Cochrane Library

Cochrane Database of Systematic Reviews

Antibiotics versus placebo for acute bacterial conjunctivitis (Review)

Sheikh A, Hurwitz B, van Schayck CP, McLean S, Nurmatov U

Sheikh A, Hurwitz B, van Schayck CP, McLean S, Nurmatov U.
Antibiotics versus placebo for acute bacterial conjunctivitis.
Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD001211.
DOI: 10.1002/14651858.CD001211.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Antibiotics versus placebo for acute bacterial conjunctivitis

Aziz Sheikh[1], Brian Hurwitz[2], Constant Paul van Schayck[3], Susannah McLean[4], Ulugbek Nurmatov[5]

[1]Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK. [2]King's College London, London, UK. [3]Department of General Practice, Maastricht University, Maastricht, Netherlands. [4]Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK. [5]Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK

Contact address: Aziz Sheikh, Centre for Population Health Sciences, The University of Edinburgh, Medical School, Doorway 3, Teviot Place, Edinburgh, EH8 9AG, UK. Aziz.Sheikh@ed.ac.uk.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 9, 2012.

Citation: Sheikh A, Hurwitz B, van Schayck CP, McLean S, Nurmatov U. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD001211. DOI: 10.1002/14651858.CD001211.pub3.

ABSTRACT

Background

Acute bacterial conjunctivitis is an infection of the conjunctiva. Both the palpebral and the bulbar ocular conjunctival surfaces are usually affected and typically become red and inflamed. Antibiotic therapy is widely used for the treatment of acute bacterial conjunctivitis. This Cochrane Review was first published in *The Cochrane Library* in 1999; updated in 2006 and again in 2012.

Objectives

To assess the benefits and harms of antibiotic therapy in the management of acute bacterial conjunctivitis.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 7), MEDLINE (January 1950 to July 2012), EMBASE (January 1980 to July 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 18 July 2012.

Selection criteria

We included double-masked randomised controlled trials (RCTs) in which any form of antibiotic treatment had been compared with placebo/vehicle in the management of acute bacterial conjunctivitis. This included topical, systemic and combination (for example, antibiotics and steroids) antibiotic treatments.

Data collection and analysis

Two authors (UN and SM) independently checked and reviewed the titles and abstracts of identified studies. We assessed the full text of all potentially relevant studies. We graded the included RCTs for methodological quality using Cochrane methodology. We performed data extraction in a standardised manner. We performed random-effects meta-analyses using RevMan.

Main results

We identified 11 eligible RCTs which randomised a total of 3673 participants. One further trial, which was published in abstract form in 1990 but has yet to be reported fully, is currently 'awaiting assessment'. Six of the 11 included studies have been included for the first time in this latest (2012) update. The trials were heterogeneous in terms of their inclusion and exclusion criteria, the nature of the intervention, and the outcome measures assessed. We judged two of the trials to be of high quality and graded the remainder as poor quality.

Meta-analyses of data on clinical and microbiological remission rates revealed that topical antibiotics were of benefit in improving 'early' (days two to five) clinical (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.15 to 1.61) and microbiological (RR 1.55, 95% CI 1.37 to 1.76) remission rates. At the 'late' time point (days six to 10), antibiotics were found to still confer modest benefits in clinical remission (RR 1.21, 95% CI 1.10 to 1.33) and microbiological cure rates (RR 1.37, 95% CI 1.24 to 1.52). By days six to 10, 41% (95% CI 38 to 43) of cases had resolved in those receiving placebo. We found no data on the cost-effectiveness of antibiotics. No serious outcomes were reported in either the active or placebo arms of these trials, suggesting that important sight-threatening complications are an infrequent occurrence.

Authors' conclusions

Although acute bacterial conjunctivitis is frequently self limiting, the findings from this updated systematic review suggest that the use of antibiotic eye drops is associated with modestly improved rates of clinical and microbiological remission in comparison to the use of placebo. Use of antibiotic eye drops should therefore be considered in order to speed the resolution of symptoms and infection.

PLAIN LANGUAGE SUMMARY

Antibiotics versus placebo for acute bacterial conjunctivitis

Acute bacterial conjunctivitis is an infective condition in which one or both eyes become red and inflamed. The condition is not normally serious and in most cases resolves spontaneously. People with acute conjunctivitis are often given antibiotics, usually as eye drops or ointment, to speed recovery. The benefits of antibiotics to the sufferer of conjunctivitis have been questioned. We found 11 randomised controlled trial (RCTs) from different parts of the world which recruited a total of 3673 participants overall. We judged two of the trials to be of high quality, and we graded the remainder as poor quality. This updated review provides clearer evidence that use of antibiotic eye drops can speed up the resolution of symptoms and infection, and that they are unlikely to be associated with any serious side effects.

BACKGROUND

It is estimated that 2% to 5% of all general practice consultations are eye related (Dart 1986; McDonnell 1988; McCormick 1995). Data from Norway suggest that acute infective conjunctivitis is suspected in approximately 3% of patients seen in general medical practice, with this diagnosis being correct in two-thirds of patients (Hovding 1991; Hovding 2008). Acute infective conjunctivitis is therefore one of the most frequently encountered ocular disorders in primary care. Such infection is usually viral or bacterial in aetiology. Infection of the conjunctiva produces a number of local symptoms including red eyes, discharge and discomfort.

Viral conjunctivitis is usually caused by adenovirus infection, which is contagious and is responsible for many of the epidemics that occur in school-aged children, but is in most cases self limiting; a small proportion of patients may, however, develop longer-lasting visual problems.

Bacterial conjunctivitis is commonly due to infection with *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Staphylococcus aureus*. Bacterial conjunctivitis is also regarded as self limiting. However, antibiotics are generally considered desirable on the grounds that they seem to speed recovery, reduce relapse and may prevent important sight-threatening complications such as orbital cellulitis, keratitis and panophthalmitis.

As bacterial and viral conjunctivitis may be difficult to differentiate on clinical grounds, and eye swabs are not considered practical (on

grounds of delay and cost), many doctors will treat all presumed cases of infective conjunctivitis with a broad-spectrum antibiotic.

Topical antibiotic treatments are most commonly used; some of these also contain topical steroid therapy. Systemic antibiotic therapy has been advocated by some (Wald 1997) in order to prevent the development of 'conjunctivitis-otitis syndrome' (i.e. conjunctivitis followed by acute otitis media).

There has been significant public and professional concern regarding the use of chloramphenicol eye drops because of the associated rare risk of bone marrow aplasia. This concern led to a considerable reduction in its use in the United States and there have been calls for its use in the United Kingdom (UK) to also be curtailed (Doona 1995). More recent work, however, suggests that these risks of bone marrow aplasia may have been over-stated (Lancaster 1998). The widespread use of broad-spectrum antibiotics has also led to some concerns that antibiotic resistance may become a significant problem.

The management of common infections encountered in primary care has undergone a radical transformation over the past 15 years. Previously it would have been regarded as heretical to question the use of antibiotics for infections such as sinusitis, otitis media and sore throat (pharyngitis/tonsillitis), which was near universally routine. Randomised controlled trials and systematic reviews have since cast doubt on the effectiveness and cost-effectiveness of antibiotic therapy for these conditions (Del Mar 2004; Glasziou 2004).

In view of these developments, it is timely to assess whether antibiotic therapy confers significant benefit in the treatment of acute bacterial conjunctivitis. This review reports an updated assessment of the question, incorporating data on newer available treatments (McLean 2010) and in so doing updates previous versions of this review (Hurwitz 2005; New Reference; New Reference; New Reference).

OBJECTIVES

To analyze evidence from double-masked, randomised, placebo-controlled trials to ascertain if antibiotic therapy (topical or systemic) confers any benefit in the management of acute bacterial conjunctivitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included double-masked, randomised, placebo-controlled trials.

Types of participants

Participants were people with acute bacterial conjunctivitis, aged one month or older. The diagnosis of bacterial conjunctivitis may have been on clinical or microbiological grounds. 'Acute' was defined as symptoms of less than four weeks duration.

Types of interventions

We included studies in which any form of antibiotic treatment was compared with placebo in the management of acute bacterial conjunctivitis; this included topical, systemic and combination treatments (for example, one or more antibiotics, antibiotics and steroids).

Types of outcome measures

We considered the following outcome measures.

Primary outcomes

1. Time to clinical cure
2. Time to microbiological cure

Secondary outcomes

1. Recurrence of infection within four weeks
2. Cost-effectiveness of treatment
3. Compliance with treatment and number of drop-outs
4. Number of participants that experience complications of acute bacterial conjunctivitis
5. Adverse outcomes as reported in trials

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 7, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 18 July 2012), MEDLINE (January 1950 to July 2012), EMBASE (January 1980 to July 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic

searches for trials. We last searched the electronic databases on 18 July 2012.
See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), OpenGrey (Appendix 4), *m*RCT (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (Appendix 7).

Searching other resources

We searched the reference lists of identified trial reports to find additional trials and we contacted the first author of identified trials to ask for information on further trials. We used the Science Citation Index to find studies which had cited the identified trials. Correspondence with Alcon Laboratories helped to clarify the origin and publication of three trials referred to in a French study (Kodjikian 2010).
We contacted investigators and pharmaceutical companies to identify additional published and unpublished studies. Using MIMS (http://www.emims.net/) we identified the following pharmaceutical companies as producers of relevant ophthalmic preparations and contacted them for information about additional relevant trials: Chauvin Pharmaceuticals; Goldshield Pharmaceuticals; Leo Laboratories; Wyeth Laboratories; Hoechst Roussel; Schering-Plough; Roche Products; Dominion Pharma; Alcon Laboratories; Florizel; Allergan; Rhone-Poulenc Rorer; Typharm.

Data collection and analysis

Selection of studies

In New Reference and New Reference two authors (AS and BH) independently checked the titles and abstracts resulting from the searches.
In this update (2012) we downloaded the search results into Endnote (a citation manager) and de-duplicated. Relevant titles and abstracts were then selected by UN, AS and SM. UN then obtained the full text of any report referring to possibly or definitely relevant trials. UN and SM assessed all full-text articles using the above-described 'Criteria for considering studies for this review'. Only trials meeting these criteria were then assessed for methodological quality.

Data extraction and management

One author extracted data using a template developed for use by the Cochrane Eyes and Vision Group and entered the data in to RevMan (Review Manager 2011). A second author compared the extraction to the original reports. Due to the paucity of appropriate data it was only possible to consider the following outcomes:

1. clinical remission rate:
   i) early (days two to five post-intervention);
   ii) late (days six to 10).
2. microbiological remission rate:
   i) early (days two to five post-intervention);
   ii) late (days six to 10).

Assessment of risk of bias in included studies

We assessed trial methodological quality according to methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
These are the six parameters/questions used to assess risk of bias.

1. Was the allocation sequence adequately generated?
2. Was allocation adequately concealed?
3. Were the patients and researcher masked (blinded) to the allocated intervention?
4. Were incomplete outcome data adequately addressed?
5. Were study reports free of any suggestion of selective reporting?
6. Was the study apparently free of other problems than might cause bias?

We deemed questions that were answered 'Yes' to indicate a low risk of bias and considered those answered 'No' at high risk of bias. Sometimes, insufficient information was available to allow a parameter to be assessed in which case a question would be answered as 'Unclear'.
From this assessment, we assigned an overall grade to each study: A - low risk of bias; B - moderate risk of bias; C - high risk of bias. Two authors independently assessed trial quality and resolved any disagreements by discussion. Authors were not masked to any trial details. We documented authors' agreement on the quality assessment of included trials.

Unit of analysis issues

Acute bacterial conjunctivitis is usually a bilateral problem and all outcomes were assessed at the patient level.

Data synthesis

We undertook our quantitative meta-analyses of outcomes on an intention-to-treat basis using random-effects modelling. We expressed the results as risk ratios (RR with 95% confidence intervals (CI)) and risk difference (RD with 95% CI) for dichotomous outcomes. We performed tests for statistical heterogeneity.
We assessed clinical remission with a denominator based on the total number of participants who had been randomised and this was therefore an intention-to-treat analysis. In contrast, we assessed microbiological remission with a denominator based on those patients who had demonstrated microbiological growth in the cultures from their eyes: i.e. 'culture-confirmed' bacterial conjunctivitis. The analysis of clinical cure therefore included patients who were not confirmed to have bacterial conjunctivitis and may have had viral conjunctivitis. This reflects day-to-day clinical practice

as many clinicians will choose to start treatment in the absence of culture results.

In our meta-analyses, we included all randomised participants in the reports of clinical outcomes. However, in tests of microbiological cure we used the denominator of those who had had culture-proven bacterial conjunctivitis at the beginning of the study.

RESULTS

Description of studies

Results of the search

The initial electronic searches identified 155 reports of possible trials comparing antibiotics versus placebo in the management of acute bacterial conjunctivitis. We obtained full-text copies of five studies for potential inclusion in the review. Studies by Gigliotti 1984, Leibowitz 1991 and Miller 1992 met the inclusion criteria and were included in the review. Studies by Leibowitz 1976 and Mitsui 1986 were not eligible and were excluded from the review. Contact with the first authors of identified trials and searching the reference lists of these study reports failed to identify any additional trials.

Updated searches

The searches for the 2002 update identified 211 reports of trials but no new studies were found. The updated searches which covered the period 2002 to January 2006 identified 111 studies and from these, two trials met the inclusion criteria (Rietveld 2005; Rose 2005).

An update search was done in October 2007 which yielded a further 124 reports of studies. The Trials Search Co-ordinator (TSC) scanned the search results and removed any references which were not relevant to the scope of the review. One trial (Everitt 2006) was identified but was excluded as it was not placebo-controlled.

An update search done in July 2012 yielded a further 361 reports of studies. The TSC scanned the search results and removed 168 references which were not relevant to the scope of the review. We screened 193 records and excluded 144 records for not meeting the review criteria. Two review authors (UN and SM) reviewed the remaining 49 abstracts and excluded 45 papers as they did not meet the inclusion criteria for the review. Four new trials were identified and included in the review (Karpecki 2009; Silverstein 2011; Tauber 2011; Tepedino 2009).

Examination of the studies identified in a recent review (McLean 2010) revealed two additional RCTs (Abelson 2008; Gross 2003). We also found a report (Kodjikian 2010) providing outline details of three additional multi-centred, double-masked RCTs (C-00-02; C-00-55; C-01-66) comparing moxifloxacin 0.5% versus vehicle. We contacted Alcon Research Ltd, the pharmaceutical company responsible for producing this report, to obtain further details of peer-reviewed publications and they revealed that the detailed data from these trials had not been published in the peer-reviewed literature (personal communication Notivol 2011).

Included studies

This review therefore included a total of 11 trials satisfying the inclusion criteria (Abelson 2008; Gigliotti 1984; Gross 2003; Karpecki 2009; Leibowitz 1991; Miller 1992; Rietveld 2005; Rose 2005; Silverstein 2011; Tauber 2011; Tepedino 2009) (*see* the 'Characteristics of included studies' table for detailed information about the individual trials).

Participants

This review was based on trials which had randomised a total of 3673 participants. The breakdown of participants was as follows: Abelson 2008: 279 participants; Gigliotti 1984: 78 participants; Gross 2003: 73 participants; Karpecki 2009: 269 participants; Leibowitz 1991: 177 participants; Miller 1992: 284 participants; Rietveld 2005: 181 participants; Rose 2005: 326 participants; Silverstein 2011: 202 participants; Tauber 2011: 847 participants; Tepedino 2009: 957 participants.

Abelson 2008 included participants aged from one to 96 years; the trials were heterogeneous in terms of the age groups studied with Gigliotti 1984 including children aged between one month and 18 years and Rose 2005 including children aged six months to 12 years. Karpecki 2009 included participants from one to 92 years; Tepedino 2009 from one to 98 years and Gross 2003 from one to 89 years old. Miller 1992 and Rietveld 2005 included only adults. In Leibowitz 1991 no information was provided regarding the age of participants. In Tauber 2011, participants were aged from one month to 92 years and in Silverstein 2011, participants were aged from one to 86 years old.

The trials differed in the diagnostic inclusion criteria used. Gigliotti 1984 included only those that were swab-positive for *Haemophilus influenzae* or *Streptococcus pneumoniae*; Leibowitz 1991 included only those with microbiologically proven bacterial conjunctivitis; Miller 1992 and Karpecki 2009 included those with a clinical diagnosis of acute bacterial conjunctivitis or blepharoconjunctivitis. Abelson 2008, Gross 2003, Rietveld 2005, Rose 2005 and Tepedino 2009 included those with a clinical diagnosis of infective conjunctivitis. Tauber 2011 included participants with a clinical diagnosis of conjunctivitis independent of a positive bacterial culture result at day one. Silverstein 2011 included participants with a clinical diagnosis of conjunctivitis.

In Abelson 2008, a best-corrected visual acuity (BCVA) score of 20/100 or better in each eye was also required for inclusion. Karpecki 2009, Tepedino 2009 and Silverstein 2011 required a pinhole visual acuity $\geq$ 20/200 in both eyes.

Interventions

Abelson 2008 examined 1% azithromycin in DuraSite. Gigliotti 1984 examined an ophthalmic ointment containing 10,000 U/gm polymyxin and 500 U/gm bacitracin. Gross 2003 investigated 0.5% moxifloxacin. Leibowitz 1991 studied ciprofloxacin 0.3% eye drops. Miller 1992 examined 0.3% norfloxacin eye drops. Rietveld 2005 studied fusidic acid gel 1%. Rose 2005 examined 0.5% chloramphenicol eye drops. Karpecki 2009, Tepedino 2009 and Silverstein 2011 studied 0.6% besifloxacin ophthalmic suspension. Tauber 2011 studied a new formulation of moxifloxacin containing xanthum gum so as to be retained in the eye.

Controls

All of the trials were 'vehicle-controlled', i.e. they used control preparations that did not contain any active antibiotic-related ingredient. However, in some trials the vehicle drop mixture contained an antiseptic, which may have had an impact on outcomes in the placebo arm. The active and placebo ingredients are detailed in Table 1. In order to quantify the effect size of the antiseptic on acute bacterial conjunctivitis it would be necessary to investigate these drops separately against saline controls or no treatment arms. A no treatment arm would be impossible to mask and so would be open to bias. The results of the trials we present are the results measuring the additional effect of the antibiotic over the vehicle drops.

Outcome measures

Abelson 2008 used the outcome of clinical resolution which was evaluated at day six or seven. Clinical resolution was considered to be the absence of the three signs of bulbar conjunctival injection, palpebral conjunctival injection and ocular discharge. The secondary outcome was microbiological eradication, also at day six or seven, and was scored categorically from zero (eradicated) to three (worsening) compared with baseline, following gram-staining and other tests.

The trials used different combinations of outcome measures. Gigliotti 1984 used clinical cure and microbiological eradication which were each assessed as a dichotomous outcome: cured or not cured, at two points in time after treatment was commenced: 'early' days three to five, and 'late' days eight to 10. This trial considered a participant to be clinically cured "if the eye was normal by physical examination"; participants' symptoms were not included in this assessment.

Gross 2003 used a culture test-of-cure taken at the visit on day seven. This indicated the outcome of bacterial eradication. The secondary outcome of 'clinical cure' was assessed from bulbar conjunctival injection and conjunctival discharge.

Karpecki 2009 defined the primary outcome as clinical resolution, i.e. the absence of conjunctival discharge and bulbar conjunctival injection at day eight. All signs and symptoms of acute bacterial conjunctivitis were rated on a four-point scale.

Leibowitz 1991 classified 'early' as day three and measured microbiological outcome as one of four categories: pathogen eradication, pathogen reduction, pathogen persistence or pathogen proliferation. The eradication and reduction group were grouped together as signifying a positive outcome, and persistence and proliferation were grouped together to represent a negative outcome.

Miller 1992 classified 'early' as days two to three and assessed clinical outcome categorically as either: cured, improved, no change or worsened: the cured and improved categories were combined together as a positive outcome. This trial categorised clinical outcome on the basis of a combination of physical signs and participant symptoms. Microbiological outcome was also recorded at days two to three as: pathogen eradication, pathogen suppression or pathogen persistence; these measures were also measured at a 'late' stage in the trial at days five to seven. To facilitate analysis the eradicated and suppressed group were combined together as reflecting a positive outcome.

Rietveld 2005 used clinical remission at day seven, defined as the absence of any symptoms or signs of conjunctivitis, which was confirmed by the general practitioner. Microbiological eradication rates were also assessed at day seven.

Rose 2005 used clinical cure at seven days as the primary outcome measure, this being assessed from a parent-held diary. Three categories were used for microbiological outcomes: reduced, unchanged and increased colony counts of three organisms: *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Moraxella catarrhalis*.

Silverstein 2011 examined clinical resolution in all randomised patients at day four or five and also eradication of the baseline bacterial infection in those with culture-confirmed bacterial conjunctivitis. Secondary outcomes included clinical and microbiological resolution at day seven ± one day. Individual clinical outcomes were graded on a four-point scale with the aid of standardised photographs.

Tauber 2011 concentrated on microbiology outcomes at day four ± one day. Microbiological success was determined in the "worst eye" if all bacterial isolates which had been recovered at day one were eradicated by day four.

Tepedino 2009 assessed early clinical remission and microbiological eradication at day five ± one day and late clinical remission and microbiological eradication at day eight or nine. All clinical signs and symptoms of acute bacterial conjunctivitis and their assessment were graded in the same way as the Karpecki 2009 study: on a four-point scale.

Excluded studies

Three potentially eligible studies were excluded from the review. One was excluded because it was single-masked (Leibowitz 1976). One study, published in Japanese, was excluded following trans-

lation of the abstract because it did not include a placebo group (Mitsui 1986). The third study (Everitt 2006) was not placebo-controlled. These three studies randomised 823 participants. *See* 'Characteristics of excluded studies' for further details.

Seven studies were excluded from the update search in January 2012 as they were not placebo-controlled trials (Bremond-Gignac 2010; Denis 2008; Granet 2008; McDonald 2009; Robert 2010; Szaflik 2009; Ta 2007).

Studies awaiting assessment

One study, which randomised 132 participants, has been published as an abstract only (Ofloxacin 1990) and we have written to the authors for further information.

We also wrote to the Medical Product Information, Global Medical Affairs Alcon Research Ltd. Dr. Ricardo Notivol, 17 June 2011) for further information about three trials (C-00-02; C-00-55; C-01-66). In a response letter they confirmed that all trials have been conducted but have not been published in peer-reviewed journals

Risk of bias in included studies

See Figure 1; Figure 2

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

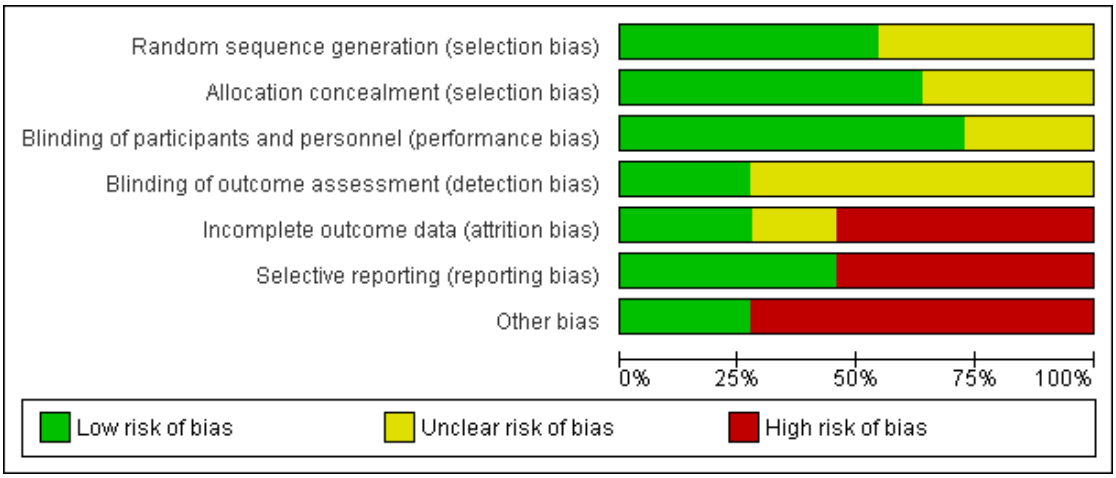
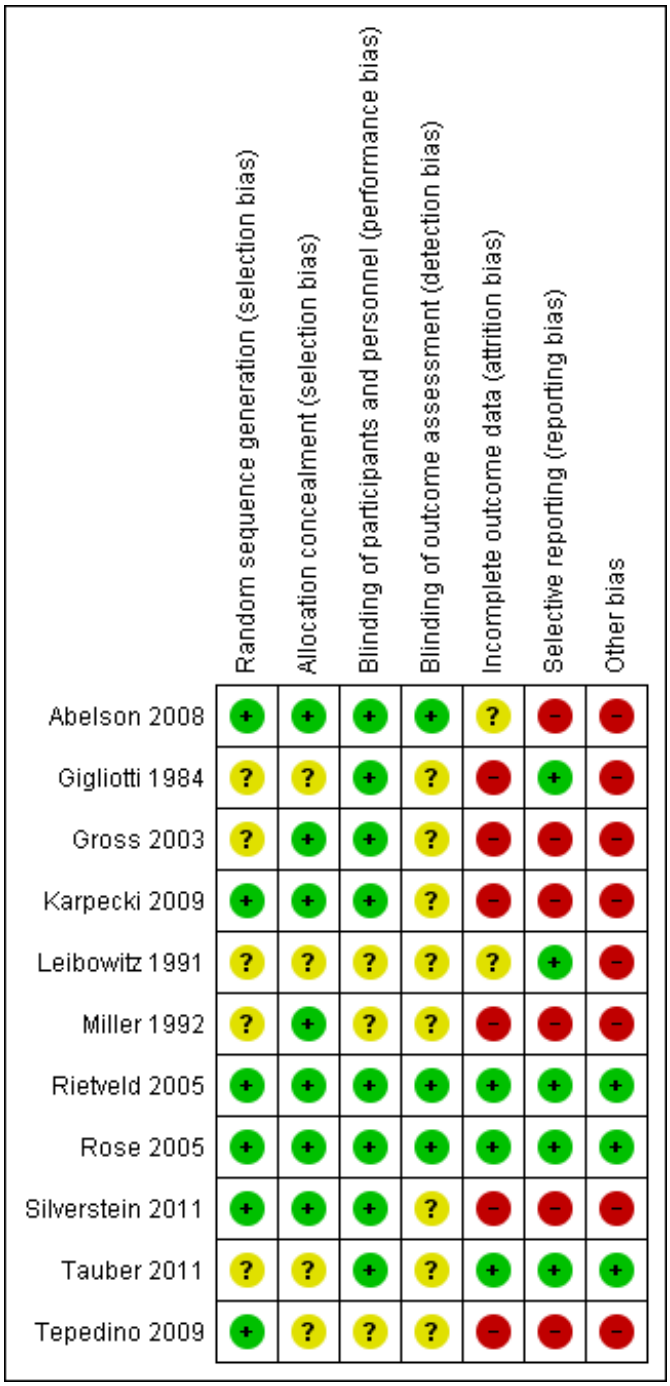


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Sample size

Six trials (Gigliotti 1984; Leibowitz 1991; Miller 1992, Gross 2003, Silverstein 2011; Tauber 2011) did not record information on a priori sample size calculations. It is therefore not possible to make any unequivocal comment on the adequacy of the size of the individual trials. Abelson 2008, Tepedino 2009 and Karpecki 2009 were all large, multi-centre trials and had been planned so as to be adequately powered. The two community-based trials (Rietveld 2005; Rose 2005) were adequately powered.

Allocation

Random sequence generation

Gigliotti 1984, Gross 2003, Leibowitz 1991, Miller 1992 and Tauber 2011 did not provide sufficient information regarding randomisation. Abelson 2008, Karpecki 2009, Rietveld 2005, Rose 2005, Silverstein 2011 and Tepedino 2009 all provided details of an adequate randomisation procedure. However, although adequately described there were some mis-randomisations reported by the Tepedino 2009 study. Fourteen patients randomised to besifloxacin received vehicle and 12 patients randomised to vehicle received besifloxacin.

Allocation concealment

Abelson 2008, Rietveld 2005, Rose 2005, Silverstein 2011 and Tepedino 2009 all stated that they had used a central centre for randomisation. The information for allocation concealment for Gigliotti 1984, Leibowitz 1991, Tauber 2011 and Tepedino 2009 was unclear. Gross 2003 described the use of sealed envelopes and Miller 1992 used identical plastic dropper vials. At no point did any study state that the envelopes were opaque.

Masking

Abelson 2008 described how formulations of vehicle with and without the active drug were identically packaged. In Karpecki 2009 the intervention was coded by its packaging site. Rietveld 2005 and Rose 2005 described the use of identical dropping bottles, as did Silverstein 2011.

Blinding

Performance bias

Abelson 2008, Gross 2003, Rietveld 2005, Rose 2005, Tauber 2011 and Silverstein 2011 all described masking of both participants and investigators.

Detection bias

In terms of masking (blinding), none of the following five trials provided sufficient information: Gigliotti 1984; Leibowitz 1991; Miller 1992; Tepedino 2009 or Karpecki 2009.

Incomplete outcome data

Leibowitz 1991 reported why patient data were missing in a table, however no provision was made to impute these data into the results calculations. Abelson 2008 reported that more than twice as many patients in the vehicle group discontinued the treatment early, because of lack of efficacy, than patients in the treatment group, however, it was unclear as to whether outcome data for such patients were somehow incorporated into the results calculations. In Gigliotti 1984, patients who failed to return for a final visit were not included in the intention-to-treat analysis and there was no mechanism for dealing with these missing data. In Gross 2003, it was unclear as to how data were analysed for patients who were not bacterial culture-positive. In Karpecki 2009 and Miller 1992, there were significantly different withdrawal rates between groups, which were not taken into account in the analysis. However, in Rietveld 2005 they provided a table of all patients lost to follow-up and undertook additional analysis with the explicit assumption that these patients had not recovered by seven days to produce the most conservative estimate for efficacy. Similarly in Rose 2005, an intention-to-treat analysis was performed as if those lost to follow-up had been treatment failures. Silverstein 2011 documented all losses to follow-up and reasons for other missing data and all missing data were imputed by the last-observation-carried-forward method. The missing data from Tauber 2011 were not relevant to the calculations for microbial resolution. Tepedino 2009 reported results using a different denominator for the number of patients randomised to each arm of the trial. Their 2009 study randomised total of 957 patients (besifloxacin = 475 and vehicle = 482, however, for clinical resolution early and late they used only the limited culture-proven population (besifloxacin = 199 and vehicle = 191) instead of the clinical intention-to-treat population, which should have included all randomised patients.

Selective reporting

None of the papers had an a priori trial protocol published detailing outcomes that would be reported on. Only Tauber 2011 reported microbiological, 'early' outcomes - it may be that a future publication will detail clinical outcomes.

Other potential sources of bias

Other bias

In terms of other possible biases, there may be evidence of some selection bias where studies are conducted in a specialist setting (Gigliotti 1984; Gross 2003; Leibowitz 1991). Furthermore, Aziz Sheikh (AS) (lead author on this review) was a co-author on the Rose trial, and in order to minimise any risk of bias he was not involved in the selection, quality assessment or data extraction discussions in relation to this study.

Publication bias

We created funnel plots to help the assessment of publication bias. Though their interpretation is complex, 'by eye' only and they have been criticised (Terrin 2005) as misleading even with expert assessment, and they offer only limited information in the context of meta-analyses with smaller numbers of trials, they revealed a relative paucity of small negative studies, which indicates the possibility of publication bias, as small studies may only have been published if they yielded positive results (Stern 2011).

Overall grading

Overall we graded the studies as follows:
A: low risk of bias: Rietveld 2005; Rose 2005;
C: high risk of bias: Abelson 2008; Gigliotti 1984; Gross 2003; Karpecki 2009; Leibowitz 1991; Miller 1992; Silverstein 2011; Tauber 2011; Tepedino 2009.

Effects of interventions

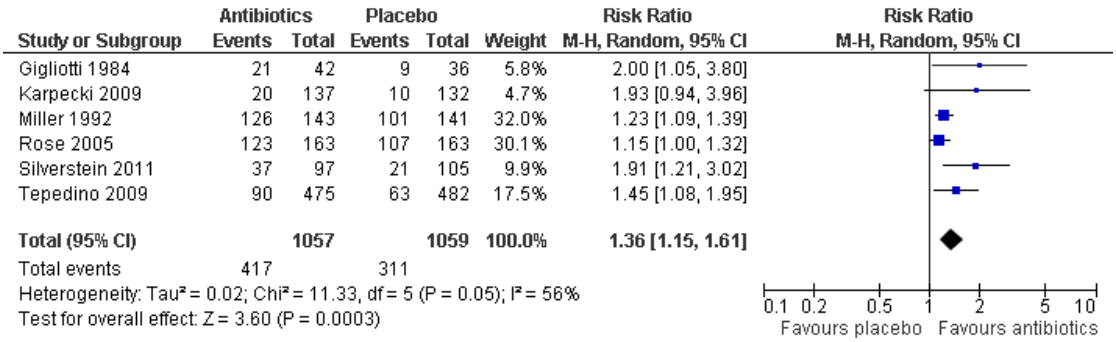
Primary outcomes

Despite relatively high heterogeneity between different studies (discussed below), given that the trial effects were all in the same direction, we considered it appropriate to pool data across studies for 'early' and 'late' outcomes for rates of both clinical and microbiological remission.

'Early' clinical remission: days two to five

Pooling the data from six trials (Gigliotti 1984; Karpecki 2009; Miller 1992; Rose 2005; Silverstein 2011; Tepedino 2009), we calculated a risk ratio (RR) of 1.36 (95% confidence interval (CI) 1.15 to 1.61) for 'early' (day two to five) clinical remission with antibiotics when compared with placebo. There was high heterogeneity I^2 = 56%; this is according to the commonly used threshold of I^2 > 40% being considered to be high. This is probably a reflection of the fact that the different studies used different ages of participants, infected with different types of bacteria and treated with different antibiotics - sometimes in different strengths of preparation. These factors are the most likely explanations for the high heterogeneity. In this context, authors are sometimes hesitant to pool data into a meta-analysis, however, we believe that this exercise is justified as there appeared to be broad agreement between the studies of the direction of the effect (Analysis 1.1; Figure 3). By day five, 30% (95% CI 27 to 35) of cases receiving placebo had improved and 40% (95% CI 27 to 43) of those receiving antibiotics had improved. The cure rate in the placebo arm is 30% (derived by dividing numbers of cure events in the placebo group by the total number of participants in the placebo group (control event rate) and calculating 95% CIs for this outcome). The cure rate in the antibiotic group is 40% (similarly derived by dividing the number of cure events in the antibiotic group by the total number of participants in the antibiotic group). Therefore, the summary risk difference was 10% (40% to 30%) in those receiving two to five days of antibiotic treatment.

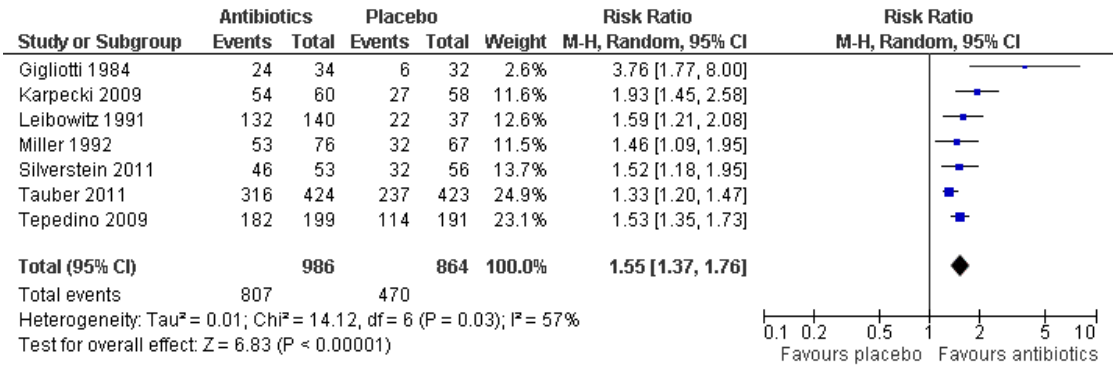
Figure 3. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.1 Clinical remission (early).



'Early' microbiological remission: day two to five

Meta-analysis of data from seven trials (Gigliotti 1984; Karpecki 2009; Leibowitz 1991; Miller 1992; Silverstein 2011; Tauber 2011; Tepedino 2009) revealed a RR of 1.55 (95% CI 1.37 to 1.76) for 'early' microbiological remission, i.e. by days two to five. There was high heterogeneity among these studies I^2 = 57% (Analysis 1.2; Figure 4).

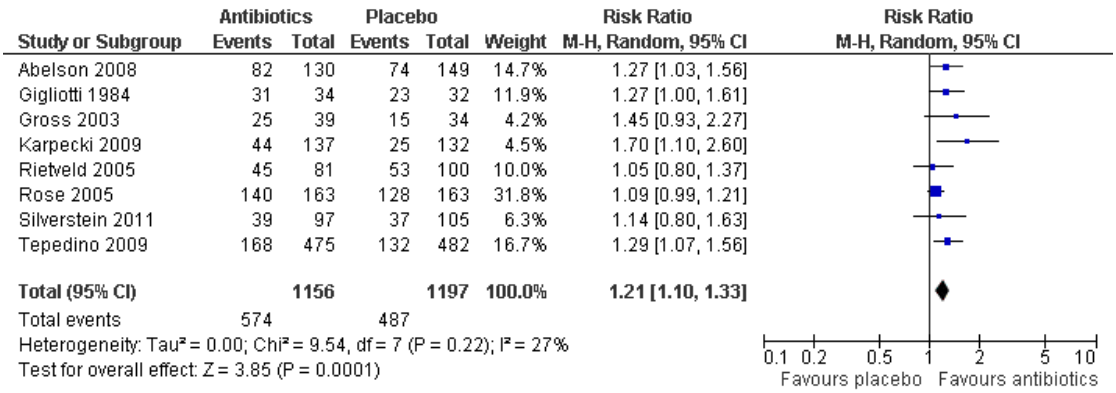
Figure 4. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.2 Microbiological remission (early).



'Late' clinical remission: day six to 10

We calculated a RR of 1.21 (95% CI 1.10 to 1.33) from eight trials (Abelson 2008; Gigliotti 1984; Gross 2003; Karpecki 2009; Rietveld 2005; Rose 2005; Silverstein 2011; Tepedino 2009) for 'late' clinical remission over days six to 10 with antibiotics as opposed to with placebo. This is very similar to the proportion in 'early' clinical remission. There was modest heterogeneity: I^2 = 27% (Analysis 1.3; Figure 5). By this later time point, 41% (95% CI 38 to 43) of the cases receiving placebo had been cured.

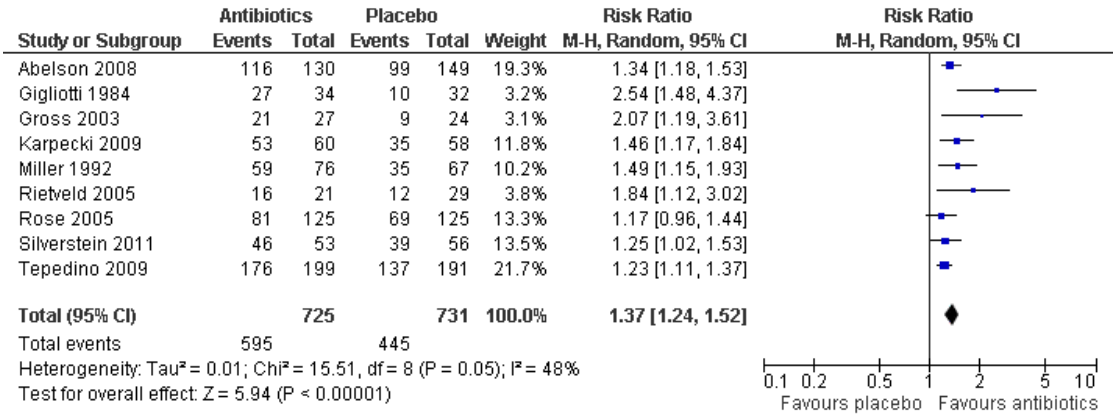
Figure 5. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.3 Clinical remission (late).



'Late' microbiological remission: day six to 10

The RR of 'late' microbiological remission was 1.37 (95% CI 1.24 to 1.52) across nine trials (Abelson 2008; Gigliotti 1984; Gross 2003; Karpecki 2009; Miller 1992; Rietveld 2005; Rose 2005; Silverstein 2011; Tepedino 2009) with high heterogeneity I^2 = 48% (Analysis 1.4; Figure 6).

Figure 6. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.4 Microbiological remission (late).



Other outcomes

Secondary outcomes

1. Recurrence of infection within four weeks. This outcome was not reported on in any of the trials.
2. Cost-effectiveness of treatment. This outcome was not

reported on in any of the trials.

3. Compliance with treatment, and number of drop-outs. This outcome is incorporated into the 'Risk of bias' tables under the 'Incomplete reporting' section.

4. Number of participants that experience complications of acute bacterial conjunctivitis. This outcome was not reported on in any of the trials.

5. Adverse outcomes as reported in trials. No serious adverse outcomes were reported in either the active or placebo arms of the trials, indicating that important sight-threatening complications such as bacterial keratitis and orbital cellulitis are an infrequent occurrence in patients with acute bacterial conjunctivitis. The whole spectrum of all other sight-threatening complications were not reported.

DISCUSSION

Summary of main results

The increased absolute risk difference due to treatment with antibiotic eye drops was 11% for 'early' clinical remission and 9% for 'late' clinical remission, in comparison to treatment with placebo drops. The baseline remission rate of 30% with placebo by day five could be considered to be quite high. There may be some effect of administering antiseptic vehicle-placebo eye drops three or four times a day which may have contributed to this. However, there may also be some bias, as in Abelson 2008 twice as many participants discontinued in the placebo arm as in the treatment arm due to lack of efficacy. This would increase the measured effectiveness of the placebo arm as these data were not imputed in any way.

Antibiotic treatment was associated with a risk ratio (RR) of 1.36 (95% confidence interval (CI) 1.15 to 1.61) for 'early' clinical remission and a RR of 1.21 (95% CI 1.10 to 1.33) for 'late' clinical remission. It was also associated with a RR of 'early' microbiological cure of 1.55 (95% CI 1.37 to 1.76) and 'late' microbiological cure of 1.37 (95% CI 1.24 to 1.52). It appears that there is a higher rate for 'early' microbiological cure than for 'early' clinical cure, suggesting that clinical cure lags behind microbiological eradication. This lag may also be in evidence at the 'late' time point.

Overall completeness and applicability of evidence

There are several limitations to this review. Acute bacterial conjunctivitis is frequently cited to be a 'self limiting' condition. However, its natural history cannot be inferred from the trials included in this review because there is likely to be some effect of applying placebo eye drops containing antiseptic three or four times a day. This is perhaps reflected in the relatively high proportion (30%) of placebo arm patients who achieved clinical cure by day five (and 41% by days six to 10).

All the studies used different antibiotics, so no recommendations can be made on the basis of this review as to which of these is superior to any other or indeed which may be particularly useful for specific organisms.

There was no attempt in any of the studies to determine the cost-effectiveness of treating acute bacterial conjunctivitis. This would be a very useful study in the context of a self limiting condition.

As all of the trials show some benefit of antibiotics over placebo it would seem reasonable to conclude that these results are generalisable to the use of similar antibiotics for acute bacterial conjunctivitis in similar primary and secondary care settings.

Quality of the evidence

We clearly assessed the two primary care studies (Rietveld 2005; Rose 2005) as being of higher quality than the remaining studies. We assessed the remaining nine trials (Abelson 2008; Gigliotti 1984; Gross 2003; Karpecki 2009; Leibowitz 1991; Miller 1992; Silverstein 2011; Tauber 2011; Tepedino 2009) as being at high risk of bias and thus lower quality.

In three of the four meta-analyses we found high heterogeneity (I^2 > 40%). The different antibiotics used across the studies may partly account for this and when there are appropriate studies available in the future it may help to do a subgroup analysis according to antibiotic.

Another factor possibly contributing to this heterogeneity was the differing time periods of administration of antibiotics. For example, although studies included in the 'early' groups administered antibiotics for approximately five days, this may have actually been for a total of three to six days of antibiotic drops. Therefore this is a highly heterogeneous group and it is difficult to give clear recommendations on the appropriate time period for antibiotic administration.

Potential biases in the review process

As AS was an author of Rose 2005, he did not participate in selection, quality assessment, data extraction and interpretation of this trial; instead, this was done by UN and SM.

This review process should have minimum bias. The broad search strategy, performed in conjunction with *The Cochrane Library*, should have captured as many relevant studies as possible. This means that both completed and ongoing trials which have been appropriately coded by the Cochrane Eyes and Vision Group were included. Two authors then independently chose the relevant articles from this list. We included trials published in any language, thus minimising bias.

Agreements and disagreements with other studies or reviews

This latest review confirms the previous evidence that treatment of acute bacterial conjunctivitis with antibiotics offers some benefits in speeding up early resolution and more clearly establishes that more modest benefits are also apparent in relation to later resolution (Hurwitz 2005). Jefferis 2011 conducted an individual patient data meta-analysis of these trials, which also found that antibiotics confer modest benefits in improving symptom resolution.

AUTHORS' CONCLUSIONS

Implications for practice

There remains only a small evidence base of two trials directly relevant to primary care (Rietveld 2005; Rose 2005) where the majority of cases are seen and managed. However, the remaining nine trials may be generalised to some extent and add to this evidence. Early clinical and microbiological remission rates by day five are improved following administration of a topical broad-spectrum antibiotic and these benefits persist but are more modest for later resolution. Given the self limiting nature of conjunctivitis, operating a wait and see policy to see if symptoms/infection spontaneously resolve appears reasonable. It is also appropriate to consider use of antibiotic eye drops as these increase the speed of resolution of symptoms associated with acute bacterial conjunctivitis.

Implications for research

Further research is required in primary care assessment and treatment to understand better the natural history of conjunctivitis in these settings, to ascertain whether with no active treatment the resolution rates seen in the placebo arm are indeed due to spontaneous resolution or whether they reflect the impact of the vehicle of the placebo. In addition, further research is needed to assess cost-effectiveness in this setting in terms of improving quality of life and reducing time off work and education.

ACKNOWLEDGEMENTS

- Our thanks to the Cochrane Eyes and Vision Group (CEVG) for their support throughout this review, and especially to Iris Gordon, Trials Search Co-ordinator for CEVG and Anupa Shah, Managing Editor for CEVG.

- We thank Andrew Tullo for peer reviewing a previous version of this review and Steve Tuft and Catey Bunce for reviewing the 2012 update.

Richard Wormald (Co-ordinating Editor for CEVG) acknowledges financial support for his CEVG research sessions from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health.

REFERENCES

References to studies included in this review

Abelson 2008 *{published data only}*
Abelson MB, Heller W, Shapiro AM, Si E, Hsu P, Bowman LM. Clinical cure of bacterial conjunctivitis with azithromycin 1%: vehicle-controlled, double-masked clinical trial. *American Journal of Ophthalmology* 2008;**145**: 959–65.

Gigliotti 1984 *{published data only}*
Gigliotti F, Hendley JO, Morgan J, Michaels R, Dickens M, Lohr J. Efficacy of topical antibiotic therapy in acute conjunctivitis in children. *Journal of Pediatrics* 1984;**104**: 623–6.

Gross 2003 *{published data only}*
Gross RD, Lichtenstein SJ, Schlech BA, Gower LA, Potts SL. Early clinical and microbiological responses in the treatment of bacterial conjunctivitis with moxifloxacin ophthalmic solution 0.5% (Vigamox TM) using b.i.d dosing. *Today's Therapeutic Trends* 2003;**21**(2):227–37.

Karpecki 2009 *{published data only}*
Karpecki P, DePaolis M, Hunter JA, White EM, Rigel L, Brunner LS, et al. Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: a multicenter, prospective, randomized, double-masked, vehicle-controlled, 5-day efficacy and safety study. *Clinical Therapeutics* 2009;**31**(3):514–26.

Leibowitz 1991 *{published data only}*
Leibowitz HM. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. *American Journal of Ophthalmology* 1991; **112**:29S–33S.

Miller 1992 *{published data only}*
Miller IM, Wittreich J, Vogel R, Cook TJ. The safety and efficacy of topical norfloxacin compared with placebo in the treatment of acute, bacterial conjunctivitis. *European Journal of Ophthalmology* 1992;**2**:58–66.

Rietveld 2005 *{published data only}*
Rietveld RP, ter Riet G, Bindels PJ, Bink D, Sloos JH, van Weert HC. The treatment of acute infectious conjunctivitis with fusidic acid: a randomised controlled trial. *British Journal of General Practice* 2005;**55**:924–30.

Rose 2005 *{published data only}*
Rose PW, Harnden A, Brueggemann AB, Perera R, Sheikh A, Crook D, et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial. *Lancet* 2005;**366**:37–43.

Silverstein 2011 *{published data only}*
Silverstein BE, Allaire C, Bateman KM, Gearinger LS, Morris TW, Comstock TL. Efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days in the treatment of bacterial conjunctivitis: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study in adults and children. *Clinical Therapeutics* 2011;**33**(1):13–26.

Tauber 2011 *{published data only}*
Tauber S, Cupp G, Garber R, Bartell J, Vohra F, Stroman D. Microbiological efficacy of a new ophthalmic formulation of moxifloxacin dosed twice-daily for bacterial conjunctivitis. *Advances in Therapy* 2011;**28**(7):566–74.

Tepedino 2009 *{published data only}*
Tepedino ME, Heller WH, Usher DW, Brunner LS, Morris TW, Haas W, et al. Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. *Current Medical Research and Opinion* 2009;**25**(5):1159–69.

References to studies excluded from this review

Bremond-Gignac 2010 *{published data only}*
Bremond-Gignac D, Mariani-Kurkdjian P, Beresniak A, El Fekih L, Bhagat Y, Pouliquen P, et al. Efficacy and safety of azithromycin 1.5% eye drops for purulent bacterial conjunctivitis in pediatric patients. *Pediatric Infectious Disease Journal* 2010;**29**(3):222–6.

Denis 2008 *{published data only}*
Denis F, Chaumeil C, Goldschmidt P, Delval L, Pouliquen P, Cochereau I, et al. Microbiological efficacy of 3-day treatment with azithromycin 1.5% eye-drops for purulent bacterial conjunctivitis. *European Journal of Ophthalmology* 2008;**18**(6):858–68.

Everitt 2006 *{published data only}*
Everitt HA, Little PS, Smith PW. A randomised controlled trial of management strategies for acute infective conjunctivitis in general practice. *BMJ* 2006;**333**(7563): 321.

Granet 2008 *{published data only}*
Granet DB, Dorfman M, Stroman D, Cockrum P. A multicenter comparison of polymyxin B sulfate/ trimethoprim ophthalmic solution and moxifloxacin in the speed of clinical efficacy for the treatment of bacterial conjunctivitis. *Journal of Pediatric Ophthalmology and Strabismus* 2008;**45**(6):340–9.

Leibowitz 1976 *{published data only}*
Leibowitz HM, Pratt MV, Flagstad IJ, Berrospi AR, Kundsin R. Human conjunctivitis. II. Treatment. *Archives of Ophthalmology* 1976;**94**:1752–6.

McDonald 2009 *{published data only}*
McDonald MB, Protzko EE, Brunner LS, Morris TW, Haas W, Paterno MR, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. *Ophthalmology* 2009;**116**(9): 1615–23.

Mitsui 1986 *{published data only}*
Mitsui Y, Matsuda H, Miyajima T, Tazawa, Kumagai S. Therapeutic effects of ofloxacin eye drops (DE-055) on external infection of the eye: multicentral double blind test. *Japanese Review of Clinical Ophthalmology* 1986;**80**: 1813–28.

Robert 2010 *{published data only}*
Robert PY, Bourcier T, Meddeb-Ouertani A, Khairallah M, Zaghloul K, Amraoui A, et al. Efficacy assessment of azithromycin 1.5% eye drops versus tobramycin 0.3% on clinical signs of purulent bacterial conjunctivitis. *Journal Français D'Ophtalmologie* 2010;**33**(4):241–8.

Szaflik 2009 *{published data only}*
Szaflik J, Szaflik JP, Kaminska A, Levofloxacin Bacterial Conjunctivitis Dosage Study Group. Clinical and microbiological efficacy of levofloxacin administered three times a day for the treatment of bacterial conjunctivitis. *European Journal of Ophthalmology* 2009;**19**(1):1–9.

Ta 2007 *{published data only}*
Ta CN, Sinnar S, He L, Myung D, Mino De Kaspar H. Prospective randomized comparison of 1-day versus 3-day application of topical levofloxacin in eliminating conjunctival flora. *European Journal of Ophthalmology* 2007; **17**(5):689–95.

References to studies awaiting assessment

NCT00509873 *{published data only}*
NCT00509873. A study of the safety and efficacy of gatifloxacin in patients with bacterial conjunctivitis. http: //clinicaltrials.gov/ct2/show/NCT00509873 (accessed 8 January 2012).

NCT00518089 *{published data only}*
NCT00518089. A study of the safety and efficacy of gatifloxacin in patients with bacterial conjunctivitis. http: //clinicaltrials.gov/ct2/show/NCT00518089 (accessed 8 January 2012).

NCT01175590 *{published data only}*
NCT01175590. Safety of Besivance™ (Besifloxacin ophthalmic suspension) 0.6% compared to vehicle. http: //clinicaltrials.gov/ct2/show/NCT01175590 (accessed 8 January 2012).

Ofloxacin 1990 ***{published data only}***

Oxfloxacin Study Group III. A placebo-controlled clinical study of the fluoroquinolone ofloxacin in patients with external infection. *Investigative Ophthalmology & Visual Science* 1990;**31**(4):572.

Additional references

Dart 1986

Dart JKG. Eye disease at a community health centre. *BMJ* 1986;**293**:1477–80.

Del Mar 2004

Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD000023.pub3]

Doona 1995

Doona M, Walsh JB. The use of chloramphenicol as topical eye medication: time to cry halt?. *BMJ* 1995;**310**:1217–8.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *2006* 64;**2**:130–6.

Glasziou 2004

Glasziou PP, Del Mar CB, Sanders SL, Hayem M. Antibiotics versus placebo for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD000219.pub2]

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hovding 1991

Hovding G, Bratland SZ, Digranes A. *Rodt oye - praktisk veiledning i allmenn praksis*. Oslo: Lovens Kemiske Fabrik, 1991.

Hovding 2008

Hovding G. Acute bacterial conjunctivitis. *Acta Ophtalmologica* 2008;**86**:5–17.

Hurwitz 2005

Hurwitz B, Sheikh A. Topical antibiotics for acute bacterial conjunctivitis: Cochrane systematic review and meta-analysis update. *British Journal of General Practice* 2005;**55**: 962–4.

Jefferis 2011

Jefferis J, Perera R, Everit H, van Weert H, Rietveld R, Glasziou P, et al. Acute infective conjunctivitis in primary care: who needs antibiotics? An individual patient data-analysis. *British Journal of General Practice* 2011;**61**(690): e542–8.

Kodjikian 2010

Kodjikian L, Lafuma A, Khoshnood B, Laurendeau C, Berdeaux G. Efficacy of moxifloxacin in treating bacterial conjunctivitis: a meta-analysis. *Journal Francais D'Ophtalmologie* 2010;**33**:227–33.

Lancaster 1998

Lancaster T, Swart AM, Jick H. Risk of serious haematological toxicity with use of chloramphenicol eye drops in a British general practice database. *BMJ* 1998;**316** (7132):667.

McCormick 1995

McCormick A, Fleming D, Charlton J. *Morbidity statistics from general practice. Fourth national study 1991-2*. London: HMSO, 1995.

McDonnell 1988

McDonnell PJ. How do general practitioners manage eye disease in the community?. *British Journal of Ophthalmology* 1988;**72**:733–6.

McLean 2010

McLean S, Sheikh A. Effectiveness, tolerability and safety of azithromycin 1% in DuraSite for acute bacterial conjunctivitis. *Patient Preference and Adherence* 2010;**4**: 69–76.

Review Manager 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Stern 2011

Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Terrin 2005

Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *Journal of Clinical Epidemiology* 2005;**58** (9):894–901.

Wald 1997

Wald ER. Conjunctivitis in infants and children. *Pediatric Infectious Diseases Journal* 1997;**16**:S17–20.

References to other published versions of this review

Sheikh 2000

Sheikh A, Hurwitz B, Cave J. Antibiotics for acute bacterial conjunctivitis. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD001211]

Sheikh 2001

Sheikh A, Hurwitz B. Topical antibiotics for acute bacterial conjunctivitis: Cochrane systematic review. *British Journal of General Practice* 2001;**51**:473–7.

Sheikh 2006

Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD001211.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abelson 2008

Methods	Randomised controlled trial, double-masked Method of randomisation: centrally randomised Randomisation in block format, an equal probability randomisation procedure was employed
Participants	Country: USA Setting: specialist care Participants recruited from clinical centres Number of randomised: 279 patients Age: 1 to 96 years Gender: not reported Ethnicity: not reported Inclusion criteria: the diagnosis was confirmed on the basis of a best-corrected visual acuity (BCVA) score of 20/100 or better in each eye; a minimum score of 1 (on a scale from 0 (absent/normal) to 3 (severe)) for ocular discharge and either bulbar or palpebral conjunctival injection in the same eye Exclusion criteria: debilitating disease, prior or concomitant use of any antibiotic or topical ophthalmic solution, suspected viral or allergic conjunctivitis, or positive pregnancy test results
Interventions	Treatment: 1% azithromycin in DuraSite Control: vehicle
Outcomes	Clinical resolution and bacterial eradication at visit 3 (day 6 or 7); safety data; compliance
Notes	Adequately powered study

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"were randomised in block format"; "an equal probability randomization procedure was used."
Allocation concealment (selection bias)	Low risk	"vehicle was identically supplied and formulated except that it contained no azithromycin"

Abelson 2008 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"study personnel and participants were masked from their treatment assignments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"only the study statistician and data-monitoring committee saw unmasked data, but these team members did not have any contact with study participants"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"more than twice as many in the vehicle group were discontinued early because of lack of efficacy?" (bias)
Selective reporting (reporting bias)	High risk	Only results for "per-protocol" group of 279
Other bias	High risk	Reporting, selection bias

Gigliotti 1984

Methods	Randomised controlled trial, double-masked Coding of trial medication was carried out by Burroughs Wellcome Method of randomisation: not described
Participants	Country: USA Setting: specialist care Participants recruited from a paediatric practice, hospital paediatric clinic and a hospital walk-in clinic Number randomised: 66 children Age: 1 month to 18 years Gender: not reported Ethnicity: not reported Inclusion criteria: swab-proven *Haemophilus influenzae* or *Streptococcus pneumoniae* and the presence of conjunctival inflammation or exudate Exclusion criteria: history suggestive of allergy; history of trauma; foreign body in eye; use of antibiotics within the preceding week
Interventions	Treatment: ophthalmic ointment containing 10,000 U/gm polymyxin and 500 U/gm bacitracin 4 times daily for 7 days Control: ointment vehicle without antibiotic
Outcomes	Early (days 3 to 5) and late (days 8 to 10) clinical and microbiological cure; symptoms reported by parents; compliance
Notes	There were 3 arms to this study: topical antibiotic, topical placebo and systemic antibiotics. As participants were allocated to the systemic antibiotic arm in a non-random method these participants have not been included in this review. Although symptoms reported by the participants were recorded these were not analysed by the authors

Gigliotti 1984 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomised" but no details were given
Allocation concealment (selection bias)	Unclear risk	"numbered multidose tube, code was broken when the study was terminated"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomised, double-masked trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients who failed to return for final follow-up were not included in intention-to-treat analysis and missing data were not addressed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Population bias; no baseline data on age, sex or race between groups

Gross 2003

Methods	Randomised, multicentre, double-masked, parallel-group trial Method of randomisation: insufficient information "Randomised" but no details; insufficient information
Participants	Country: USA Setting: specialist care Participants recruited from clinical centres Number of randomised: 73 patients Age: 1 to 89 years Gender: male = 37%; female = 63% Ethnicity: Caucasian = 86.3%; African-American = 8.2%; Other = 5.5% Inclusion criteria: "All patients had to have a rating of 1 (mild) or greater on a scale of 0 to 3 (absent to severe) for conjunctival discharge/exudates; patients $\leq$ 5 years of age a rating of at least 1 (mild) on a scale of 0 to 3 (normal to severe) for bulbar conjunctival injection, and patients > 5 years of age a rating of at least 2 for bulbar conjunctival injection. Only "culture-positive" patients were included in the evaluation of efficacy Exclusion criteria: no detailed information

Gross 2003 (*Continued*)

Interventions	Treatment: 0.5% moxifloxacin Control: vehicle
Outcomes	Clinical resolution and bacterial eradication at visit on day 7 test-of-cure (TOC); safety data
Notes	22 patients are omitted from reports and information about loss to follow-up not given

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomised" but no details; insufficient information
Allocation concealment (selection bias)	Low risk	"seal envelope with treatment code" Each investigator received a sealed envelope containing the description of the study medication assigned to each patient number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double masked"; "investigators and staff masked as to treatment group"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	What happened to patients who were not culture-positive in analysis is unclear; missing data not addressed
Selective reporting (reporting bias)	High risk	Loss to follow-up
Other bias	High risk	Selection bias

Karpecki 2009

Methods	Randomised controlled trial, double-masked, vehicle-controlled Method of randomisation: centrally randomised Randomisation was performed using customised software
Participants	Country: USA Setting: specialist care Participants recruited from clinical centres Number of randomised: 269 patients Age: 1 to 92 years

Karpecki 2009 (*Continued*)

	Gender: besifloxacin group - female 62.8%; male 37.2%; vehicle group - female 57.6%; male 42.4% Ethnicity: besifloxacin group - white 84.7%; Hispanic 8.8%; black 4.4%; other 2.2%; vehicle group - white 80.3%; Hispanic 6.1%; black 8.3%; other 5.3% Inclusion criteria: at least 1 year of age; a minimum of grade 1 for purulent conjunctival discharge (crusty or sticky eyelids) and a minimum of grade 1 for either bulbar or palpebral conjunctival injection in at least 1 eye on ocular examination; pinhole visual acuity $\geq$ 20/200 in each eye, a negative result on pregnancy testing Exclusion criteria: hypersensitivity to fluoroquinolones, besifloxacin ophthalmic suspension; patients who used topical ophthalmic anti-inflammatory agents or solutions (artificial tears) within 48 hours before or during the study; suspected viral or allergic conjunctivitis, iritis; a history of recurrent corneal erosion syndrome, ulcerative active keratitis
Interventions	Treatment: 0.6% besifloxacin ophthalmic suspension Control: vehicle
Outcomes	Clinical resolution and microbiological efficacy of besifloxacin; safety data; compliance
Notes	Adequately powered study; this study was conducted at 35 centres in the United States

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed using customised software in blocks
Allocation concealment (selection bias)	Low risk	"coded by packaging site"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"patients were given their randomised study medication, which was coded by the packaging site"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Whether different investigators assessed the outcomes is unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	There was a statistically significant difference in withdrawal rates between groups
Selective reporting (reporting bias)	High risk	Clinical resolution was assessed only in culture-proven patients; selective reporting
Other bias	High risk	Selective reporting; interpretation and presentation bias

Leibowitz 1991

Methods	Randomised controlled study, double-masked Method of randomisation: not described
Participants	Country: USA Setting: specialist care Participants recruited from hospital clinic Number randomised: 177 patients randomised: 140 in the ciprofloxacin arm and 37 in the placebo arm Age and gender: not reported Ethnicity: not reported Inclusion criteria: swab-proven conjunctivitis Exclusion criteria: antibiotics or anti-inflammatory medication during the preceding 48 hours
Interventions	Treatment: ciprofloxacin 0.3% 1 to 2 drops into affected eye every 2 hours whilst awake on days 0 and 1, and every 4 hours whist awake on day 2 Control: ciprofloxacin vehicle
Outcomes	Repeat swabs were taken on day 3, at least 12 hours after the last dose of medication Outcomes: pathogen eradication; pathogen reduction; pathogen persistence; pathogen proliferation
Notes	Proxy outcome measures

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	"Double masked", "coded medication?"; insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Table provided of why patients were excluded but this may affect results
Selective reporting (reporting bias)	Low risk	All outcomes are completed
Other bias	High risk	Only 288 patients "met all clinical criteria for study evaluation"

Miller 1992

Methods	Randomised controlled study, double-masked Method of randomisation: not described
Participants	Countries: USA, Mali and Morocco Setting: specialist care Participants appear to have been recruited from hospital centres Number randomised: 284 participants randomised (143 in antibiotic arm and 141 in placebo arm) Age: greater than 18 years with mean of 38 years in both arms Gender: 73 (51%) female in antibiotic arm and 86 (61%) female in placebo arm Ethnicity: 75% Caucasian in either arm Inclusion criteria: clinical diagnosis of acute bacterial conjunctivitis or blepharoconjunctivitis, with the presence of conjunctival hyperaemia Exclusion criteria: conjunctivitis due to *Neiserria gonorrhoeae*, a sensitivity to quinolones or benzalkonium chloride, or those who had received topical antibacterial agents in the preceding 48 hours
Interventions	Treatment: norfloxacin 0.3% + 0.0025% benzalkonium chloride preservative, 1 drop into each affected eye every 2 hours of the waking day for the first day, and then 4 times a day for a maximum of 7 days Control: 0.01% benzalkonium chloride
Outcomes	Global clinical outcome: cured (signs and symptoms of infection clear), improved (signs and/or symptoms still present but of less severity), no change or worsened Microbiological outcome was categorised as: pathogen eradication, pathogen suppression or pathogen persistence Clinical outcomes were recorded at days 2 to 3; microbiological outcomes were recorded at days 2 to 3 and days 5 to 7 All symptoms and signs were recorded, specifically including: symptoms of blurred vision, eye burning, foreign body sensation, photophobia, tearing and itching of eye; signs of conjunctival hyperaemia, discharge, oedema and follicles, active infiltrates and corneal staining with fluorescein, lid oedema and exudates
Notes	The following symptoms were reported to be significantly better (although data are not presented) at day 2 to 3: burning eye and foreign body sensation. This significant improvement was not maintained at the day 5 to 7 assessment. The following signs were reported to be significantly better at the day 2 to 3 assessment (although individual data are not presented): discharge, chemosis, hyperaemia and lid oedema. This significant improvement was not maintained at the day 5 to 7 assessment. Subgroup analysis for Type A organisms (*Staphylococcus aureus*, Streptococcus or Gram-negative organisms)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomised" but no details given

Miller 1992 (*Continued*)

Allocation concealment (selection bias)	Low risk	"identical plastic dropper vials"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Significantly more placebo patients discontinued treatment for lack of improvement
Selective reporting (reporting bias)	High risk	Selection made according to bacteria grown
Other bias	High risk	"bias due to early stopping"

Rietveld 2005

Methods	Randomised controlled trial, double-masked Method of randomisation: centrally randomised
Participants	Country: Holland Setting: primary care Number randomised: 181 Age: mean age 41 (14.6) in the placebo arm and 45 8 (14.7) in the antibiotic arm Gender: 59% female Ethnicity: not recorded Inclusion criteria: red eye and either mucopurulent discharge or sticking of the eyelids Exclusion criteria: age younger than 18, pre-existing symptoms longer than 7 days, acute loss of vision, wearing of contacts, systemic or local antibiotic use within the previous 2 weeks ciliary redness, eye trauma and a history of eye operation
Interventions	Treatment: fusidic acid gel 1% 4 times daily over a week Control: placebo
Outcomes	Patient-assessed cure, confirmed by clinician assessment
Notes	Adequately powered study; external validity questionable

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists

Rietveld 2005 (*Continued*)

Allocation concealment (selection bias)	Low risk	The study medication was repacked into identical tubes by a local pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The GPs and patients received coded tubes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The pharmacist was the only person in possession of the randomisation lists and was not involved in outcome measurement or data analysis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes are reported
Selective reporting (reporting bias)	Low risk	No reporting bias
Other bias	Low risk	No other bias

Rose 2005

Methods	Randomised controlled trial, double-masked Method of randomisation: centrally randomised
Participants	Country: UK Setting: primary care Number randomised: 326 Age: 6 months to 12 years Gender: 52% male Ethnicity: not reported Inclusion criteria: working clinical diagnosis of acute infective conjunctivitis Exclusion criteria: known allergy to chloramphenicol, current antibiotic or antibiotic treatment within the previous 48 hours, immunocompromised or evidence of server infection (e.g. periorbital cellulitis)
Interventions	Treatment: chloramphenicol 0.5% Control: placebo
Outcomes	Parent-assessed cure as recorded in daily diary
Notes	Adequately powered study

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Rose 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code was employed
Allocation concealment (selection bias)	Low risk	Identical bottles prepared externally
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and personnel were masked
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"the main analysis was undertaken before the randomisation code was broken"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis performed as if those lost to follow-up were treatment failures
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other bias

Silverstein 2011

Methods	Randomised controlled trial, double-masked, vehicle-controlled Method of randomisation: centrally randomised Randomisation: a computer-generated randomisation schedule was used in a 1:1 ratio
Participants	Country: USA Setting: specialist care Participants recruited from clinical centres Number of randomised: 202 patients Age: 1 to 86 years Gender: besifloxacin group - female 58.8%; male 41.2%; vehicle group - female 55.2%; male 44.8% Ethnicity: besifloxacin group - not Hispanic 68.0%; Hispanic 30.9%; missing data 1%; vehicle group - not Hispanic 73.3%; Hispanic 26.7%; missing data 0% Inclusion criteria: at least 1 year of age; a minimum of grade 1 for purulent conjunctival discharge (crusty or sticky eyelids) and a minimum of grade 1 for either bulbar or palpebral conjunctival injection in at least 1 eye on ocular examination; pinhole visual acuity $\geq$ 20/200 in each eye, a negative result on pregnancy testing Exclusion criteria: hypersensitivity to fluoroquinolones, besifloxacin ophthalmic suspension; if patients required or had used ocular immunosuppressants within 30 days before the start of the study; suspected viral or allergic conjunctivitis, iritis; a history of recurrent corneal erosion syndrome, ulcerative active keratitis
Interventions	Treatment: 0.6% besifloxacin ophthalmic suspension Control: vehicle

Silverstein 2011 (*Continued*)

Outcomes	Clinical resolution and microbiological efficacy of besifloxacin; safety data; compliance
Notes	Besifloxacin was given twice daily for 3 days only

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centrally computer-generated randomisation code was employed
Allocation concealment (selection bias)	Low risk	Masked kits were packaged in identical white plastic bottles
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"the investigator was not present during first installation; therefore both patient and investigator were blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	202 patients randomised and had treatment; only 109 patients' data for clinical resolution were reported
Selective reporting (reporting bias)	High risk	Clinical intention-to-treat population analysis made according to culture-positive patients (n = 109), although all 202 patients had treatment
Other bias	High risk	Selection, reporting bias

Tauber 2011

Methods	Randomised controlled trial, double-masked, vehicle-controlled Method of randomisation: unclear Randomisation: eligible patients were randomised in a 1:1 ratio
Participants	Country: USA Setting: specialist care Number of randomised: 847 patients Age: > 28 days old Gender: MOXI-AF group - female 59.5%; male 40.5%; vehicle group - female 57.7%; male 42.3% Ethnicity: MOXI-AF group - Hispanic, Latino or Spanish 23.8.0%; not Hispanic, Latino or Spanish 76.2%; vehicle group - Hispanic, Latino or Spanish 25.9.0%; not Hispanic,

Tauber 2011 (*Continued*)

	Latino or Spanish 74.1% Inclusion criteria: at least 28 days old; a minimum of grade 1 for purulent conjunctival discharge (crusty or sticky eyelids) and a minimum of grade 1 for either bulbar or injection in one or both eyes Exclusion criteria: if signs and symptoms of bacterial conjunctivitis had began longer than 4 days prior to the first visit
Interventions	Treatment: an alternative formulation of 0.5% moxifloxacin ophthalmic solution (MOXI-AF) Control: vehicle
Outcomes	Microbiological efficacy of MOXI-AF; safety data; compliance
Notes	Only microbiological outcomes were reported

Risk of bias ***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 of participants and personnel (performance bias) All outcomes	Low risk	"to maintain masking, specifically designated site personnel other than the study investigator instilled the first dose of medication at the day 1 visit"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	"microbiological intent-to-treat population" - MITT (427 treated with MOXI-AF and 423 with vehicle) was done
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other bias

Tepedino 2009

Methods	Randomised controlled trial, double-masked, vehicle-controlled Method of randomisation: centrally randomised Randomisation: a computer-generated randomisation schedule was used in a 1:1 ratio
Participants	Country: USA Setting: specialist care Participants recruited from clinical centres Number of randomised: 957 patients Age: 1 to 98 years Gender: besifloxacin group - female 63.6%; male 36.4%; vehicle group - female 62.2%; male 37.8% Ethnicity: besifloxacin group - American Indian/Alaskan Native 0.2%; Asian 2.1%; Black 9.3%; Native Hawaiian/Pacific Islander 0.2%; white 65.7%; other 22.5%; vehicle group - American Indian/Alaskan Native 0.2%; Asian 1.5%; Black 9.5%; Native Hawaiian/Pacific Islander 0.6%; white 64.7%; other 23.4% Inclusion criteria: at least 1 year of age; a minimum of grade 1 for purulent conjunctival discharge (crusty or sticky eyelids) and a minimum of grade 1 for either bulbar or palpebral conjunctival injection in at least 1 eye on ocular examination; pinhole visual acuity $\geq$ 20/200 in each eye, a negative result on pregnancy testing Exclusion criteria: hypersensitivity to fluoroquinolones, besifloxacin ophthalmic suspension; patients who used topical ophthalmic anti-inflammatory agents or solutions (artificial tears) within 48 hours before or during the study; suspected viral or allergic conjunctivitis, iritis; a history of recurrent corneal erosion syndrome, ulcerative active keratitis
Interventions	Treatment: 0.6% besifloxacin ophthalmic suspension Control: vehicle
Outcomes	Clinical resolution and microbiological efficacy of besifloxacin; safety data; compliance
Notes	Adequately powered study; this study was conducted at 58 sites in the United States between 5 June 2006 and 7 November 2007; a limitation of this study was the lack of a non-treatment control group

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised in a 1:1 ratio stratified by investigative site; computer-generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There is no information about the preparation of active and vehicle solutions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information

Tepedino 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	26 patients in ITT population discontinued, 8 with intervention and 18 placebo
Selective reporting (reporting bias)	High risk	Wrong denominator for clinical resolution
Other bias	High risk	Misrandomisation

BCVA: best-corrected visual acuity
ITT: intention-to-treat
MOXI-AF: moxifloxacin ophthalmic solution
TOC: test-of-cure

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bremond-Gignac 2010	Not a placebo-controlled trial
Denis 2008	Not a placebo-controlled trial
Everitt 2006	Not a placebo-controlled trial
Granet 2008	Not a placebo-controlled trial
Leibowitz 1976	Single-masked
McDonald 2009	Not a placebo-controlled trial
Mitsui 1986	No placebo group
Robert 2010	Not a placebo-controlled trial
Szaflik 2009	Not a placebo-controlled trial
Ta 2007	Not a placebo-controlled trial

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

NCT00509873

Methods	Double-masked, placebo-controlled RCT
Participants	
Interventions	Gatifloxacin 0.5% eye drops versus placebo
Outcomes	Percentage of patients with clearing (clinical success) of conjunctival hyperaemia and conjunctival discharge at day 6; percentage of patients with microbiological cure at day 6; percentage of patients with clinical improvement of ocular signs at day 6; percentage of patients with clinical improvement of ocular symptoms at day 6
Notes	

NCT00518089

Methods	Double-masked, placebo-controlled RCT
Participants	
Interventions	Gatifloxacin 0.5% eye drops versus placebo
Outcomes	Percentage of patients with clearing (clinical success) of conjunctival hyperaemia and conjunctival discharge at day 6; percentage of patients with microbiological cure at day 6; percentage of patients with clinical improvement of ocular signs at day 6; percentage of patients with clinical improvement of ocular symptoms at day 6
Notes	

NCT01175590

Methods	Double-masked, vehicle-controlled RCT
Participants	
Interventions	Besivance versus vehicle
Outcomes	Treatment-emergent adverse events; clinical resolution; microbial eradication; individual clinical outcomes; microbial outcome and clinical outcome; visual acuity
Notes	

Ofloxacin 1990

Methods	Double-masked, parallel group
Participants	Country: USA Number recruited: 132 patients
Interventions	Loxacin 0.3% eye drops versus placebo instilled 6 times daily for 2 days
Outcomes	Efficacy and safety; microbial reinfection rate
Notes	

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Antibiotics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical remission (early)	6	2116	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.15, 1.61]
2 Microbiological remission (early)	7	1850	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.37, 1.76]
3 Clinical remission (late)	8	2353	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.10, 1.33]
4 Microbiological remission (late)	9	1456	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.24, 1.52]

Analysis 1.1. Comparison 1 Antibiotics versus placebo, Outcome 1 Clinical remission (early).

Review: Antibiotics versus placebo for acute bacterial conjunctivitis

Comparison: 1 Antibiotics versus placebo

Outcome: 1 Clinical remission (early)

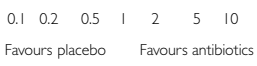
Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Gigliotti 1984	21/42	9/36		5.8 %	2.00 [1.05, 3.80]
Karpecki 2009	20/137	10/132		4.7 %	1.93 [0.94, 3.96]
Miller 1992	126/143	101/141		32.0 %	1.23 [1.09, 1.39]
Rose 2005	123/163	107/163		30.1 %	1.15 [1.00, 1.32]
Silverstein 2011	37/97	21/105		9.9 %	1.91 [1.21, 3.02]
Tepedino 2009	90/475	63/482		17.5 %	1.45 [1.08, 1.95]
Total (95% CI)	**1057**	**1059**		**100.0 %**	**1.36 [1.15, 1.61]**

Total events: 417 (Antibiotics), 311 (Placebo)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 11.33$, df = 5 (P = 0.05); $I^2 = 56\%$

Test for overall effect: Z = 3.60 (P = 0.00031)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Antibiotics versus placebo, Outcome 2 Microbiological remission (early).

Review: Antibiotics versus placebo for acute bacterial conjunctivitis

Comparison: 1 Antibiotics versus placebo

Outcome: 2 Microbiological remission (early)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Gigliotti 1984	24/34	6/32		2.6 %	3.76 [1.77, 8.00]
Karpecki 2009	54/60	27/58		11.6 %	1.93 [1.45, 2.58]
Leibowitz 1991	132/140	22/37		12.6 %	1.59 [1.21, 2.08]
Miller 1992	53/76	32/67		11.5 %	1.46 [1.09, 1.95]
Silverstein 2011	46/53	32/56		13.7 %	1.52 [1.18, 1.95]
Tauber 2011	316/424	237/423		24.9 %	1.33 [1.20, 1.47]
Tepedino 2009	182/199	114/191		23.1 %	1.53 [1.35, 1.73]
Total (95% CI)	**986**	**864**		**100.0 %**	**1.55 [1.37, 1.76]**

Total events: 807 (Antibiotics), 470 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 14.12$, df = 6 (P = 0.03); $I^2 = 57\%$

Test for overall effect: Z = 6.83 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Antibiotics versus placebo, Outcome 3 Clinical remission (late).

Review: Antibiotics versus placebo for acute bacterial conjunctivitis

Comparison: 1 Antibiotics versus placebo

Outcome: 3 Clinical remission (late)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Abelson 2008	82/130	74/149		14.7 %	1.27 [1.03, 1.56]
Gigliotti 1984	31/34	23/32		11.9 %	1.27 [1.00, 1.61]
Gross 2003	25/39	15/34		4.2 %	1.45 [0.93, 2.27]
Karpecki 2009	44/137	25/132		4.5 %	1.70 [1.10, 2.60]
Rietveld 2005	45/81	53/100		10.0 %	1.05 [0.80, 1.37]
Rose 2005	140/163	128/163		31.8 %	1.09 [0.99, 1.21]
Silverstein 2011	39/97	37/105		6.3 %	1.14 [0.80, 1.63]
Tepedino 2009	168/475	132/482		16.7 %	1.29 [1.07, 1.56]
Total (95% CI)	**1156**	**1197**		**100.0 %**	**1.21 [1.10, 1.33]**

Total events: 574 (Antibiotics), 487 (Placebo)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.54$, df = 7 (P = 0.22); $I^2 = 27\%$

Test for overall effect: Z = 3.85 (P = 0.00012)

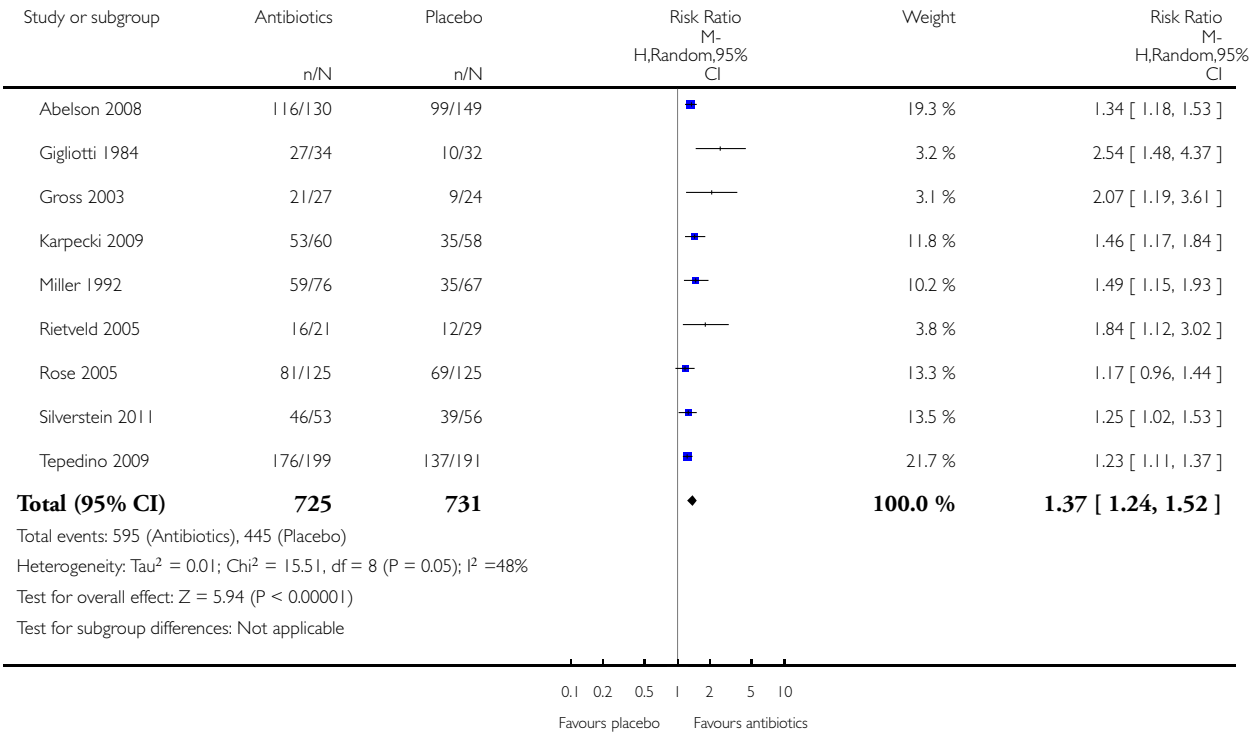
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Antibiotics versus placebo, Outcome 4 Microbiological remission (late).

Review: Antibiotics versus placebo for acute bacterial conjunctivitis

Comparison: 1 Antibiotics versus placebo

Outcome: 4 Microbiological remission (late)



ADDITIONAL TABLES

Table 1. Ingredients of eye drops

Studies	Active treatment ingredient	Placebo vehicle ingredient
Abelson 2008	1% azithromycin in DuraSite	0.01% benzalkonium chloride (BAK), a potent antiseptic
Gigliotti 1984	Ointment containing polymyxin and bacitracin	Neutral ointment
Gross 2003 and Tauber 2011	0.5% moxifloxacin	No information

Table 1. Ingredients of eye drops (*Continued*)

Karpecki 2009; Tepedino 2009; and Silverstein 2011	0.6% besifloxacin	0.01% benzalkonium chloride (BAK), a potent antiseptic
Leibowitz 1991	0.3% ciprofloxacin	No information
Miller 1992	0.3% norfloxacin	0.01% benzalkonium chloride (BAK), a potent antiseptic
Rietveld 2005	1% fusidic acid gel	Placebo gel Vidisic 2 mg/g does not contain an antiseptic
Rose 2005	0.5% chloramphenicol	Boric acid/borax - also has antiseptic properties

APPENDICES

Appendix 1. CENTRAL search strategy

1 MeSH descriptor Conjunctivitis, Bacterial
#2 conjunctiv* near (acute or infect* or bacteria*)
#3 (#1 OR #2)
#4 MeSH descriptor Anti-Bacterial Agents
#5 antibiotic*
#6 (#4 OR #5)
#7 (#3 AND #6)

Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp conjunctivitis,bacterial/
14. ((acute or infect$ or bacteria$) adj4 conjunctiv$).tw.
15. or/13-14
16. exp anti-bacterial agent/

17. antibiotic$.tw.
18. or/16-17
19. 15 and 18
20. 12 and 19

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

Appendix 3. EMBASE (OvidSP) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp conjunctivitis/
34. bacteria$.tw.
35. 33 and 34
36. ((acute or infect$ or bacteria$) adj4 conjunctiv$).tw.
37. or/35-36
38. exp antibiotic agent/
39. antibiotic$.tw.
40. or/38-39
41. 35 and 40
42. 32 and 41

Appendix 4. Open Grey search strategy

bacterial conjunctivitis

Appendix 5. *meta*Register of Controlled Trials search strategy

(bacterial conjunctivitis) and antibiotic

Appendix 6. ClinicalTrials.gov search strategy

Bacterial Conjunctivitis AND Antibiotic

Appendix 7. ICTRP search strategy

Bacterial Conjunctivitis = Condition AND Antibiotic = Intervention

WHAT'S NEW

Last assessed as up-to-date: 18 July 2012.

Date	Event	Description
1 August 2012	New citation required and conclusions have changed	Issue 9, 2012: The conclusion of the previous version of this review was that antibiotics resulted in significantly improved rates of early remission; these benefits were more modest in relation to later resolution. This updated version confirms these early benefits but also more clearly points to benefits with later resolution
1 August 2012	New search has been performed	Issue 9, 2012: Updated searches yielded six new trials (Abelson 2008; Gross 2003; Karpecki 2009; Silverstein 2011; Tauber 2011; Tepedino 2009) that met the inclusion criteria and were included in the review. One new author, Ulugbek Nurmatov, joined the review team and took the lead in updating the review

HISTORY

Protocol first published: Issue 3, 1998

Review first published: Issue 3, 1999

Date	Event	Description
30 October 2008	Amended	Converted to new review format.
30 January 2008	New search has been performed	Issue 2 2008: Updated searches did not yield any new trials.
23 January 2006	New citation required and conclusions have changed	Substantive amendment. Updated searches identified two new RCTs (Rose 2005 and Rietveld 2005), which have been incorporated into the review.
26 May 2001	Feedback has been incorporated	Feedback incorporated.

CONTRIBUTIONS OF AUTHORS

Conceiving the study: AS

Formulating the protocol: AS

Searching databases: IG

Selecting trials: UN, SM, AS

Extracting data: UN, SM

Checking extracted data: AS

Performing data synthesis: UN, SM

Writing the review: UN, SM, CS, AS, BH

DECLARATIONS OF INTEREST

AS was a co-author on the Rose 2005 trial. James Cave jointly conceived the study and formulated the protocol for this review.

SOURCES OF SUPPORT

Internal sources

- University of Edinburgh, UK.
- King's College London, UK.

External sources

- Maastricht University, Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In previous versions of the review we have not separated primary and secondary outcomes of interest. In this updated review we have divided all outcome measures into two: primary and secondary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*therapeutic use]; Conjunctivitis, Bacterial [*drug therapy]; Induction Chemotherapy [methods]; Ophthalmic Solutions; Randomized Controlled Trials as Topic

MeSH check words

Humans