Antibiotics versus placebo for acute bacterial conjunctivitis: findings from a Cochrane Systematic Review

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ABSTRACT (word limit: 250; current: 232)

Purpose: To summarize key findings from a Cochrane Review of the benefits and safety of antibiotic therapy compared with placebo (or vehicle) for acute bacterial conjunctivitis.

Design: Systematic review.

Methods: We included placebo-controlled randomized controlled trials (RCTs) that compared topical antibiotics with placebo. We followed Cochrane methods for trial selection, data extraction, risk of bias assessment, and evidence synthesis.

Results: Twenty-one RCTs involving 8805 participants with acute bacterial conjunctivitis were included. Fifteen (71%) RCTs examined fluoroquinolone (FQ) drops, three tested macrolides, alone or in combination with steroids, and another three compared other non-FQ antibiotics. Intention-to-treat (ITT) estimates suggested that compared with placebo, antibiotics may increase clinical recovery by 26% (risk ratio [RR] 1.26 [95% confidence interval (CI) 1.09 - 1.46] at the end of therapy (5 RCTs, 1474 participants). Modified ITT estimates, in which only participants with laboratory-confirmed bacterial conjunctivitis were analyzed, indicated that antibiotics were associated with 53% higher likelihood of microbiological cure as compared with placebo (RR 1.53 [95% CI 1.34 - 1.74]; 10 RCTs, 2827 participants). Non-FQs (RR 4.05 [95% CI 1.36 - 12.00]), but not FQs (RR 0.70 [95%CI 0.54 - 0.90]), were likely to increase treatment-associated ocular complications such as eye pain, discomfort, and allergic reactions; the certainty of level of evidence was very low.

Conclusions: Moderate level certainty of evidence suggested that antibiotics may increase the likelihood of clinical recovery and microbiological clearance compared with

placebo. Very low-level certainty of evidence suggested that antibiotics may be associated with potential harm in patients with acute bacterial conjunctivitis, but the potential risk of bias from study design, inconsistency in outcome measurement and reporting limit the evidence to very low certainty.

INTRODUCTION

Acute conjunctivitis, characterized by red eyes, discharge, and discomfort, has been estimated to account for 3% of patients seen in general medical practice, where most patients with red eye seek help.(Høvding, Bratland et al. 1991, Høvding 2008) Infection is one etiology of conjunctivitis. The majority of acute infectious conjunctivitis cases in children and large proportion of adult cases are caused by bacteria.(Høvding 2008) However, because obtaining a culture of the patients' conjunctiva is not practical and because many antibiotics are broad-spectrum, many doctors treat presumed cases of infectious conjunctivitis empirically. Patients who see optometrists, urgent care doctors, pediatricians, internists, or family practitioners for conjunctivitis have much higher odds of antibiotic script fill than do patients who saw ophthalmologists.(Shekhawat, Shtein et al. 2017) One survey found that 95% of general practitioners in the UK prescribe antibiotics for conjunctivitis despite more than half believing in a viral etiology.(Everitt and Little 2002) In addition, pressure from patients to return to work or school also may influence antibiotic dispensing practice,(Rose 2007) even though widespread use of broad-spectrum antibiotics can lead to antibiotic resistance.(Peng, Cevallos et al. 2018, D'Oria, Buonamassa et al. 2023) as happens with systemic antibiotic use.(Rosenfeld, Singer et al. 2007, Falagas, Giannopoulou et al. 2008, Venekamp, Sanders et al. 2015, Lemiengre, van Driel et al. 2018, Spinks, Glasziou et al. 2021)

The management of many common infections encountered in primary care underwent a radical transformation over the past 25 years. Whereas antibiotics previously were

standard of care for infections such as sinusitis, otitis media and sore throat (pharyngitis/tonsillitis), randomized controlled trials (RCTs) and systematic reviews have since cast doubt on the clinical and cost-effectiveness of antibiotic therapy for these conditions, especially as many of them resolve without treatment.(Jefferis, Perera et al. 2011) An earlier systematic review even found that 65% of patients with conjunctivitis resolve without antibiotic treatment within 2-5 days of symptom onset.(Rose 2007)

The main objective of this summary of our Cochrane review findings is to report the assessment results on the effectiveness and safety of antibiotic therapies compared with placebo in the treatment of acute bacterial conjunctivitis based on the best currently available evidence.

METHODS

We included placebo-controlled randomized trials (RCTs) in our review following the standard methods in the Cochrane Handbook for Systematic Reviews of Interventions.(Higgins JPT 2021) Methods for conducting the review are briefly summarized below; details can be found in the full Cochrane systematic review.(Chen, Liu et al. 2023) Eligible trials compared antibiotic treatment in any form – topical, systemic, or in combination with steroid – with placebo or vehicle. The diagnosis of bacterial conjunctivitis may have been made on a clinical basis or by microbiological testing. 'Acute' was defined as signs and symptoms of less than four weeks duration. We considered trials that had enrolled participants aged one month or older, except one

trial that included infants younger than one month old and assessed only microbiological efficacy.(Leibowitz 1991)

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) on May 11, 2022 to identify potentially eligible placebo-controlled RCTs for this review. We did not impose restrictions on the search date or language of publication. We also hand-searched the reference lists of identified trial reports and contacted report authors to query additional data or clarification when necessary. We further searched regulatory documents for clinical trials without published trial results.

Study selection

Pairs of review authors worked independently to review titles and abstracts to identify citations that met or possibly met inclusion criteria. The final eligibility decision was based on independent review of the full-text records; disagreements were resolved by discussion.

Outcomes of interest

The primary review outcomes included (1) the proportion of participants (or eyes) with clinical recovery based on resolution of signs or symptoms of acute conjunctivitis and (2) the proportion of participants (or eyes) with microbiological clearance as determined

by culture results. For secondary outcomes, we considered (1) the proportion of participant drop-outs, withdrawals, or loss to follow-up; (2) the proportion of participants (or eyes) with persistent clinical signs of conjunctivitis such as injection or discharge after one course of antibiotic therapy; (3) treatment-associated ocular (allergic, sensitivity, or toxic reaction, the latter two of which might be indicated by follicular conjunctival reaction, ocular pain, discomfort, or swelling of the eyelids) and non-ocular complications (sensitivity to systemic antibiotics, allergic or anaphylactic reaction, bacterial overgrowth from long-term antibiotic use). An additional outcome was the cost-effectiveness of treatment.

Data collection and risk of bias assessment

We extracted the following information for each included study: trial characteristics, methods, participants, interventions, outcomes, and source of funding. Two review authors independently applied Cochrane's Risk of Bias version 2 (RoB2) tool to assess risk of bias for one of the primary outcomes – treatment effectiveness in clinical recovery.(Boutron, Page et al. 2022) We evaluated each eligible study that reported clinical effectiveness for potential sources of bias and judged each study to have been at low or high risk of bias or to raise some concerns for risk of bias. For eligible studies that did not report this outcome, we used Cochrane’s Risk of Bias (RoB1) tool to assess study-level risk of bias.(Higgins and Altman 2017) We resolved any disagreements by discussion within the author team.

Data analysis and synthesis

For comparison of continuous outcomes (visual acuity and quality of life scores), we calculated the estimated difference in means ("mean difference") (MD) with 95% confidence intervals (CI). For dichotomous outcomes, we calculated the estimated risk ratios (RR) with 95% confidence intervals (CIs). For trials that reported numbers of treatment-associated ocular adverse events judged to be treatment-associated by individual event type, we also calculated cumulative incidence ratios and cumulative incidence differences and the associated 95% CIs to approximate RR and risk difference (RD) in person-time during the treatment period, in accordance with Chapter 5 of the Handbook.(Higgins and Deeks 2022) We decided to use treatment duration, rather than the overall trial period, for calculating the associated person-time at risk for treatment-related ocular adverse events.

To determine if trial results were combinable in meta-analyses, we assessed the included trials for both clinical and methodological diversity by examining characteristics of the trial design, eligibility of trial participants, intervention and comparator differences, and outcome definitions. We evaluated and interpreted the amount of statistical heterogeneity using the I^2 statistic as guided by the Cochrane Handbook.(Deeks, Higgins et al. 2021) We also graded the overall certainty of the evidence for each outcome using the GRADE classification,(Schünemann, Higgins et al. 2021) downgrading the certainty to moderate, low, or very low when there was evidence of high risk of bias, inconsistency, indirectness, or imprecision.

RESULTS

The electronic searches, hand-searches, and searches of references of a published meta-analysis and associated regulatory documents yielded 528 titles and abstracts that we screened. We reviewed 12 full-text publications and included 7 new trials (C-00-02; C-00-55; C-01-66; Comstock 2012; Hwang 2003; Malhotra 2013; Yang 2013) that were added to the 14 trials from the original review and the 3 previous updates.(Sheikh, Hurwitz et al. 2000, Sheikh and Hurwitz 2006, Sheikh, Hurwitz et al. 2012) Therefore, we included 21 trials in the updated review, listing 2 as awaiting classification (Figure 1).

Description of included studies

All 21 included trials were placebo-controlled, parallel-group, 2-arm RCTs, except for one 4-arm trial.(Comstock, Paterno et al. 2012) In this trial, the investigators tested tobramycin 0.3%, loteprednol etabonate, and the combination of the two against vehicle but only reported microbiological outcomes. We combined and analyzed data of a 4-arm, dose-ranging trial (C-00-02) as if it were a 2-arm RCT. Sixteen (76%) RCTs were conducted in the U.S.A. More than two-thirds of the trials received funding from pharmaceutical companies; authors of four trials did not disclose funding information.(Gigliotti, Hendley et al. 1984, Miller, Wittreich et al. 1992, Gross, Lichtenstein et al. 2003, Yang, Pan et al. 2013)

The included trials reported data from 8,805 eligible participants who were randomized, with a median number of 326 participants (IQR: 180 to 544) per trial. Most study participants were white or Caucasian (median 74.6%) and female (median 58%). All

interventions were topical drops or ointment: 15 (71%) utilized fluoroquinolone (FQ) drops; three tested macrolides, alone or in combination with steroids; and another three tested non-FQ antibiotics (Table 1).

We assessed 18 of the 21 included trials that reported “clinical efficacy” for risk of bias using the Cochrane RoB 2 tool.(Boutron, Page et al. 2022) Four (19%) of the 21 trial outcome results were judged to have had an overall low risk of bias; one had high overall risk of bias (5%); the remaining 16 (76%) trials raised some concerns for risk of bias (Figure S1). The randomization process was the domain for which we judged the largest number of trials to be at risk. We reported two sets of RoB2 results for three trials reporting “clinical efficacy” on both the intention-to-treat (ITT) and the modified ITT (mITT) population.(Research 2002, Research 2002, Rose, Harnden et al. 2005) The mITT population was defined by the trial investigators as a subset of randomized participants whose baseline culture results confirmed bacterial conjunctivitis; the ITT population consisted of the randomized participants without regard to baseline culture results.

Comparative analyses

Trials differed in whether they reported outcomes based on the ITT population or mITT population and whether they measured clinical recovery at the “end-of-therapy” visit or the “test of cure” visit, which could occur at variable time points following the last antibiotic administration and at which time a confirmatory culture was obtained (Table 2).

Effectiveness and safety of interventions

Critical outcomes

Five trials reported clinical recovery at the '**end-of-therapy**' visit based on the ITT population.(Miller, Wittreich et al. 1992, Research 2002, Research 2002, Rose, Harnden et al. 2005, Yang, Pan et al. 2013) Compared with placebo, topical antibiotics increased the likelihood of clinical resolution by 26% (risk ratio [RR] 1.26 [95% CI 1.09 -1.46]). Fluoroquinolone (FQ) had 22% increased likelihood of clinical cure compared with placebo (RR 1.22 [95% CI 1.09 -1.37]). There was no evidence of a difference in clinical cure between participants receiving non-FQs and those receiving placebo (RR 1.36 [95% CI 0.83 - 2.23]). Despite the difference in results between FQs and non-FQs, the results were combinable because there was no evidence of subgroup differences (P = 0.67, Figure 2). After removing a study judged to possess high risk of bias, the combined risks were similar (RR 1.29 [95% CI 1.21- 1.38]).

Eleven trials reported clinical cure at the **end-of-therapy** visit based on the mITT population. Estimated RRs indicated that compared with placebo, topical antibiotics had increased participants' likelihood of clinical cure by 26% at the end of a given treatment course (RR 1.26 [95%CI 1.17-1.37]). Five trials reported clinical efficacy at the **test-of-cure** visit.(Gross, Lichtenstein et al. 2003, Hwang, Schanzlin et al. 2003, Rose, Harnden et al. 2005, Abelson, Heller et al. 2008, Karpecki, Depaolis et al. 2009) When compared with placebo, FQ use was associated with a 44% increased likelihood of clinical recovery (RR 1.44 [95% CI 1.21-1.71]). Non-FQ use was not associated with

this finding; there was statistical evidence of subgroup differences at a pre-defined threshold of 0.1 (P = 0.08, Table 2). We assessed the evidence to be of moderate certainty that topical antibiotics confer a higher likelihood of clinical cure than does placebo.

One trial assessed microbiological cure at the **end-of-therapy** visit based on the ITT analysis,(Gigliotti, Hendley et al. 1984) and showed that antibiotics had increased microbiological cure when compared with placebo (RR 2.54 [95% CI 1.48 - 4.37]) (Table 2). Estimated RRs from another 10 trials that reported microbiological efficacy outcomes at the **end-of-therapy** visit based on the mITT population,(Leibowitz 1991, Miller, Wittreich et al. 1992, Rietveld, ter Riet et al. 2005, Abelson, Heller et al. 2008, Tepedino, Heller et al. 2009, NCT00518089 2011, Tauber, Cupp et al. 2011, DeLeon, Silverstein et al. 2012, Malhotra, Ackerman et al. 2013, NCT01740388 2013) indicated topical antibiotics had increased microbiological cure by 53% compared with placebo (RR 1.53 [95% CI 1.34 - 1.74]) (Figure 3). Twelve trials showed comparable intervention effects at the **test-of-cure** visit for the mITT population (RR 1.38 [95% CI 1.27 - 1.50]). The certainty of evidence was moderate that topical antibiotics had improved microbiological cure after one treatment course.

Important outcomes

Based on analysis of twelve trials,(Gigliotti, Hendley et al. 1984, Miller, Wittreich et al. 1992, Kodjkian, Lafuma et al. 2002, Research 2002, Rietveld, ter Riet et al. 2005, Karpecki, Depaolis et al. 2009, Tepedino, Heller et al. 2009, NCT00518089 2011,

DeLeon, Silverstein et al. 2012, Malhotra, Ackerman et al. 2013, NCT01740388 2013, Yang, Pan et al. 2013) the evidence was of moderate certainty that, compared with placebo use, antibiotic use had decreased the risk of treatment incompletion by 36% (RR 0.64, 95% CI 0.52 to 0.78) (Table 2).

The certainty of evidence was rated as moderate around the estimate that antibiotics offer a 27% reduced risk for persistent clinical signs or symptoms compared with placebo (RR 0.73 [95% CI 0.65-0.81]).

Seven trials reported treatment-related ocular adverse events.(Miller, Wittreich et al. 1992, Rietveld, ter Riet et al. 2005, Rose, Harnden et al. 2005, Tepedino, Heller et al. 2009, Tauber, Cupp et al. 2011, Comstock, Paterno et al. 2012, DeLeon, Silverstein et al. 2012) Compared with placebo, FQs were associated with an overall decreased risk of ocular complications (RR 0.70 [95% CI 0.54 - 0.90]), and non-FQs were associated with an increased risk (RR 4.05 [95% CI 1.36 - 12.0) (Figure 4). However, the evidence for both associations was of very low certainty because of risk of bias and extreme imprecision.

Because no events had been reported in the placebo or vehicle group, we estimated incidence rate differences for 11 trials.(Gigliotti, Hendley et al. 1984, Research 2002, Hwang, Schanzlin et al. 2003, Abelson, Heller et al. 2008, Karpecki, Depaolis et al. 2009, Tepedino, Heller et al. 2009, NCT00518089 2011, Comstock, Paterno et al. 2012, DeLeon, Silverstein et al. 2012, Malhotra, Ackerman et al. 2013, NCT01740388 2013)

Estimates of these rate differences between participants taking antibiotics and those assigned to placebo suggested comparable risks for treatment-associated ocular adverse events (RD 1.41 [95% CI -0.93 to 3.75] per 1000 person-day of treatment). Comparisons of estimated rate ratios also suggested similar risks for the two groups (RR 1.06 [95% CI 0.79 – 1.44]) (Table 2).

There was comparable risk between antibiotics and placebo in incidence of systemic complications, of which headache and dysgeusia were most common. The certainty of evidence was very low because of extreme imprecision and risk of bias in selective reporting (Table 2).

No study evaluated or reported the cost-effectiveness of antibiotic treatment in comparison with placebo.

DISCUSSION

In this updated Cochrane review of 21 RCTs in which 8805 participants with bacterial conjunctivitis were treated and followed, we compared the effectiveness and safety of topical antibiotics relative to placebo. Evidence of moderate certainty indicated that antibiotics had improved clinical cure at the end of therapy, had increased treatment completion rates, and had reduced persistent clinical infection after one course of treatment by at least 25%. Evidence of moderate certainty also suggested that antibiotic use was associated with more participants with microbiological cure and better

treatment adherence. The certainty of evidence of a difference between antibiotics and placebo in incident adverse effects was very low.

The findings of the current review may be more applicable to acute bacterial conjunctivitis in the older pediatric and adult population than to neonatal bacterial conjunctivitis (caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae* contracted in the birth canal); neonatal as well as hyperacute conjunctivitis (usually caused by *Neisseria gonorrhoeae* or *Neisseria meningitides*) requires systemic antibiotic treatment.(Prevention 2021) Moreover, whereas the most common cause of acute bacterial conjunctivitis in the non-neonatal, pediatric population is *Haemophilus influenzae*, the most common etiology in adults is *Staphylococcus aureus*.(Mahvan, Hornecker et al. 2014)

In reported mITT results, 55.5% (408/735) of participants in the placebo group had spontaneous clinical resolution by days 4 to 9 vs. 68.2% (504/739) of those treated with an antibiotic. This finding is consistent with clinical observations and may argue against reflexive requirements of many school districts that children with conjunctivitis be prescribed an antibiotic before returning to school.(Lee and Kuo 2022) However, However, because randomization had been performed at the participant level for each RCT, the summation of events and participants for this calculation was done solely heuristically. Furthermore, the exact timing of disease onset was often poorly defined or not defined. Enrolling participants at more similar times of disease onset would allow better comparisons between studies and between treatment and placebo arms.

Not infrequently, number needed to treat (NNT) is calculated as an expression of the efficacy of an intervention in terms of people who need to be treated to prevent one additional adverse event. However, given the heterogeneity in the characteristics of the study populations, treatment and follow-up durations, antibiotics, comparator group, and timepoint of outcome assessment, NNT was not an appropriate representation of antibiotic efficacy.(Schünemann, Vist et al. 2022)

A variety of topical antibiotics was tested in the included trials. The evidence suggested that FQs were effective in increasing clinical and microbiological cure compared with placebo. In contrast, non-FQs increased only the microbiological, not the clinical, efficacy of cure. However, because of the different non-FQ drug classes and different lengths of treatment, the evidence identified in the current update does not support any conclusions about head-to-head comparisons between FQ and non-FQ, as has been done with non-ophthalmic preparations.(Huang, Lin et al. 2018, Ramos, Allen et al. 2019) Further trials will be needed to compare classes of ophthalmic antibiotics.

Future investigators also may consider comparing antiseptic treatment (for example, povidone iodine, against which there is little to no known resistance, and which is low cost) with topical antibiotics. Last, findings of this review may be limited in providing evidence on comparative efficacy for short (3 to 5 days) versus long (≥ 7 days) courses of antibiotic therapy as the treatment duration varied by the specific antibiotics used. Only trials of different duration of treatment with the same antibiotic would help answer

the question of comparative efficacy between shorter and longer treatments. Although non-FQs offer clinical efficacy as do FQs, very low-level certainty evidence suggests that in contrast with FQs, non-FQs may increase risks of ocular adverse effects when compared with placebo.

In conclusion, our review provided evidence of moderate certainty to support the use of antibiotics over placebo in clinical resolution and microbiological cure of bacterial conjunctivitis as well treatment adherence and reduction in persistent infection. Because no study examined cost of intervention, it remains to be assessed whether these advantages are offset by the cost of intervention or the immeasurable cost of increased risk of resistance to antibiotic from widespread use. The evidence is much less certain regarding differences between antibiotics and placebo in ocular adverse effects. Further research is required to assess the clinical and microbiological efficacy among different antibiotic classes, bacterial species, or treatment durations of the same antibiotic in head-to-head trials. Future research would be bolstered by attainment of consensus on time points at which patients are diagnosed with bacterial conjunctivitis (and start treatment) and time points at which efficacy outcomes are assessed and recorded, whether at the end of therapy or at a later point as in some trials in this review. Changes in study design and conduct and inclusion of cost as an outcome would aid in better estimates of differences between antibiotics and placebo and in estimates of cost effectiveness.

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Figure legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram showing identification and selection of randomized controlled trials that compared different topical antibiotics with placebo for acute bacterial conjunctivitis.

Figure 2. Forest plot of comparing topical antibiotics versus placebo, outcome: clinical cure at “end-of-therapy” visit based on the intention-to-treat population. CI = confidence interval; M-H = Mantel-Haenszel.

Figure 3. Forest plot of comparing topical antibiotics versus placebo, outcome: microbiological cure at “end-of-therapy” visit based on the modified intention-to-treat population.

Figure 4. Forest plot of comparing topical antibiotics versus placebo, outcome: treatment-associated complications during the trial period by antibiotic class.