcome** | **Comparison** | **Type of evidence** | **Quality** | **Consistency** | **Directness** | **Effect size** | **GRADE** | **Comment** |
| What are the effects of treatments in people with epithelial keratitis? | | | | | | | | | |
| At least 11 (at least 435) [10] | Healing rates | Topical antiviral agents *v* placebo | 4 | 0 | 0 | –1 | 0 | Moderate | Directness point deducted for unclear measurement of outcomes |
| At least 16 (at least 856) [10] | Healing rates | Topical antiviral agents *v* each other | 4 | 0 | 0 | –1 | 0 | Moderate | Directness point deducted for unclear measurement of outcomes |
| At least 2 (at least 105) [10] | Healing rates | Physicochemical debridement *v* placebo or no treatment | 4 | –1 | 0 | –2 | 0 | Very low | Quality point deducted for sparse data. Directness points deducted for variety of treatments used limiting applicability of summary results, and unclear measurement of outcomes |
| At least 7 (at least 269) [10] | Healing rates | Physicochemical debridement plus antiviral agents (primarily topical) *v* physicochemical debridement alone | 4 | 0 | 0 | –2 | +1 | Moderate | Directness points deducted for variety of treatments used limiting applicability of summary results, and unclear measurement of outcomes. Effect-size point added for OR greater than 2 |
| At least 7 (at least 305) [10] | Healing rates | Physicochemical debridement plus topical antiviral agents *v* topical antiviral agents alone | 4 | 0 | 0 | –2 | 0 | Low | Directness points deducted for variety of treatments used limiting applicability of summary results, and unclear measurement of outcomes |
| 1 (25) [10] | Healing rates | Physical debridement plus topical aciclovir *v* physical debridement plus topical idoxuridine | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for unclear measurement of outcome |
| At least 3 (at least 178) [10] | Healing rates | Topical interferons *v* placebo | 4 | 0 | 0 | –2 | +1 | Moderate | Directness points deducted for two interventions included in comparison, and unclear measurement of outcome. Effect-size point added for OR greater than 2 |
| At least 3 (at least 85) [10] | Healing rates | Topical interferons *v* topical antiviral agents | 4 | –1 | 0 | -1 | 0 | Low | Quality point deducted for sparse data. Directness point deducted for unclear measurement of outcome |
| At least 8 (at least 401) [10] | Healing rates | Topical interferons plus topical antiviral agents *v* topical antiviral agents alone | 4 | 0 | 0 | –1 | 0 | Moderate | Directness point deducted for unclear measurement of outcome |
| What are the effects of treatments in people with stromal keratitis? | | | | | | | | | |
| 1 (106) [11] | Healing rates | Adding topical corticosteroids to topical antiviral agents *v* adding placebo to topical antiviral agents | 4 | –3 | 0 | 0 | 0 | Very low | Quality points deducted for sparse data, incomplete reporting of results, and unclear follow-up |
| 1 (104) [12] | Treatment failure | Adding oral aciclovir to topical corticosteroids plus topical antiviral agents *v* adding placebo to topical corticosteroids plus topical antiviral agents | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for sparse data. Directness point deducted for composite outcome |
| What are the effects of interventions to prevent recurrence of epithelial or stromal ocular herpes simplex? | | | | | | | | | |

| **Important outcomes** | **Healing rates, recurrence rates, treatment failure, graft failure.** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Number of studies (participants)** | **Outcome** | **Comparison** | **Type of evi-dence** | **Quality** | **Consis-tency** | **Direct-ness** | **Effect size** | **GRADE** | **Comment** |
| 2 (779) [13] [14] | Recurrence rates | Long-term (1 year) oral aciclovir *v* placebo | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for incomplete reporting of results and sub-group analysis. Directness point deduction for inclusion of co-intervention (topical aciclovir) |
| 1 (287) [6] | Recurrence rates | Short-term (3 weeks) oral aciclovir *v* placebo | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| What are the effects of interventions to prevent recurrence of ocular herpes simplex in people with corneal grafts? | | | | | | | | | |
| 1 (22 people, 23 eyes) [15] | Recurrence rates | Oral aciclovir *v* placebo | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and lack of blindingl. Directness point deducted for differ-ence in mean follow-up length of groups |
| 1 (22 people, 23 eyes) [15] | Graft failure | Oral aciclovir *v* placebo | 4 | –2 | 0 | 0 | 0 | Very low | Quality points deducted for sparse data and lack of blinding |

Type of evidence: 4 = RCT; 2 = Observationa. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio