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[Intervention Protocol]

Topical pharmacologic interventions versus placebo for epidemic keratoconjunctivitis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of various topical pharmacological therapies versus placebo for adults with epidemic keratoconjunctivitis (EKC).

BACKGROUND

Description of the condition

Viruses cause about 80% of all cases of acute conjunctivitis (Fitch 1989; Matsui 2008; Ronnerstam 1985; Stenson 1982; Uchio 2000; Woodland 1992). Human adenoviruses (HAdVs) are believed to account for 65% to 90% of cases of viral conjunctivitis (O'Brien 2009), or 20% to 75% of all causes of infectious keratoconjunctivitis worldwide, making them the most common cause of viral conjunctivitis (Gigliotti 1981; Ishii 1987; Woodland 1992).

Epidemic keratoconjunctivitis (EKC) is a highly infectious subset of conjunctivitis caused by HAdVs. In a six-month period in Chicago, 401 individuals (patients, staff, doctors) developed EKC at the Illinois Eye and Ear Infirmary, University of Illinois, Chicago, USA (Warren 1989). EKC is accompanied by severe conjunctival inflammation, watery discharge, and light sensitivity, and can lead to chronic complications such as corneal and conjunctival scarring (Dawson 1972). These clinical findings are accompanied by discomfort and poor quality of vision.

There are seven species of HAdVs; HAdV types in the B and D species can cause ocular infections. In addition to HAdV-D8, D19 (now retyped as D64; Zhou 2012) and D37 cause EKC. In the last two decades new viral genomes that can cause EKC have been identified. Some B-species types (for example, type 3) cause less severe conjunctivitis (Meyer-Rusenberg 2011), but can cause fatal pneumonia especially in individuals with immature or compromised immune systems such as neonates (Sammons 2019). Other HAdV types can cause pneumonia, encephalitis, sepsis, and death in healthy people; hence the development and use of a vaccine for type 7 [HBS1] in military recruits. It is important to note that the original nomenclature is undergoing revision as a result of whole genome sequencing, which also is leading to identification of new pathogens that cause EKC. Recombination events, to which HAdV-D types are susceptible, are also leading to the evolution of new pathogen genomes.

The incubation period for adenoviral ocular infections is 2 to 14 days. EKC begins unilaterally, but often spreads to the unaffected eye. Patients with EKC present with severe inflammation of the cornea and conjunctiva accompanied by clear discharge, lid swelling, light sensitivity, and foreign body sensation. This acute phase can last two weeks. In a subset of patients with EKC, complications such as corneal subepithelial infiltrates (SEIs) develop. SEIs can affect vision for months to a year (Butt 2006), and can result in permanent corneal scarring and permanent decreased vision. Other complications include symblepharon, conjunctival scarring, lacrimal drainage abnormalities (Hyde 1988), dry eye, and symblepharon formation (Hammer 1990).

Epidemiology

Most cases of EKC affect adults aged 20 to 40 years old, and males and females are affected equally (Ford 1987). Precise incidence and prevalence rates of EKC are unknown because most cases of "red eye" (including EKC) are seen first by non-ophthalmologists; in one study of patients in a national managed care network, over 80% of cases of acute conjunctivitis were seen by non-ophthalmologists (Shekhawat 2017).

Adenoviral infections (including conjunctivitis) are reportable to national registries in Japan and German for national surveillance

(Hiroi 2013; Meyer-Rusenberg 2011; Tabbara 2010), but are not reportable in most countries (CDC 2013; Ford 1987). The Centers for Disease Control and Prevention (CDC) in the USA established a voluntary registry for adenoviral infections in 2014 (CDC 2017).

Transmission of adenoviral infection is predominantly through contact with ocular secretions via contaminated surfaces, instruments, eyedroppers, bottle tips, or hands. It is believed that a person can be infectious from a few days before symptoms develop to approximately 14 days after symptom onset. Infection rates vary, but have been reported to be as high as 50% in a long-term care facility in France (Piednoir 2002). Investigators of another study based on a simultaneous outbreak of EKC in a large ophthalmologic institute in Chicago and in the community estimated the secondary household attack rates to be 20% (Vastine 1976).

Presentation

Symptoms of EKC usually appear within 14 days after exposure and typically last 7 to 21 days (Meyer-Rusenberg 2011). Corneal involvement (keratitis and SEIs; hence, the term "keratoconjunctivitis") can occur in 50% of patients with EKC (Tabbara 2010). Epithelial keratitis occurs around day 7; in the corresponding subepithelial locations, SEI can develop as early as in the second week of presentation, but usually in the 3rd or 4th week after onset of acute infection (Dosso 2008). SEIs are considered pathognomonic for previous EKC; they represent cellular immune reaction to viral antigens deposited beneath Bowman's layer (Jones 1958).

Histopathological investigation of SEIs reveals lymphocytes, histiocytes, and fibroblasts that are accompanied by disruption of the collagen fibers of the Bowman layer (Lund 1978). Pseudomembranes may occur in a high proportion of patients with EKC (Fukumi 1958; Laibson 1968). Pseudomembranes are sheets of fibrin-rich exudate lacking blood or lymphatic vessels adhered to the upper and lower tarsal conjunctiva. SEI has been observed in over 40% of cases in an outbreak. In a six-year study at a tertiary ophthalmology clinic, 25% of patients had symptomatic infiltrates persisting 45 days after presentation (Butt 2006). These infiltrates can persist for months to years and cause disabling visual symptoms, such as blurriness, glare, haloes, and light sensitivity. In some cases, SEIs are permanent. In the same study (Butt 2006), 24% of patients had pseudomembranes or membranes; 15% of this subset developed symblepharon, which can cause dry eye symptoms, diplopia from restriction of ocular motility, mucus discharge, and redness.

Outbreaks of EKC typically occur in healthcare environments such as hospitals and eye clinics (Hamada 2008; Montessori 1998; Warren 1989), but also occur in the community (Darougar 1983; Dawson 1963; Jawetz 1959; Kuo 2018). EKC is diagnosed more often from July through September (Lee 2018). Global health impacts of EKC outside high-income countries are not widely known. It is known, however, that seasonal and spontaneous outbreaks of adenoviral infections, ocular or not, occur in Africa and Asia that are unrelated to exposure in healthcare environments. In fact, studies indicate that adenoviral infections are endemic in the community with shifting prevalence of causative types (Barnadas 2018; Hiroi 2013; Kuo 2018; Lin 2019).

Diagnosis

Diagnosis is primarily clinical because laboratory testing, using the gold standards of viral culture or polymerase chain reaction (PCR) assays to detect HAdV in conjunctival specimens, is not widely available or routinely performed. Whole genome sequencing may soon be the next gold standard, but this testing is not yet widely available (Singh 2015).

Rapid point-of-care testing for adenoviral conjunctivitis (based on virus hexon antigen detection) has variable sensitivity, from 39.5% to 90% against the gold standards of PCR or culture (Kam 2015; Sachdev 2018).

Lack of a rapid, accessible diagnostic test makes diagnosis of adenoviral conjunctivitis in "red eyes" difficult for non-ophthalmologists.

In an unpublished study, clinical diagnosis of adenoviral conjunctivitis by corneal specialists had a clinical accuracy of 48% (unpublished data alluded to in O'Brien 2009). Of all presentations of ocular adenoviral infection, EKC is the most striking. Therefore, clinical accuracy is likely higher for EKC than it is for adenoviral conjunctivitis in general. Moreover, because the signs and symptoms of EKC can be severe, it is believed that most affected patients will be seen by an ophthalmologist for diagnosis.

Treatment options

No antiviral drug is available for treating EKC. Antibiotics are not effective against adenovirus or EKC. Shekhawat 2017 found that non-ophthalmologists prescribed antibiotics for patients with acute conjunctivitis, many with presumed viral conjunctivitis, at a much higher rate than ophthalmologists. This practice increases antibiotic resistance, particularly for fluoroquinolones, which are commonly first-line treatment prescribed for red eye by many non-ophthalmologists; they are used more judiciously by ophthalmologists (Asbell 2015; McDonald 2010). Surprisingly, many non-ophthalmologists also prescribe steroid-antibiotic combination drops for acute conjunctivitis (Shekhawat 2017), despite the inherent risks of topical steroid use. Treatment preferences for EKC are wide-ranging, reflecting lack of accessible, accurate diagnostic testing; the wide range of providers (pediatricians, urgent care doctors, internists, ophthalmologists; physicians, optometrists, and nurses) who treat such patients; and lack of consensus on the best treatment.

Description of the intervention

The goals of pharmacotherapy are to lessen the severity of symptoms, to shorten the duration of signs and symptoms from infection and inflammation, to restore comfort and visual function, and to decrease the likelihood of long-term morbidity and complications without long-term dependence on pharmacotherapy. One outcome in studies, although not common, is prevention of transmission to the fellow eye. This outcome is difficult to ascertain. As incubation time in the fellow eye may precede initiation of pharmacotherapy, many therapies may be ineffective against fellow eye transmission.

Although the sequelae of EKC can be long-lasting, EKC is usually self-limited. Supportive care in the form of lubrication and cold compresses can provide symptom relief. Other treatments include topical corticosteroids (Laibson 1970), virustatic agents

like cidofovir (Hillenkamp 2001), interferon B (Romano 1980), cyclosporine A (CsA) (Hillenkamp 2001; Reinhard 2000), tacrolimus (Berisa 2017), non-steroidal anti-inflammatory drugs (Shiuey 2000), antiseptic povidone iodine (PVP-I) (Isenberg 2002; Kovalyuk 2017; Pelletier 2009), and combination PVP-I and corticosteroid (Pepose 2018).

How the intervention might work

It is believed that an immune response to viral antigens occurs on the cornea SEI, which then diffuses into the cornea (Dawson 1972; Jones 1958). Corticosteroids suppress the inflammatory response and delay infiltrate formation, thus relieving symptoms caused by SEI. Given early in the course of infection, corticosteroids may increase viral replication and prolong viral shedding (Romanowski 1996; Romanowski 2001). However, when corticosteroid use is discontinued, the infiltrates return (Laibson 1970). The other risks of topical steroid use include increased intraocular pressure (putting the eye at risk for developing glaucoma) and cataract formation.

Topical cyclosporine A (CsA), interferon, and tacrolimus may both modulate and suppress inflammatory responses. A study of the effects of topical CsA yielded the same results of corticosteroids with improved symptoms during medication use, but recurrence of SEI when the medication was discontinued (Jeng 2011).

Interferon-b, an immunomodulator secreted by virally-infected cells, may act by inducing an antiviral state or modulating the immune response (Uchio 2011).

Topical tacrolimus has also been used for SEIs (Berisa 2017). With a median of about a year of follow-up, in about 60% of eyes tacrolimus drops or ointment for a median time of six months reduced the number and size of SEIs, and in 32% SEIs were eliminated. The improvement in visual acuity after treatment was statistically significant. About 19% of eyes had recurrence after discontinuation for a mean of seven months.

Topical virustatic agents, such as cidofovir, may reduce viral replication and possibly prevent some sequelae of infection. Cidofovir (a cytosine analog) inhibits DNA polymerase. Topical cidofovir has been shown to be effective against adenovirus in cases of pediatric bone marrow transplantation and may be effective in EKC (Hillenkamp 2001). It was shown, however, to cause ocular surface toxicity. When tested in humans with and without cyclosporine, cidofovir appeared to have no effect on the disease course or the symptoms of SEI (Hillenkamp 2002).

Topical antiseptic agents, such as PVP-I, can potentially reduce the viral load by killing the infectious agent on contact (Isenberg 2002). Recent clinical trials of PVP-I and combination dexamethasone with PVP-I showed promising results in improving clinical symptoms and shortening recovery time compared with vehicle (Pepose 2018). PVP-I is a broad-spectrum antiseptic that is effective at inactivating adenovirus on contact (Isenberg 2002). Results from a randomized, controlled phase 2 trial of PVP-I 0.6% and dexamethasone 0.1% vs PVP-I alone vs vehicle for treatment of adenoviral conjunctivitis in 144 patients in India were recently published (Pepose 2018). Combining a topical antiseptic such as PVP-I with corticosteroids may mitigate viral replication while suppressing the formation of SEI.

PVP-I alone was no different from PVP-I/dexamethasone in viral eradication (as measured by negative cell culture immunofluorescence assay (CC-IFA)) and no different in length of time to clinical resolution (Pepose 2018). Phase 3 trials that include pediatric patient are underway.

Endogenous antimicrobial N-chlorotaurine (Teuchner 2005) has been tried for treatment of EKC but is not as effective as cidofovir (Romanowski 2006; Teuchner 2005; Uchio 2010).

Topical NSAIDs, such as ketorolac, are sometimes used to reduce inflammation without the side effects of topical corticosteroids but have not been shown to reduce signs or symptoms of adenoviral conjunctivitis (Shiuey 2000).

Why it is important to do this review

A clear “standard of care” is lacking because of lack of consensus about the efficacy of any pharmacotherapy in altering the clinical course. Therefore, we will compare virustatic agents and immune-modulating topical therapies against placebo. We will consider the ones believed to be the most promising as some treatments, such as ketorolac and chlorotaurine, have been shown to be ineffective and are rarely used anymore. Supportive care in the case of EKC usually entails artificial tears. Investigators of most published studies have compared medications against artificial tears or vehicle drops. A few studies reported a three-way comparison of povidone-iodine 0.6% and dexamethasone 0.1% (PVP-I/dexamethasone) vs povidone-iodine 0.6% vs vehicle (1:1:1) (Pepose 2018). Another three-arm trial compared non-preserved artificial tears, prednisolone acetate 1% non-preserved artificial tears, and cyclosporine 2% and non-preserved artificial tears (Asena 2017).

It is important to examine the evidence for pharmacologic therapies for epidemic keratoconjunctivitis because it is unclear whether these therapies offer quicker resolution of signs and symptoms than no treatment or vehicle (which is usually artificial tears, an over-the-counter saline solution). There are also unintended effects of treatment as well as costs associated with treatment. Therapies may induce drug allergy, sensitivity, or toxicity to the patient's eye and may cost much more than vehicle or no treatment.

OBJECTIVES

To assess the efficacy and safety of various topical pharmacological therapies versus placebo for adults with epidemic keratoconjunctivitis (EKC).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs). If we do not identify any RCTs, we will include quasi-randomized clinical trials (those using quasi-random methods of treatment allocation such as alternation, date of birth, or case record number).

Types of participants

We will include studies that enrolled adult participants with clinically-suspected or laboratory-confirmed epidemic

keratoconjunctivitis (EKC). We will exclude studies of acute hemorrhagic conjunctivitis, which can be caused by viruses other than adenovirus, or pharyngoconjunctival fever which is caused by adenovirus but is less severe than EKC.

Types of interventions

Main interventions of interest are corticosteroids, antiseptic agents (PVP-I), and CsA.

Control: placebo, vehicle, or no treatment.

Types of outcome measures

Primary outcomes

- Symptom resolution.

Mean time (days) from initiation of treatment until symptoms of tearing and discomfort are resolved. Symptoms of discomfort include pain, itching, foreign body sensation, and photophobia.

Proportion of participants with subjectively resolved symptoms by day 7 after initiation of treatment.

- Sign resolution.

Mean time (days) from initiation of treatment until signs are resolved. Examples of signs assessed clinically would be chemosis, hyperemia, bulbar conjunctival injection (redness), and SEI. Proportion of participants with resolved signs by day 7 after initiation of treatment.

Secondary outcomes

RCTs on treatment of epidemic keratoconjunctivitis report on a wide variety of outcomes. Therefore, we included as many outcomes we believed might be relevant but not all outcomes will likely be evaluated in any one study.

- Proportion of participants in whom SEIs had developed by day 21 after initiation of treatment.
- Proportion of participants with disappearance of SEIs by day 21 after initiation of treatment. If SEIs do not resolve, this finding should be recorded as well.
- Proportion of participants who discontinued medication for infiltrates without rebound signs and symptoms by day 21 after initiation of treatment.
- Proportion of participants with evidence of adenoviral eradication (i.e. negative cell culture immunofluorescence assay (CC-IFA) or other test) by day 14 after initiation of treatment.
- Proportion of fellow eyes with signs/symptoms of infection within 7 days of onset of signs/symptoms in first eye.

For all primary and secondary outcomes, if data at the time point(s) of interest are unavailable, we will use the data at the time point closest to the one(s) specified.

Adverse effects

We will report proportion of participants with:

- Severe discomfort in the eye
- Severe conjunctival reaction such as redness or excessive tearing or other discharge (which would indicate toxicity)

- Rebound of SEIs after cessation of topical medication (and length of time between cessation and rebound occurrence if length of time was noted)
- Higher than average intraocular pressure (which topical steroid drops can cause (≥ 22 mmHg))
- Bacterial superinfection (presumably from immune suppression by study medication)

at the longest follow-up time point.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision (CEV) Information Specialist will search the following electronic databases for RCTs and controlled clinical trials. There will be no restrictions to language or year of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the CEV Trials Register) in the Cochrane Library (latest issue) ([Appendix 1](#)).
- MEDLINE Ovid (1946 to present) ([Appendix 2](#)).
- Embase (1947 to present) ([Appendix 3](#)).
- PubMed (1948 to present) ([Appendix 4](#)).
- LILACS (Latin American and Caribbean Health Science Information Database (1982 to present) ([Appendix 5](#)).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) ([Appendix 6](#)).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip) ([Appendix 7](#)).

Searching other resources

We will search reference lists of included studies to identify any additional eligible studies. We will not handsearch conference proceedings or journals specifically for this review; abstracts from many conferences have been identified by Cochrane collaborators and included in CENTRAL.

Data collection and analysis

Selection of studies

After duplicates are removed from the search results, two review authors will independently screen titles and abstracts of all records identified by the search using the internet-based review management software Covidence ([Covidence](#)). The review authors will classify each record as either relevant or irrelevant for full-text review. Two review authors will independently assess the full-text copies of all reports from studies that they identify as relevant during title and abstract screening to determine whether the studies meet the inclusion criteria. We will contact the trial authors to clarify any details necessary to make a complete assessment of study eligibility. If the trial authors do not respond within 14 days, we will proceed with information available from publications and trial registers. We will document reasons for exclusion for each study assessed as ineligible after assessment of the full-text articles, and will record the reasons for exclusion in a 'Characteristics of excluded studies' table. We will resolve all discrepancies between review authors by discussion at each stage of the screening process.

Data extraction and management

Two review authors will independently extract data from included trials using Covidence ([Covidence](#)). We will extract the following information: study setting, countries where participant recruitment took place, sample size, study duration, planned and actual participant follow-up time, study design features, method of analysis (e.g. intention to treat, completers only), sources of funding, and potential conflicts of interests, characteristics of the participants), underlying disease conditions, prevalence of symptoms at time of diagnosis (pain, tearing/watery discharge, itching, foreign body sensation, and photophobia), clinical findings at diagnosis (chemosis, hyperemia, bulbar conjunctival injection, epithelial keratitis, subepithelial epithelial infiltrates, medical history (clinically-suspected or laboratory-confirmed EKC), type of topical interventions (e.g. virustatic agents (cidofovir), antiseptic agents, immune modulators and suppressors (e.g. corticosteroid, interferon, cyclosporine A, tacrolimus), alternative medication, or placebo (no treatment)), outcomes (e.g. domain, specific measurement, specific metric, method of aggregation, and timeframe), and quantitative results.

Two review authors will compare the extracted data and resolve any discrepancies by discussion. One review author will enter data into Review Manager 5 ([Review Manager 2014](#)), and a second review author will verify data entry.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in included studies, following guidance described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2017](#)). Specific items for consideration will include random sequence generation and allocation concealment before treatment allocation (selection bias), masking of participants and study personnel (performance bias), masking of outcome assessors (detection bias), missing data and intention-to-treat analysis (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. We will assign each item as having 'low risk', 'high risk', or, if the information provided is insufficient to make an assessment, 'unclear risk'. We will document reasons for those assessments and resolve any discrepancies through discussion. We will summarize the overall assessments of the potential for bias using 'Risk of bias' summary figure and graph ([Higgins 2017](#)).

Measures of treatment effect

We will use mean difference values for comparison of continuous outcomes, including mean time (days) from initiation of treatment until clinically assessed signs and symptoms are resolved. We will use relative risks for comparison dichotomous or categorical outcomes, including the proportion of participants with resolved clinical signs and subjective symptoms, proportion of participants who developed SEIs, developed SEIs, saw a disappearance in SEIs, and any adverse effects.

Unit of analysis issues

Although EKC is often bilateral, unilateral infection can occur. We will assess whether the included studies included one or both eyes from each participant and whether study investigators randomized at the participant level or at the eye level. We will extract estimates that properly accounted for the correlation of two eyes from the

same participant. Since certain medical treatments, such as topical beta blockers when used in one eye, have the potential to influence the outcome in the contralateral eye, in the sensitivity analysis we will exclude studies that had a paired design.

Dealing with missing data

Where data on included studies are unclear or missing, we will request information from the authors of study reports. Should there be no response within two weeks, we will analyze the data using the best information available. In the event that the quality of the available data prevents any meaningful analysis, we will omit the study from quantitative analyses and note this decision in the discussion.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by examining participant characteristics, pharmacotherapies, and outcomes by carefully reviewing the study reports and taking into consideration potential risk of bias. We will summarize findings in forest plots and examine the I^2 value and its confidence interval. We will consider an I^2 value greater than 50% as indicative of substantial statistical heterogeneity, suggesting that a meta-analysis may not be appropriate; however, we will consider to the consistency of the effect estimates across studies. If all estimates are in the same direction, we may report a meta-analysis even in the presence of substantial statistical heterogeneity and will comment on the heterogeneity.

Assessment of reporting biases

We will assess small study effect, which could be due to publication bias, using funnel plots when there are more than 10 trials that met the eligibility criteria for this review. We will assess selective reporting as part of the 'Risk of bias' assessment.

Data synthesis

We will follow the recommendations in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* for data synthesis and analysis (Deeks 2017). We will use random-effects models to compute overall effect estimates except when we have fewer than three included studies in an analysis. Otherwise, we will provide a descriptive qualitative synthesis of studies and their results. We will compare antiviral agents (cidofovir), antiseptic agents, immune modulators and suppressors (e.g. corticosteroid, interferon, cyclosporine A, tacrolimus) versus placebo or no treatment.

Subgroup analysis and investigation of heterogeneity

We will analyze outcomes by type of pharmacological intervention.

Sensitivity analysis

We will conduct sensitivity analyses to determine the impact of source of study funding and studies that used a paired eye design.

Summary of findings

We will use the GRADE approach to assess the certainty of evidence (effect estimates) and will present a 'Summary of findings' table that includes estimates for no more than seven outcomes. The seven outcomes will include the primary outcome and all secondary outcomes.

The primary outcomes are mean time from initiation of treatment until resolution of signs, symptoms, or both, and proportion of participants with resolved signs, symptoms, or both by days 7 after treatment initiation.

The secondary outcomes are:

- proportion of participants in whom SEIs had developed by day 21 after initiation of treatment.
- proportion of participants with disappearance of SEIs by day 21 after initiation of treatment.
- proportion of participants who discontinued medication for infiltrates without rebound signs and symptoms by day 21 after initiation of treatment.
- proportion of participants with evidence of adenoviral eradication (i.e. CC-IFA or other test) by day 14 after initiation of treatment.
- proportion of fellow eyes with signs/symptoms of infection within seven days of onset of signs/symptoms in first eye.

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APPENDICES

Appendix 1. CENTRAL search strategy

```
#1 MeSH descriptor: [Keratoconjunctivitis] explode all trees
#2 MeSH descriptor: [Conjunctivitis] this term only
#3 MeSH descriptor: [Conjunctivitis, Viral] explode all trees
#4 MeSH descriptor: [Keratitis] explode all trees
#5 (Keratoconjunctiv* or Conjunctiv* or keratiti* or EKC or AKC)
#6 (pink eye* or pinkeye*)
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Adenoviridae Infections] this term only
#9 MeSH descriptor: [Adenovirus Infections, Human] explode all trees
#10 MeSH descriptor: [Adenoviridae] explode all trees
#11 MeSH descriptor: [Adenoviruses, Human] explode all trees
#12 (adenoviridae* or adenovirus* or adenoviral* or (adeno NEXT/1 virus*) or (adeno NEXT/1 viral*) or antiadenoviral* or antiadenovirus*)
#13 (pharyngo conjunctival Fever or pharyngoconjunctival fever or pharyngeal conjunctival fever or pharyngealconjunctival fever)
#14 epidemic*
#15 (virus* or viral* or antiviral*)
#16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 #7 AND #16
#18 MeSH descriptor: [Eye] explode all trees
#19 MeSH descriptor: [Eye Infections] this term only
#20 MeSH descriptor: [Eye Infections, Viral] explode all trees
#21 (eye* or ocular*)
#22 #18 or #19 or #20 or #21
#23 #8 or #9 or #10 or #11 or #12 or #13
#24 #22 and #23
#25 #17 OR #24
```

Appendix 2. MEDLINE Ovid search strategy

```
1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
```

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Keratoconjunctivitis/
13. Conjunctivitis/
14. exp Conjunctivitis, Viral/
15. exp Keratitis/
16. (Keratoconjunctiv* or Conjunctiv* or keratiti* or EKC or AKC).tw.
17. (pink eye* or pinkeye*).tw.
18. 12 or 13 or 14 or 15 or 16 or 17
19. Adenoviridae Infections/
20. exp Adenovirus Infections, Human/
21. exp Adenoviridae/
22. exp Adenoviruses, Human/
23. (adenoviridae* or adenovirus* or adenoviral* or adeno virus* or adeno viral* or antiadenoviral* or antiadenovirus*).tw.
24. (pharyngo conjunctival Fever or pharyngoconjunctival fever or pharyngeal conjunctival fever or pharyngealconjunctival fever).tw.
25. epidemic*.tw.
26. (virus* or viral* or antiviral*).tw.
27. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 18 and 27
29. exp eye/
30. Eye Infections/
31. exp Eye Infections, Viral/
32. (eye* or ocular*).tw.
33. 29 or 30 or 31 or 32
34. 19 or 20 or 21 or 22 or 23 or 24
35. 33 and 34
36. 28 or 35
37. 11 and 36

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

Appendix 3. Embase 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 'keratoconjunctivitis'/exp
#34 'viral conjunctivitis'/exp
#35 'conjunctivitis'/de
#36 'acute hemorrhagic conjunctivitis'/exp
#37 'hemorrhagic conjunctivitis'/exp
#38 'keratitis'/de
#39 'virus keratitis'/exp
#40 (Keratoconjunctiv* or Conjunctiv* or keratiti* or EKC or AKC):ab,ti,kw
#41 ('pink eye*' or pinkeye*):ab,ti,kw
#42 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
#43 'human adenovirus infection'/exp
#44 'adenovirus infection'/de
#45 'adenovirus'/exp
#46 (adenoviridae* OR adenovirus* OR adenoviral* OR 'adeno virus' OR 'adeno viral' OR antiadenoviral* OR antiadenovirus*):ab,ti,kw
#47 ('pharyngoconjunctival fever' OR 'pharyngo conjunctival fever' OR 'pharyngeal conjunctival fever' OR 'pharyngealconjunctival fever'):ab,ti,kw
#48 epidemic*:ab,ti,kw
#49 (virus* OR viral* OR antiviral*):ab,ti,kw
#50 #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
#51 #42 AND #50
#52 'eye'/exp
#53 'eye infection'/de
#54 'viral eye infection'/exp
#55 (eye* OR ocular*):ab,ti,kw
#56 #52 OR #53 OR #54 OR #55
#57 #43 OR #44 OR #45 OR #46 OR #47
#58 #56 AND #57
#59 #51 OR #58
#60 #32 AND #59
```

Appendix 4. PubMed search strategy

```
1. ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
2. (Keratoconjunctiv*[tw] OR Conjunctiv*[tw] OR keratiti*[tw] OR EKC[tw] OR AKC[tw])
3. (pink eye*[tw] OR pinkeye*[tw])
4. #2 OR #3
5. (adenoviridae*[tw] OR adenovirus*[tw] OR adenoviral*[tw] OR adeno virus*[tw] OR adeno viral*[tw] OR antiadenoviral*[tw] OR antiadenovirus*[tw])
6. (pharyngo conjunctival Fever[tw] OR pharyngoconjunctival fever[tw] OR pharyngeal conjunctival fever[tw] OR pharyngealconjunctival fever[tw])
7. epidemic*[tw]
8. (virus*[tw] OR viral*[tw] OR antiviral*[tw])
9. #5 OR #6 OR #7 OR #8
10. #4 AND #9
11. (eye*[tw] OR ocular*[tw])
12. #5 OR #6
13. #11 AND #12
14. #10 OR #13
15. #1 AND #14
16. Medline[sb]
17. #15 NOT #16
```

Appendix 5. LILACS search strategy

```
((MH:C11.187.183.394$ OR MH:C11.204.564.585$ OR Keratoconjunctiv$ OR MH:C11.187.183 OR MH:SP4.001.012.168.289 OR Conjunctiv$ OR keratiti$ OR EKC OR AKC OR MH:C02.325.250$ OR MH:C11.187.183.240$ OR MH:C11.294.800.250$ OR MH:C11.204.564$ OR "pink eye" OR pinkeye) AND (MH:C02.256.076$ MH:C02.256.076.045$ OR MH:B04.280.030$ OR MH:B04.280.030.500.350$ OR Adenoviridae$ OR Adenovirus$ OR adenoviral$ OR antiadenoviral$ OR antiadenovirus$ OR epidemic OR virus$ OR viral$ OR antiviral$ OR "pharyngo
```


conjunctival Fever" OR "pharyngoconjunctival fever" OR "pharyngeal conjunctival fever" OR "pharyngealconjunctival fever")) OR ((MH:A01.456.505.420\$ OR MH:A09.371\$ OR MH:C01.539.375\$ OR MH:C11.294 OR MH:C02.325\$ OR MH:C11.294.800\$ OR eye\$ OR ocular \$) AND (MH:C02.256.076\$ MH:C02.256.076.045\$ OR MH:B04.280.030\$ OR MH:B04.280.030.500.350\$ OR Adenoviridae\$ OR Adenovirus \$ OR adenoviral\$ OR (adeno virus\$) OR (adeno viral\$) OR antiadenoviral\$ OR antiadenovirus\$ OR "pharyngo conjunctival Fever" OR "pharyngoconjunctival fever" OR "pharyngeal conjunctival fever" OR "pharyngealconjunctival fever"))

Appendix 6. ClinicalTrials.gov search strategy

(Keratoconjunctivitis OR conjunctivitis OR "pink eye" OR keratitis) AND (Adenoviridae OR Adenovirus OR adenoviral OR antiadenoviral OR antiadenovirus OR epidemic OR virus OR viral OR antiviral)

Appendix 7. WHO ICTRP search strategy

Keratoconjunctivitis AND Adenoviridae OR Keratoconjunctivitis AND Adenovirus OR Keratoconjunctivitis AND adenoviral OR Keratoconjunctivitis AND antiadenoviral OR Keratoconjunctivitis AND antiadenovirus OR Keratoconjunctivitis AND epidemic OR Keratoconjunctivitis AND virus OR Keratoconjunctivitis AND viral OR Keratoconjunctivitis AND antiviral

conjunctivitis AND Adenoviridae OR conjunctivitis AND Adenovirus OR conjunctivitis AND adenoviral OR conjunctivitis AND antiadenoviral OR conjunctivitis AND antiadenovirus OR conjunctivitis AND epidemic OR conjunctivitis AND virus OR conjunctivitis AND viral OR conjunctivitis AND antiviral

pink eye AND Adenoviridae OR pink eye AND Adenovirus OR pink eye AND adenoviral OR pink eye AND antiadenoviral OR pink eye AND antiadenovirus OR pink eye AND epidemic OR pink eye AND virus OR pink eye AND viral OR pink eye AND antiviral

keratitis AND Adenoviridae OR keratitis AND Adenovirus OR keratitis AND adenoviral OR keratitis AND antiadenoviral OR keratitis AND antiadenovirus OR keratitis AND epidemic OR keratitis AND virus OR keratitis AND viral OR keratitis AND antiviral

Appendix 8. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	<ul style="list-style-type: none"> Parallel group RCT <i>i.e. people randomized to treatment</i> Within-person RCT <i>i.e. eyes randomized to treatment</i> Cluster RCT <i>i.e. communities randomized to treatment</i> Cross-over RCT Other, specify 	Exclusions after randomization Losses to follow-up Number randomized/analyzed
Eyes or Unit of randomization/unit of analysis	<ul style="list-style-type: none"> One eye included in study, <i>specify how eye selected</i> Two eyes included in study, both eyes received same treatment, <i>briefly specify how analyzed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye</i> Two eyes included in study, eyes received different treatments, <i>specify if correct pair-matched analysis done</i> 	How were missing data handled? <i>e.g. available case analysis, imputation methods</i> Reported power calculation (Y/N), <i>if yes, sample size and power</i> Unusual study design/issues
Participants		
Country		Setting
Total number of participants	<i>This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.</i>	Ethnic group Equivalence of baseline characteristics (Y/N)

(Continued)

Number (%) of men
and women

Average age and age
range

Inclusion criteria

Exclusion criteria

Interventions

Intervention (n =)	• Number of people randomised to this group
Comparator (n =)	• Drug (or intervention) name
	• Dose
See MECIR 65 and 70	• Frequency
	• Route of administration

Outcomes

Primary and secondary outcomes as defined in study reports	List outcomes	Planned/actual length of follow-up
	Adverse events reported (Y/N)	
	Length of follow-up and intervals at which outcomes assessed	
See MECIR R70		

CONTRIBUTIONS OF AUTHORS

All protocol authors contributed to the conception and design of study, drafted the protocol, or commented on it critically for intellectual content, and approved the final version for publication.

DECLARATIONS OF INTEREST

IK: Received a one-time consulting fee to participate in a focus group of corneal specialists asked by the company Okogen in their development of meaningful endpoints in successful treatment of adenoviral conjunctivitis.

MR: no financial or other interests.

KL: no financial or other interests.

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