Topical antibiotics for acute bacterial conjunctivitis: a systematic review

Aziz Sheikh and Brian Hurwitz

SUMMARY

There has been uncertainty about whether antibiotic therapy confers significant benefit in the treatment of acute bacterial conjunctivitis. This study aimed to assess the efficacy of antibiotic therapy in the management of acute bacterial conjunctivitis. Using standard Cochrane search methods, we identified double-blind randomised controlled trials in which any form of antibiotic treatment (topical, systemic or combination) had been compared with placebo in the management of acute bacterial conjunctivitis. Data extraction and analysis followed a pre-defined protocol. Meta-analysis was performed to obtain summary measures of relative risk. Six published trials were identified, of which three fulfilled the eligibility criteria for inclusion in this review. The trials were heterogeneous in terms of their inclusion and exclusion criteria, the nature of the intervention, and the outcome measures assessed. Meta-analysis indicates that acute bacterial conjunctivitis is frequently a self-limiting condition, as clinical remission occurred by days 2 to 5 in 64% (95% confidence interval (CI) = 57–71) of those treated with placebo. Treatment with antibiotics was, however, associated with significantly better rates of clinical remission (days 2 to 5: relative risk (RR) = 1.31, 95% CI = 1.11–1.55), with a suggestion that this benefit was maintained for late clinical remission (days 6 to 10: RR = 1.27, 95% CI = 1.00–1.61). Acute bacterial conjunctivitis is frequently a self-limiting condition but the use of antibiotics is associated with significantly improved rates of early clinical remission, and early and late microbiological remission. Since trials to date have been conducted in selected specialist care patient populations, generalisation of these results to a primary care-based population should be undertaken with a degree of caution.

Keywords: *antibiotics; acute bacterial conjunctivitis; clinical trials; systematic review.*

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Submitted: 10 July 2000; Editor's response: 27 October 2000; final acceptance: 5 January 2001.

Introduction

SCRUTINY of primary health care has highlighted how tenuous are some of the links between many of the commonly employed treatments of general practice and a sound evidence base.[1,2] In the developed world, the syndrome of acute 'red eye' accounts for between 1% and 4% of consultations with primary care physicians,[4-6] and results from one of several possible conditions (viral, bacterial and allergic conjunctivitis, keratitis, episcleritis, iritis, iridocyclitis, acute angle-closure glaucoma, corneal erosion and abrasion, and dysthyroid disorders).[3] In the majority of cases an acute bacterial conjunctivitis is diagnosed,[5-10] the pathogens most frequently responsible being *Streptococcus pneumoniae, Haemophilus influenza* and *Staphylococcus aureus*.[10-12] The condition affects both sexes, all ages, and all races.[4] Generally considered to be a self-limiting disorder, antibiotics are nevertheless usually prescribed in the belief that they speed recovery, reduce the risk of developing sight-threatening complications, and reduce the rate of re-infection.[13,14] Guidelines on the management of conjunctivitis recommend their routine use where bacterial infection is suspected,[15-17] with distinct national preferences in the topical agent used.[18] In this review we ask: 'what is the efficacy of antibiotic treatment in the management of acute bacterial conjunctivitis?'

Method

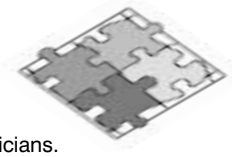
Study inclusion criteria and search strategy

We aimed to include all double-blind, randomised, placebo controlled trials comparing antibiotics with placebo in the management of acute bacterial conjunctivitis. Studies were identified from the Cochrane Eyes and Vision Group Register, Cochrane Controlled Trials Register, and Medline, using a search strategy that we have reported elsewhere;[19] the Science Citation Index was used to look for additional studies that had cited the trials identified. Bibliographies of identified trials were searched manually to find additional trials and we wrote to first authors of identified studies, and to pharmaceutical companies identified as producers of relevant ophthalmic preparations, to enquire about other relevant published and unpublished studies.[19] The most recent searches were performed in September 1998; there was no language restriction in the selection of trials.

Selection of trials

Two reviewers independently checked the titles and abstracts of all studies identified from the searches, and the full text was obtained of each report referring to other possibly relevant trials. Two reviewers assessed all full text articles to ensure that only trials meeting the inclusion criteria for this review were assessed for methodological quality.

HOW THIS FITS IN



What do we know?

The syndrome of 'acute red eye' accounts for between 1% and 4% of consultations with primary care physicians. Bacterial conjunctivitis is the commonest condition diagnosed that underpins treatment with topical antibiotics, in the belief that they speed recovery and reduce the risk of sight-threatening complications.

What does this paper add?

Systematic review and meta-analysis of double blind antibiotic placebo controlled trials indicates that acute bacterial conjunctivitis is frequently a self-limiting condition. Antibiotic treatment does, however, result in significantly improved rates of clinical and microbiological remission. No serious adverse outcomes were reported in either placebo or antibiotic treated patients in these trials, suggesting that important sight-threatening complications are an infrequent complication of acute bacterial conjunctivitis.

Assessment of methodological quality

Trial quality was assessed independently by both reviewers according to the following criteria: allocation concealment, method of allocation to treatment, documentation of exclusions, completeness of follow-up, and methods of documentation of complications. Any disagreement between reviewers was resolved by discussion. Each trial was graded A — low risk of bias, B — moderate risk of bias, and C — high risk of bias, from which an overall grade of quality was developed for each trial, according to predefined criteria.[20] Only trials awarded an overall A or B grade were included in the review. Reviewers of this work were neither masked to report authors nor to trial results.

Data extraction and statistical methods

One reviewer extracted data onto a standard pro-forma, the accuracy of which was checked by the second reviewer. Authors of reports and the trial funding agencies were contacted in an attempt to obtain missing data. Review Manager software was used to analyse the data, a fixed effect model was preferred in the absence of detecting significant statistical heterogeneity. Quantitative analyses of outcomes were performed on an intention to treat basis and results expressed as relative risk (RR) with 95% confidence intervals (CI).

Results

Electronic searches identified 155 reports of possible trials comparing antibiotics versus placebo in the management of acute bacterial conjunctivitis, from which four randomised controlled trials were identified.[21-24] Contacting pharmaceutical companies identified one additional trial.[25] Searching the reference lists of these studies did not bring to light any other trials, and writing to first authors of identified trials failed to generate additional relevant information. Three trials satisfied the inclusion criteria;[21-23] two were excluded (one because it was single-blind,[24] the other because it was incompletely reported[25]). Two of the eligible trials were based in the United States,[21,22] with the third recruiting patients from the United States, Mali, and Morocco.[23]

Altogether 527 patients were enrolled in the trials included in this review. Table 1 describes their characteristics, and shows them to be heterogeneous for age groups of patients studied, diagnostic inclusion criteria adopted by the trials, and for antibiotic treatments used, all of which involved topical preparations. Two of the trials included only those with swab-confirmed bacterial infection.[21,22] In the study by Gigliotti *et al,* children from the community recruitment centre were randomised and treated immediately, but excluded from the analysis if swab cultures were negative.[21] Children enrolled from the hospital clinic, however, were randomised and treated only if cultures were positive. In the study by Leibowitz, all patients were randomised and treated, those with negative swab results being subsequently excluded from the analysis.[22] The paper by Leibowitz presents combined results from two separate trials, one comparing the efficacy of ciprofloxacin with placebo, the other comparing ciprofloxacin with tobramycin, this accounting for the imbalance in patient numbers between placebo and active treatment arms (Table 1).[22] Attempts at contacting the author to obtain clarification concerning the division of patients enrolled in each individual study were unsuccessful. The three trials included in the meta-analysis used different combinations of outcome measures, and focused upon clinical cure, microbiological cure, or a combination of these. Clinical and microbiological outcomes were assessed 'early' (days 2 to 5, post-intervention) and 'late' (days 6 to 10, post-intervention).

Despite clinical differences in the patient groups and interventions employed in the trials studied, there was no strong evidence of statistical heterogeneity, as revealed by the results of χ^2 tests (early clinical remission: $\chi^2 = 3.79$, df = 1, $P = 0.05$; late clinical remission: not applicable; early microbiological remission: $\chi^2 = 5.64$, df = 2, $P = 0.06$; late microbiological remission: $\chi^2 = 3.20$, df = 1, $P = 0.07$).[19] Meta-analysis showed acute bacterial conjunctivitis frequently to be a self-limiting condition, as clinical remission (defined as clinical cure or significant clinical improvement) occurred by days 2 to 5 in 64% (95% CI = 57–71) of those treated with placebo. Treatment with topical antibiotics was associated with significantly better rates of early clinical remission (days 2 to 5: RR = 1.31, 95% CI = 1.11–1.55) (Figure 1) and suggested that the benefit was maintained for late clinical remission (days 6 to 10: RR = 1.27, 95% CI = 1.00–1.61). Antibiotic treatment was associated with improved rates of microbiological remission, defined as pathogen eradication or reduction (days 2 to 10: RR = 1.71, 95% CI = 1.32–2.21; days 6 to 10: RR = 1.71, 95% CI = 1.26–2.34) (Figure 2). Sensitivity analysis, excluding the study by Leibowitz, did not significantly alter the results for rates of early microbiological remission (RR = 1.81, 95% CI = 1.38–2.39), the only data provided by this trial.[22] No serious outcomes were reported in either the active or the placebo arms of these trials, nor among the 275 patients enrolled in the antibiotic versus placebo trials excluded from the meta-analysis.[24,25]

Discussion

In these studies, acute bacterial conjunctivitis is shown gen-

Table 1. Characteristics of included studies: double-blind randomised controlled trials comparing antibiotics versus placebo for acute bacterial conjunctivitis.[19]

Author, year, reference	Participants (age, setting, country)	Number in active and control arms	Disease definition	Interventions	Outcomes
Gigliotti, 1984[21]	Children aged 1 month–18 years recruited from general and hospital paediatric practice, USA	24/32	Clinical evidence of conjunctivitis and swab-proven *Haemophilus influenzae* or *Streptococcus pneumoniae*	10 000 U/g polymyxin and 500 U/g bacitracin. 4 times daily for 7 days.	Clinical and microbiological remission at days 3–5 and days 5–8.
Leibowitz, 1991[22]	Participants (age not specified) recruited from hospital clinic, USA	140/37	Swab-proven bacterial conjunctivitis	Study 1: ciprofloxacin 0.3% 1–2 drops 2-hourly on days 0–1 and 4-hourly on day 2 versus placebo. Study 2: tobramycin drops 0.3% 2-hourly on days 0–1 and 4-hourly on days 2–6 versus ciprofloxacin 0.3% 1–2 drops 2-hourly on days 0–1, and 4-hourly on days 2–6.	Microbiological remission at day 3.
Miller, 1992[23]	Adults (aged 18 and over) recruited from hospital centres in USA, Mali, and Morocco	143/141	Clinical diagnosis of acute bacterial conjunctivitis	Norfloxacin 0.3% + 0.0025% benzalkonium chloride preservative, 1 drop 2-hourly on day 1, and 4 times/day for a maximum of 7 days.	Clinical remission at days 2–3. In those with swab-proven bacterial infection, microbiological remission at days 2–3 and 5–7.

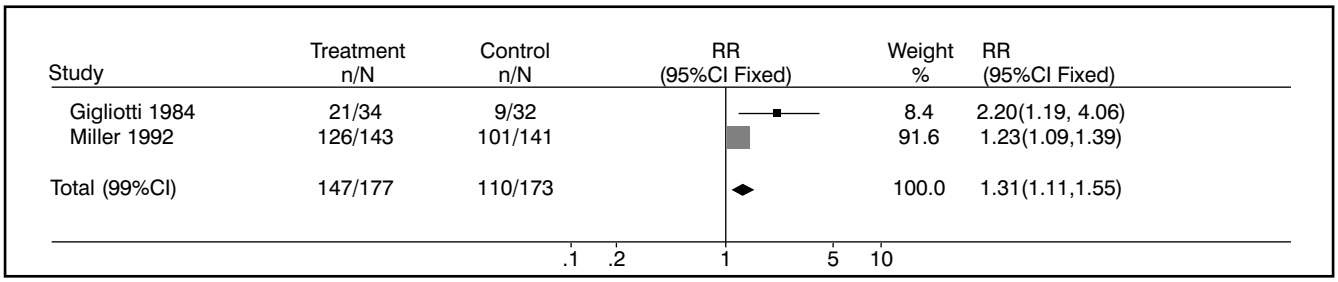


Figure 1. Early clinical remission.

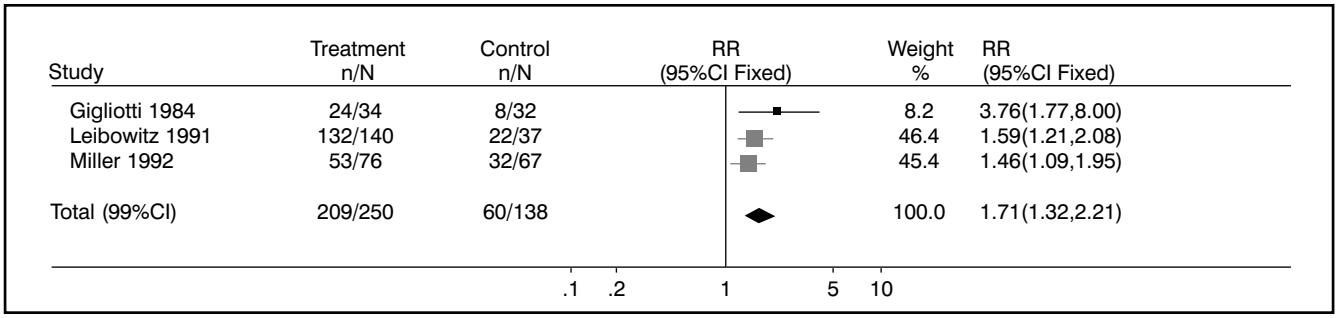


Figure 2. Early microbiological remission.

erally to be a self-limiting condition; in the placebo group clinical and microbiological remission occurring early, by days 2 to 5, in 64% (95% CI = 57–71) and 44% (95% CI = 36–52) respectively. But meta-analysis reveals topical antibiotic treatment to be associated with significantly better rates of early clinical and microbiological remission than is treatment with placebo, and also suggests this benefit is maintained for late (days 6 to 10) clinical remission. Despite a degree of clinical heterogeneity between the three trials included in the review, in the absence of statistical heterogeneity, meta-analysis is likely to be valid. No serious adverse events were noted in the 802 patients enrolled in all five antibiotic–placebo controlled trials that have reported to date, suggesting that important sight-threatening complications infrequently result from a diagnosis of acute bacterial conjunctivitis. But in view of the probable rarity of such adverse events, the possibility of type II errors cannot be entirely excluded.

The outcome measures adopted by studies included in this review do not distinguish patient-orientated outcomes (such as mean interval from treatment to relief of symptoms) from doctor-orientated outcomes (such as clinical and microbiological remission rates). Despite the self-limiting nature of acute bacterial conjunctivitis documented by the studies, and concerns regarding antibiotic safety[17] and resistance,[26,27] it is surprising that none of the trials attempted to determine the cost-effectiveness of topical antibiotic treatment, or assessed the impact of treatment upon re-infection rates.

How, if at all, should the findings of this review influence the prescribing practices of primary care clinicians in the treatment of acute bacterial conjunctivitis? Delayed treatment strategies, in which all patients are prescribed topical antibiotics but are advised to use them only if symptoms persist for longer than five days, might be considered an option.[28] However, accurate estimates of the risks of sight-threatening complications without antibiotic treatment are lacking; we cannot therefore exclude the possibility that a treatment strategy that recommends systematic delay in administering antibiotics could compromise safety in a very small number of patients. Although the studies in this meta-analysis recruited trial participants mainly from hospital clinic settings in the USA, the findings of this review are likely to be applicable to primary care settings elsewhere, since hospital clinics encompass primary care functions in the USA and, in terms of prevalence and severity of disease encountered, are likely to be more similar to primary care in the UK than, for example, UK specialist practice. Nevertheless, since treatment in general practice is usually pragmatic (whereas in the trials reviewed it was not), and is offered without microbiological assessment, it is likely that the number needed to treat will be higher in general medical practice than in a population selected for having proven bacterial infection.

The microbiology of acute bacterial conjunctivitis is reasonably well described and varies little by geography; the results of the meta-analysis are likely to be applicable in countries in which fluoroquinolones or polymyxin/bacitracin preparations are preferred first-line treatment for the condition (Table 1). Chloramphenicol accounts for over 90% of topical anti-infective eye preparations dispensed in Australia,[29] while in the USA treatment with aminoglycosides and sulfacetamide (10% solution) remains common.[14,15] In England, 3.4 million community prescriptions for topical ocular antibiotics are issued each year, over 95% of which are for chloramphenicol (67%) or fusidic acid (29%), at a cost to the National Health Service of £4.7 million.[30] Given concerns about emerging bacterial resistance to fluoroquinolones,[26,27] and in the absence of identifying any controlled trials that compare aminoglycosides, sulfacetamide, chloramphenicol, or fusidic acid with placebo, how generalisable are our results to treatment with other topical antibiotics?

Comparative studies of topical antibiotic treatments have shown many different broad spectrum treatments to be of similar efficacy in the treatment of bacterial conjunctivitis.[31-44] This suggests that extrapolation of results from this review to treatment with other agents active against the Gram-positive organisms, typically responsible for acute infection, is reasonable.

Choice of treatment should be guided by relative cost and risk of adverse effects. In the UK, where there is an almost 10-fold difference in antibiotic treatment costs, and now that doubts about safety have, to a large extent, been allayed,[45-47] we believe that topical chloramphenicol remains the treatment of choice for acute bacterial conjunctivitis, although we recognise that there is no direct evidence from placebo-controlled trials to support this conclusion. A primary care-based trial designed to assess the cost-effectiveness of the most commonly used antibiotic(s) versus placebo can, therefore, be justified. Such a trial should be conducted in primary care, needs to focus on symptomatic improvement, and should also seek to clarify whether treatment with antibiotics confers any benefits with respect to rates of re-infection. In addition, it remains to be ascertained how accurately and reliably GPs can differentiate bacterial from viral and allergic causes of conjunctivitis (or indeed the more important causes of acute 'red eye') in routine practice.[48]

Acknowledgements

We thank the Cochrane Eyes and Vision Group and the Systematic Reviews Training Unit for their assistance in preparing this paper, and Professor Simon Thompson, Dr Tim Lancaster, and Professor Tom Rogers for their comments on earlier drafts of the manuscript. This review was conceived when Aziz Sheikh held a London Academic Trainee Fellowship; he is now funded by the NHS R&D National Primary Care Training Programme.

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