Topical antibiotics for the management of bacterial keratitis: an evidence-based review of high quality randomised controlled trials

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ABSTRACT

Background Severe bacterial keratitis (BK) typically requires intensive antimicrobial therapy. Empiric therapy is usually with a topical fluoroquinolone or fortified aminoglycoside–cephalosporin combination. Trials to date have not reached any consensus as to which antibiotic regimen most effectively treats BK.

Methods A systematic review and meta-analysis using Cochrane methodology was undertaken to evaluate the effectiveness of topical antibiotics in the management of BK. Outcomes included treatment success, time to cure, serious complications of infection and adverse effects.

Results A comprehensive search for trials resulted in 27 956 abstracts for review. This eventually resulted in 16 high quality trials involving 1823 participants included in the review. Treatment success, time to cure and serious complications of infection were comparable among all antibiotic treatments included in the review. Furthermore, there was no evidence of difference in the risk of corneal perforation with any included antibiotics or antibiotic classes. Fluoroquinolones significantly reduced risk of ocular discomfort and chemical conjunctivitis but increased the risk of white precipitate formation compared with aminoglycoside–cephalosporin. Fortified tobramycin–cefazolin was approximately three times more likely to cause ocular discomfort than other topical antibiotics.

Conclusions Results of this review suggest no evidence of difference in comparative effectiveness between fluoroquinolones and aminoglycoside–cephalosporin treatment options in the management of BK. There were differences in safety profile, however. Fluoroquinolones decreased the risk of ocular discomfort and chemical conjunctivitis while ciprofloxacin increased the risk of white corneal precipitate compared with aminoglycoside–cephalosporin.

INTRODUCTION

Bacterial keratitis (BK) remains a leading cause of ocular morbidity worldwide.[1] The effects of BK range from mild corneal irritation to visual loss, corneal perforation or blindness. Severe infection may require hospitalisation and is typically treated with an intensive empiric regimen consisting of 15 min to hourly instillation of topical fortified aminoglycoside–cephalosporin (combination therapy) or topical fluoroquinolone (monotherapy), following corneal scrape and cultures.[2 3] Severe bacterial infection may result in significant stromal scarring, which may eventually require corneal transplantation to restore vision.

While empiric treatment of BK is necessary when awaiting the outcome of culture and sensitivity testing, or where culture facilities are unavailable, the antibiotic regimen chosen should be of a sufficiently broad spectrum to cover likely pathogens while considering bacterial prevalence, antibiotic sensitivities and geographically-specific epidemiological data. In this respect, a systematic review[4] investigating geographic variations in microbial keratitis highlighted major differences. USA (Los Angeles)[5] and Australia (Adelaide)[6] reported the highest percentages of bacterial cases (95% in both countries); Paraguay[7] had the highest percentage of Staphylococcal infection (79%). Thailand (Bangkok)[8] reported the highest percentage of Pseudomonas infections (55%) while India (Tamil Nadu)[9] reported the highest percentage of Streptococcal infections (47%).

Despite the publication of numerous clinical trials, there remains a lack of consensus as to which topical antibiotics and which regimen (ie, monotherapy or combination therapy) provide superior clinical outcomes. Therefore, the objective of this systematic review was to quantify the comparative effectiveness and safety of various topical antibiotics for BK.

MATERIALS AND METHODS

Eligibility criteria

A systematic review of randomised controlled trials was conducted comparing the effectiveness of different topical antibiotics in the management of patients with BK.

Types of participants

Participants were patients of any age or ethnicity diagnosed with bacterial infection of the cornea either by cultures or clinical judgment of diagnosing physician in either community-based or hospital-based settings.

Types of interventions

Trials were included that compared two or more topical ocular antibiotics administered for at least 7 days. Placebo controlled trials were excluded. While variability between dosing schedules was expected, all trials were expected to provide intensive topical ocular antibiotic cover (drops administered every 30–60 min) for the first 48 h followed by at least a 2–4-h regime by day, until day 5. Ocular antibiotics were then administered at the discretion of the treating physician. Permitted co-interventions included cycloplegics, glaucoma drugs, vitamins, oral analgesics, ocular lubricants, topical ocular corticosteroids and lid hygiene.

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Types of outcomes

The primary outcome was treatment success, defined as complete re-epithelialisation of the cornea. Overall treatment success was reported at the conclusion of each trial in order to account for all participants. Secondary outcomes included time to cure (number of days treatment was instilled before physician's judgment designated BK as cured), adverse effects defined as any effects related to application of trial medication such as ocular discomfort (eg, pain, pruritus, burning, stinging, irritation), chemical conjunctivitis (eg, ocular/conjunctival toxicity or bulbar ulceration) or white precipitate, and serious complications of infection defined as complications requiring surgical intervention typically related to ocular bacterial infection rather than trial medication (eg, corneal perforation, therapeutic keratoplasty or enucleation).

Literature search

The following databases were searched for potential trials without language restriction: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, EMBASE, Scopus, BioMed Central, Trials Central, Clinical Trials, Controlled Clinical Trials, Web of Science, Latin American and Caribbean Health Sciences Literature (LILIACS) and relevant online medical journal websites. All databases were searched from the date of inception until the end of March 2013, and the reference lists of articles were also searched to identify potential trials of interest. The search strategy is available online as supplementary appendix 1. Authors of identified trials and pharmaceutical companies producing topical antibiotics were contacted for additional published, unpublished or ongoing trials. Authors of identified trials were also contacted if there were insufficient or missing data. This review was conducted following methodology guidance outlined in the Cochrane Handbook for Systematic Review.[10] Review Manager 5.1 was used for meta-analysis.[11]

Data extraction and management

One reviewer conducted the electronic searchers. Two reviewers (EM and FR) independently selected trials for inclusion and assessed those that appeared potentially relevant. Full text articles were retrieved and translated where necessary. A third reviewer (CNJM) was available to arbitrate if there was failure in resolving disagreement between the first two reviewers. Random sequence generation, allocation concealment, masking of participants and personnel, masking of outcome assessment, incomplete outcome data and other identified bias of included trials were scored using the Cochrane Risk of Bias tool[12] (see online supplementary figure S1).

Statistical analysis

Treatment differences were calculated using Mantel–Haenszel fixed-effect analysis,[13 14] and random-effects analysis was to be used if there was evidence of statistical heterogeneity.[12] Continuous outcomes were analysed using mean difference (MD) and reported with 95% CIs. Relative risk (RR) with 95% CI was reported for dichotomous outcomes. Where appropriate, the number needed to treat to benefit (NNT_B) or harm (NNT_H) and 95% CI were calculated.[15] The NNT is the inverse of the absolute risk reduction. The NNT_B gives a measure of the number of patients that need to be treated in order to provide the benefit outcome for one patient. Likewise, NNT_H provides the same measure in order to prevent the harmful outcome to one patient.

RESULTS

Trial selection and quality

Electronic searching yielded 27 957 abstracts, with 27 924 excluded as not relevant. The remaining 33 full text articles were obtained and independently reviewed by two authors, resulting in a further 17 trials being excluded. The remaining 16 trials,[16–31] involving 1823 participants, were included as described in our Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) statement (figure 1). Two reviewers (EM and FR) were in full agreement regarding trial selection. Characteristics of included trials are reported in online supplementary table S1.

Assessment of risk of bias in included trials

Risk of bias summary of included trials is reported in online supplementary figure S1.

Random sequence generation and allocation concealment

Method of randomisation was clearly described and adequate in 12 trials.[16 17 19–21 23 25–29 31] Four trials did not provide sufficient information with two described as randomised, double-masked, controlled trials,[18 24] and two as randomised controlled trials.[22 30] The overall risk of selection bias was low. Eight trials adequately described methods of allocation concealment.[16 19 20 23 24 27 28 31]

Masking

Nine trials were described as double-masked and provided methods for masking.[16 19–21 23–27] Three of the trials were single-masked.[17 28 31] Overall, the risk of detection bias was low.

Incomplete outcome data

All trials accounted for all participants. The risk of attrition bias was deemed to be low.

Other potential sources of bias

Six trials were funded by drug companies producing at least one of the trial drugs.[17 20 21 23 25 26] Three trials reported no financial/conflict of interest,[17 21 23] while two others did not provide sufficient information to ascertain level of drug company involvement.[20 25] One trial stated their statistical analysis was funded by a drug company.[26]

Additional considerations

In all, 10 of the 14 trials[16 19 21–25 27–29] reporting treatment success had a study duration between 21 and 37 days with two trials allowing up to 90 days for follow-up.[17 31] One trial[20] reported treatment success by 14 days, while another did not specify study duration but measured treatment success at days 7 and 14.[26] The study duration of one trial written in Portuguese was not stated in translation.[30]

Details for outcome comparisons are summarised in tables 1–4. There was no evidence of heterogeneity within any of the comparisons.

Treatment success

Treatment success was reported in each of the included trials as a dichotomous outcome at trial conclusion, although a few trials reported treatment success at specific time-points. There was no evidence of difference in RR of treatment success when moxifloxacin was compared with tobramycin–cefazolin[28 31] (RR 1.02: 95% CI 0.91 to 1.14), when ciprofloxacin was compared with gentamicin–cefazolin[22 30] (RR 1.11: 95% CI 0.84 to 1.45) or when moxifloxacin,[17 28] ofloxacin[17 23 24 26] or ciprofloxacin[20 22 30] was

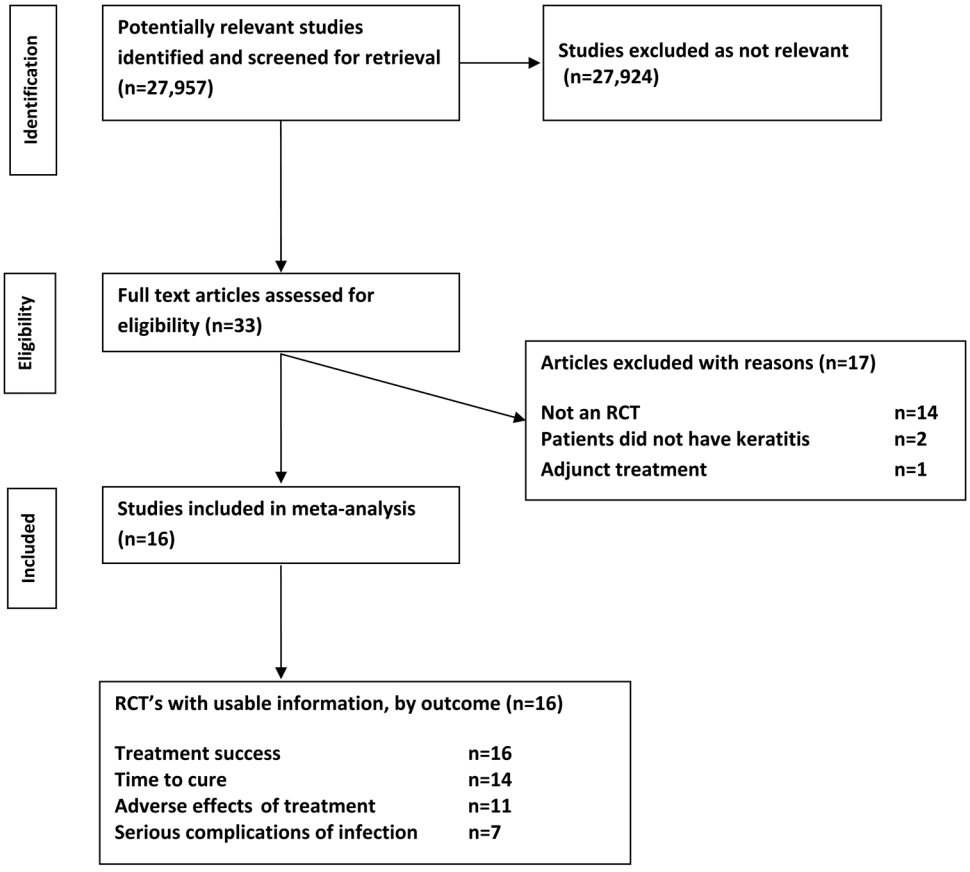

Figure 1 Summary of the trial flow and the meta-analysis profile as outlined in the Preferred Reporting of Systematic Reviews and Meta-Analysis statement.[45] RCT: randomised controlled trial.

compared with aminoglycoside–cephalosporin (RR 0.93: 95% CI 0.64 to 1.36; RR 0.94: 95% CI 0.68 to 1.30; and RR 1.02: 95% CI 0.83 to 1.25, respectively). There was also no evidence of difference in risk of treatment success when moxifloxacin,[17 28] ofloxacin,[17 27 29] ciprofloxacin,[16 25 27] gatifloxacin[25 28] or tobramycin–cefazolin[17 20 23 24 28] were compared with

Table 1 RR of treatment success with various topical antibiotics compared with fluoroquinolone or aminoglycoside–cephalosporin

Drug comparisons	No. of trials (participants) (ref)	Event rate $^{n}/_{N}$	I^2	p Value (het)	RR (95% CI)	p Value (effect)
Moxifloxacin compared with						
Tobramycin–cefazolin	2 (264)[28 31]	Moxi $^{107}/_{130}$ T/C $^{108}/_{134}$	0%	0.70	1.02 (0.91 to 1.14)	0.73
Aminoglycoside–cephalosporin	3 (419)[17 28 31]	Moxi $^{166}/_{207}$ A/C $^{167}/_{212}$	0%	0.86	0.93 (0.64 to 1.36)	0.72
Fluoroquinolone	2 (192)[17 28]	Moxi $^{78}/_{97}$ Fluoro $^{77}/_{95}$	0%	0.98	1.02 (0.58 to 1.80)	0.95
Ofloxacin compared with						
Aminoglycoside–cephalosporin	4 (440)[17 23 24 26]	Oflox $^{169}/_{221}$ A/C $^{164}/_{219}$	0%	0.81	0.94 (0.68 to 1.30)	0.73
Fluoroquinolone	3 (428)[17 27 29]	Oflox, $^{173}/_{216}$ Fluoro $^{160}/_{212}$	0%	0.61	0.82 (0.57 to 1.16)	0.26
Ciprofloxacin compared with						
Gentamicin–cefazolin	2 (71)[22 30]	Cipro $^{25}/_{32}$ G/C $^{27}/_{39}$	0%	0.87	1.11 (0.84 to 1.45)	0.47
Aminoglycoside–cephalosporin	3 (395)[20 22 30]	Cipro $^{100}/_{192}$ A/C $^{108}/_{203}$	0%	0.72	1.02 (0.83 to 1.25)	0.88
Fluoroquinolone	3 (362)[20 22 30]	Cipro $^{137}/_{177}$ Fluoro $^{157}/_{185}$	35%	0.80	1.44 (0.94 to 2.21)	0.10
Gatifloxacin compared with						
Fluoroquinolone	2 (145)[25 28]	Gati $^{59}/_{71}$ Fluoro $^{57}/_{74}$	0%	0.86	0.76 (0.40 to 1.44)	0.40
Tobramycin–cefazolin compared with						
Fluoroquinolone	6 (1007)[17 20 23 24 28 31]	T/C $^{318}/_{460}$ Fluoro $^{391}/_{547}$	0%	0.84	0.99 (0.91 to 1.07)	0.74
Fluoroquinolone compared with						
Aminoglycoside–cephalosporin	10 (1265)[17 20–24 26 28 30 31]	Fluoro $^{482}/_{672}$ A/C $^{414}/_{593}$	0%	0.98	1.01 (0.94 to 1.08)	0.86

p<0.05 is considered significant.
A/C, aminoglycoside–cephalosporin; Cipro, ciprofloxacin; Fluoro, fluoroquinolone; G/C, gentamicin–cefazolin; Gati, Gatifloxacin; het, heterogeneity; I^2, inconsistency index; Moxi, Moxifloxacin; n/N, number of participants with treatment success in each study arm/total number of participants in each study arm; Oflox, ofloxacin; Ref, reference; RR, relative risk; T/C, tobramycin–cefazolin.

Table 2 MD in time to cure (days) with various topical antibiotics compared with fluoroquinolone or aminoglycoside–cephalosporin

Drug comparisons	No. of trials (participants) (ref)	I^2	p Value (het)	MD (95% CI)	p Value (effect)	Range of days to cure
Moxifloxacin compared with						
Aminoglycoside–cephalosporin	2 (192)[17 28]	0%	0.89	−1.24 (−7.40 to 4.92)	0.69	Moxi: 24–36, A/C: 25–38
Fluoroquinolone	2 (190)[17 28]	39%	0.20	−4.30 (−10.86 to 2.25)	0.20	Moxi: 24–36, FL: 25–46
Ofloxacin compared with						
Aminoglycoside–cephalosporin	2 (182)[17 24]	11%	0.29	3.57 (−4.23 to 11.37)	0.37	Oflox: 15–46, A/C: 15–38
Fluoroquinolone	3 (393)[17 27 29]	65%	0.06	1.05 (−0.15 to 2.25)	0.09	Oflox: 9–46, FL: 7–36
Ciprofloxacin compared with						
Fluoroquinolone	3 (357)[16 25 27]	0%	0.71	1.13 (−0.53 to 2.80)	0.18	Cipro: 14–19, FL: 14–17
Gatifloxacin compared with						
Fluoroquinolone	2 (143)[25 28]	0%	0.44	−0.92 (−0.60 to 2.36)	0.38	Gati:14–25, FL: 17–24
Gentamicin–cefazolin compared with						
Fluoroquinolone	2 (67)[19 22]	0%	0.68	−1.97 (−5.35 to 1.41)	0.25	G/C: 9–15, FL: 12–16
Tobramycin–cefazolin compared with						
Fluoroquinolone	3 (223)[17 24 28]	0%	0.95	0.42 (−5.05 to 5.89)	0.88	T/C: 15–38, FL: 15–36
Fluoroquinolone compared with						
Aminoglycoside–cephalosporin	5 (286)[17 19 22 24 28]	0%	0.79	2.05 (−0.96 to 5.07)	0.18	FL: 7–46, A/C: 7–38

p<0.05 is considered significant.
A/C, aminoglycoside–cephalosporin; cipro, ciprofloxacin; FL, fluoroquinolone; G/C, gentamicin–cefazolin; gati, gatifloxacin; het, heterogeneity; I^2, inconsistency index; MD, mean difference (fixed); Moxi, moxifloxacin; Oflox, ofloxacin; Ref, references; T/C, tobramycin–cefazolin.

fluoroquinolones (RR 1.02: 95% CI 0.58 to 1.80; RR 0.82: 95% CI 0.57 to 1.16; RR 1.44: 95%: 0.94 to 2.21; RR 0.76: 95% CI 0.40 to 1.44; and RR 1.03: 95% CI 0.85 to 1.24, respectively).

There was no evidence of difference in risk of treatment success when fluoroquinolones as a class were compared with aminoglycoside–cephalosporin in 10 trials[17 20–24 26 28 30 31] with 1265 participants (RR 1.01: 95% CI 0.94 to 1.08). No evidence of significant heterogeneity was detected in trials comparing treatment success (table 1 and figure 2). Random-effects analysis did not provide results that differed from using fixed-effect analysis for treatment success.

Time to cure

In order to provide context for the MD, the range of days to cure has also been provided for each treatment arm in table 2. There was no evidence of difference in mean time to cure when moxifloxacin[17 28] or ofloxacin[17 24] was compared with aminoglycoside–cephalosporin (MD −1.24: 95% CI −7.40 to 4.92

Table 3 RR of serious complications with various topical antibiotics compared with fluoroquinolone or aminoglycoside–cephalosporin

Drug comparisons	No. of trials (participants) (ref)	Event rate n/N	I^2	p Value (het)	RR (95% CI)	p Value (effect)
Corneal perforation						
Moxifloxacin compared with						
Aminoglycoside–cephalosporin	2 (195)[17 28]	Moxi $^{4}/_{97}$ A/C $^{2}/_{98}$	0%	0.53	2.02 (0.38 to 10.72)	0.41
Ofloxacin compared with						
Aminoglycoside–cephalosporin	2 (270)[17 26]	Oflox $^{4}/_{133}$ A/C $^{4}/_{137}$	0%	0.97	1.04 (0.27 to 4.06)	0.95
Fluoroquinolone	2 (368)[17 27]	Oflox $^{8}/_{186}$ Fluoro $^{9}/_{182}$	0%	0.78	0.86 (0.34 to 2.18)	0.75
Tobramycin–cefazolin compared with						
Fluoroquinolone	2 (290)[17 28]	T/C $^{4}/_{98}$ Fluoro $^{9}/_{192}$	0%	0.50	0.87 (0.27 to 2.74)	0.81
Fluoroquinolone compared with						
Aminoglycoside–cephalosporin	3 (388)[17 22 26]	Fluoro $^{11}/_{227}$ A/C $^{5}/_{161}$	0%	0.82	1.52 (0.54 to 4.27)	0.43
Therapeutic keratoplasty						
Moxifloxacin compared with						
Tobramycin–cefazolin	2 (379)[17 31]	Moxi $^{3}/_{187}$ T/C $^{2}/_{192}$	27%	0.24	1.44 (0.28 to 7.25)	0.66
Ofloxacin compared with						
Aminoglycoside–cephalosporin	2 (182)[17 24]	Oflox $^{2}/_{89}$ A/C $^{2}/_{93}$	0%	0.35	1.02 (0.19 to 5.55)	0.98
Tobramycin–cefazolin compared with						
Fluoroquinolone	3 (487)[17 24 31]	T/C $^{4}/_{207}$ Fluoro $^{5}/_{280}$	0%	0.50	1.06 (0.28 to 3.96)	0.93
Fluoroquinolone compared with						
Aminoglycoside–cephalosporin	4 (524)[17 22 24 31]	Fluoro $^{7}/_{293}$ A/C $^{5}/_{231}$	0%	0.55	1.24 (0.40 to 3.79)	0.71
Enucleation						
Fluoroquinolone compared with						
Aminoglycoside–cephalosporin	2 (270)[17 22]	Fluoro $^{0}/_{168}$ A/C $^{2}/_{102}$		0.67	0.29 (0.03 to 2.51)	0.26

p<0.05 is considered significant.
A/C, aminoglycoside–cephalosporin; Fluoro, fluoroquinolone; het, heterogeneity; I^2, inconsistency index; Moxi, Moxifloxacin; n/N, number of participants with treatment success in each study arm/total number of participants in each study arm; Oflox, ofloxacin; Ref, reference; RR, relative risk (fixed effect); T/C, tobramycin–cefazolin.

Table 4 RR of adverse effects with various topical antibiotics compared with fluoroquinolone or aminoglycoside–cephalosporin

Drug comparisons	No. of trials (participants) (ref)	Event rate $^{n}/_{N}$	I^2	p Value (het)	RR (95% CI)	p Value (effect)	NNT (95% CI)
Ocular discomfort							
Ofloxacin compared with							
Aminoglycoside–cephalosporin	2 (292)[17 23]	Oflox $^{11}/_{147}$ A/C $^{47}/_{145}$	0%	0.97	0.22 (0.13 to 0.39)	<0.00001*	4 (3 to 5)
Tobramycin–cefazolin compared with							
Fluoroquinolone	3 (693)[17 20 23]	T/C $^{82}/_{309}$ Fluoro $^{27}/_{384}$	48%	0.14	3.13 (2.13 to 4.60)	<0.00001*	6 (5 to 8)
Fluoroquinolone compared with							
Aminoglycoside–cephalosporin	3 (693)[17 20 23]	Fluoro $^{27}/_{384}$ A/C$^{82}/_{309}$	48%	0.14	0.32 (0.22 to 0.47)	<0.00001*	6 (5 to 8)
Chemical conjunctivitis							
Ofloxacin compared with							
Aminoglycoside–cephalosporin	3 (410)[17 23 26]	Oflox $^{7}/_{206}$ A/C$^{37}/_{204}$	0%	1.00	0.20 (0.10 to 0.41)	<0.0001*	7 (5 to 10)
Tobramycin–cefazolin compared with							
Fluoroquinolone	2 (369)[17 23]	T/C $^{3}/_{151}$ Fluoro $^{5}/_{144}$	0%	0.08	0.60 (0.16 to 2.23)	0.45	NA
White precipitate							
Ciprofloxacin compared with							
Gentamicin–cefazolin	2 (71)[23 30]	Cipro $^{4}/_{32}$ G/C $^{0}/_{39}$	0%	0.59	6.06 (0.77 to 47.45)	0.09	NA
Aminoglycoside–cephalosporin	3 (395)[20 22 30]	Cipro $^{32}/_{192}$ A/C $^{0}/_{203}$	20%	0.29	24.37 (4.68 to 126.89)	0.0001*	6 (4 to 9)

p<0.05 is considered significant.
*Statistically significant outcome.
A/C, aminoglycoside–cephalosporin; Cipro, ciprofloxacin; Fluoro, fluoroquinolone; G/C, gentamicin–cefazolin; het, heterogeneity; I^2, inconsistency index; n/N, number of participants with treatment success in each study arm/total number of participants in each study arm; NA, not applicable; NNT, number needed to treat; Oflox, ofloxacin; Ref, reference; RR, relative risk; T/C, tobramycin–cefazolin.

and MD 3.57: 95% CI −4.23 to 11.37, respectively), or when moxifloxacin,[17 28] ofloxacin,[17 27 28] ciprofloxacin,[16 25 27] gatifloxacin,[25 28] gentamicin–cefazolin[19 22] or tobramycin–cefazolin[17 24 28] were compared with fluoroquinolones (MD -4.30: 95% CI −10.86 to 2.25; MD 1.05: 95% CI −0.15 to 2.25; MD 1.14: 95% CI −0.51 to 2.79; MD −0.92: 95% CI −0.60 to 2.36; MD −1.97: −5.35 to 1.41; and MD 0.08: 95% CI −2.47 to 2.62, respectively).

There was no evidence of difference in mean time to cure when fluoroquinolones as a class were compared with aminoglycoside–cephalosporin in four trials[17 19 24 28] with 259 participants (MD 2.09: 95% CI −1.26 to 5.44). There was no evidence of significant heterogeneity in this outcome measure (table 2).

Serious complications of infection

There was no evidence of difference in risk of corneal perforation when moxifloxacin,[17 28] ofloxacin[17 26] or fluoroquinolones as a class[17 22 26 28] was compared with aminoglycoside–cephalosporin. There were also no evidence of difference in risk of perforation when ofloxacin[17 27] or tobramycin–cefazolin[17 28] were compared with fluoroquinolones. There was also no evidence of difference in risk of therapeutic keratoplasty when moxifloxacin was compared with tobramycin–cefazolin[17 31] or when ofloxacin[17 24] and fluoroquinolones as a class[17 22 24 31] were compared with aminoglycoside–cephalosporin. Likewise, when tobramycin–cefazolin[17 24 31] were compared with fluoroquinolone, there was no evidence of difference (table 3). There was no evidence of difference in risk of enucleation when fluoroquinolones[17 22] were compared with aminoglycoside–cephalosporin. None of the comparisons reported evidence of significant heterogeneity (table 3).

Adverse effects of treatment

Ocular discomfort

When compared with aminoglycoside–cephalosporin in two trials,[17 23] ofloxacin significantly reduced risk of ocular discomfort by 78% (292 participants, RR 0.22: 95% CI 0.13 to 0.39) with an NNT_B of 4 (table 4). RR of ocular discomfort increased more than threefold when tobramycin–cefazolin were compared with fluoroquinolones in three trials[17 20 23] that included 693 participants (RR 3.13: 95% CI 2.13 to 4.60) with an NNT_H of 6. Fluoroquinolones reduced risk of ocular discomfort by 68% compared with aminoglycoside–cephalosporin in three trials[17 20 23] (693 participants, RR 0.32: 95% CI 0.22 to 0.47) with an NNT_B of 6.

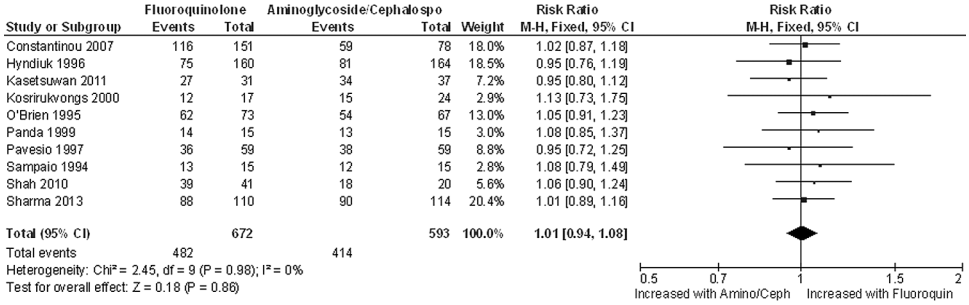

Figure 2 Forrest plot for topical fluoroquinolone compared with topical fortified aminoglycoside–cephalosporin indicating no difference in chance of treatment success.

Chemical conjunctivitis

When ofloxacin was compared with aminoglycoside–cephalosporin in three trials[17 23 26] risk of chemical conjunctivitis was reduced by 80% (410 participants, RR 0.20: 95% CI 0.10 to 0.41) with an NNT_B of 7. There was no evidence of difference in risk of chemical conjunctivitis when tobramycin–cefazolin were compared with fluoroquinolones in two trials.[17 23]

White precipitate

The risk of white precipitate formation increased 24-fold with ciprofloxacin compared with aminoglycoside–cephalosporin in three trials[20 22 30] (395 participants, RR 24.37: 95% CI 4.68 to 126.89) with an NNT_H of 6. There was no evidence of heterogeneity in trials comparing ocular discomfort, chemical conjunctivitis or white precipitate.

DISCUSSION

This review found no evidence of difference in comparative effectiveness of topical ocular antibiotics. However, combination therapy, particularly with tobramycin–cefazolin, provided evidence of increased risk of ocular discomfort up to 78%, compared with fluoroquinolones. Moreover, there was evidence that combination therapy increased the risk of chemical conjunctivitis 80% compared with ofloxacin while ciprofloxacin increased the risk of white precipitate 24-fold compared with combination therapy.

Standard treatment for BK, particularly in severe infections, often consists of intensive aminoglycoside–cephalosporin combinations. This particular combination covers a broad range of Gram negative and positive pathogens while awaiting culture results and clinical response. Although the results of this review report no evidence of difference between combination therapy and fluoroquinolones, variability has been described in pathogen susceptibility among topical ocular antibiotics with increased resistance of *Pseudomonas aeruginosa* and *Staphylococcus aureus* to fluoroquinolones in various geographical areas, particularly the Indian subcontinent.[32] A possible reason for increased resistance in this region may be attributable to widespread systemic use for infections and prophylaxis, and availability of over-the-counter antibiotics,[33] although there was no evidence of this in any of the included trials conducted in India.

An important component of treatment success is patient compliance. Clinical trials are conducted under ideal conditions where eye-drop storage, administration and regime are monitored closely and documented. In reality, patients may be more compliant with fluoroquinolones than combination therapy due to storage at room temperature, one drop required per dose and minimal ocular discomfort or chemical conjunctivitis.

This meta-analysis did not find evidence of difference in risk of corneal perforation with fluoroquinolones compared with combination therapy in 449 patients.[17 22 26 28] The fluoroquinolones included in this outcome were ofloxacin, ciprofloxacin, gatifloxacin and moxifloxacin. Perforations were not reported in trials comparing either lomefloxacin or levofloxacin with combination therapy. That said, in vitro studies have observed cytotoxic effects on corneal keratocytes under the influence of fluoroquinolones, with ciprofloxacin cited as most cytotoxic.[34] It is therefore possible that changes in corneal keratocytes resulting from stromal inflammation[35] and exposure to fluoroquinolones[34] could contribute to corneal perforation.

The current review found no evidence of difference in the risk of therapeutic keratoplasty in BK when moxifloxacin or ofloxacin was compared with combination therapy or when fortified tobramycin–cefazolin were compared with fluoroquinolones. As a class, fluoroquinolones did not increase risk of therapeutic keratoplasty compared with combination therapy. There was also no evidence of difference in risk of enucleation with fluoroquinolones compared with combination therapy. This may indicate a comparable degree of ulceration and severity of infection in the study groups compared. Only one trial[17] exclusively recruited patients with severe infection, although the definition of severe was not outlined in their protocol.

Ofloxacin reduced the risk of ocular discomfort by 78% compared with combination therapy. However, compared with fluoroquinolones, no evidence of difference in risk was noted. Tobramycin–cefazolin increased the risk of ocular discomfort threefold compared with fluoroquinolones. The three trials comprising this outcome identified predominant Gram positive infection, most commonly Staphylococci. Two of the trials used comparable drug concentrations for both fluoroquinolones and combination therapy. However, O'Brien and colleagues[23] used an increased concentration of tobramycin (1.5% compared with 1.3%) and cefazolin (10% compared with 5%), and increased dosing frequency (every 30 min compared with hourly) for the first 48 h, which could have influenced this result. However, when this study was removed from analysis, the increased risk of ocular discomfort with combination therapy remained. Ocular discomfort may also exist with other aminoglycoside–cephalosporin combinations but cannot be substantiated due to paucity of randomised controlled trials. As a class, fluoroquinolones reduced the risk of ocular discomfort by 66% compared with combination therapy. These results are in agreement with current literature as fortified combination therapy has been documented to cause increased corneal irritation and possible delay in corneal epithelialisation.[36–38] However, one of the trials included in the review[21] found faster corneal re-epithelialisation with cefazolin–amikacin compared with levofloxacin. This may be due to the absence of either gentamicin or tobramycin, both of which have been identified to cause delay in corneal re-epithelialisation.[36 39]

Ofloxacin reduced the risk of chemical conjunctivitis by 80% compared with combination therapy.[17 23 26] It is possible that the inclusion of a study[26] using fortified gentamicin 1.5% and cefuroxime 5% contributed significantly to this result as this effect disappeared when the study was removed. Moreover, the risk of chemical conjunctivitis did not increase with tobramycin–cefazolin compared with fluoroquinolones.[17 23] It is interesting to note that while tobramycin–cefazolin had a threefold increased risk of ocular discomfort compared with fluoroquinolones, this did not equate to an increased risk of chemical conjunctivitis and did not impact on treatment success, time to cure or serious complications of infection. As noted in previous trials,[16 40–44] the current meta-analysis confirms an increased risk of white precipitate formation with ciprofloxacin, which resolves following treatment discontinuation.

While included trials did not provide cost analysis, it is important to consider accessibility and time to treatment. Fluoroquinolones are generally dispensed from hospital and community pharmacies and can be kept at room temperature. Fortified aminoglycoside–cephalosporins are prepared in compounding pharmacies and must remain refrigerated as they have a shelf life of approximately 4 days. A drop of each medication needs to be given at least 5 min apart hourly, which has resource implications. The time involved preparing fortified antibiotics is also a consideration when patients present with severe bacterial infection such as *P aeruginosa* requiring immediate intervention. The current review also reported fortified aminoglycoside–cephalosporin to cause

more ocular discomfort than fluoroquinolones which can decrease patient compliance with recommended dosing schedules—leading to ineffective bacterial inhibition.

Implications for further research

There is a paucity of trials comparing differing combinations of aminoglycoside–cephalosporin other than tobramycin–cefazolin. Of interest is a possible increased risk of chemical conjunctivitis with gentamicin–cefuroxime compared with ofloxacin, and a faster time to cure with amikacin–cefazolin and levofloxacin compared with ofloxacin. However, single trials have reported these outcomes.

Clinical recommendations

This extensive study of high quality randomised controlled trials evaluating the effectiveness of topical antibiotics in the management of BK reports no evidence of difference in risk of treatment success, time to cure or serious complications of infection when fluoroquinolones were compared with fortified aminoglycoside–cephalosporin in intensive topical regimens.

While fluoroquinolones reduced the risk of ocular discomfort and ofloxacin reduced the risk of chemical conjunctivitis, this did not impact on other important clinical outcomes. Therefore, we report no evidence of difference in comparative effectiveness between fluoroquinolone and aminoglycoside–cephalosporin intensive regimens in the management of patients presenting with BK.

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REFERENCES

1 Suwan-Apichon O, Reyes JM, Herretes S, *et al*. Topical corticosteroids as adjunctive therapy for bacterial keratitis. *Cochrane Database Syst Rev* 2007:CD005430.
2 American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines: Bacterial Keratitis-Limited Revision. San Francisco, CA: American Academy of Ophthalmology, 2011. [July 11, 2013]; http://www.aao.org/ppp
3 International Council of Ophthalmology. International Clinical Guidelines: Bacterial Keratitis. International Council of Ophthalmology. 2010 [cited 2013 March 12]; http://www.icoph.org/resources/resources_detail/75/ ICO -International-Clinical-Guideline-Bacterial-Keratitis-Management-recommendations—.html
4 Shah A, Sachdev A, Coggon D, *et al*. Geographic variations in microbial keratitis: an analysis of the peer-reviewed literature. *Br J Ophthalmol* 2011;95:762–7.
5 McLeod SD, Kolahdouz-Isfahani A, Rostamian K, *et al*. The role of smears, cultures, and antibiotic sensitivity testing in the management of suspected infectious keratitis. *Ophthalmology* 1996;103:23–8.
6 Leibovitch I, Lai TF, Senarath L, *et al*. Infectious keratitis in South Australia: emerging resistance to cephazolin. *Eur J Ophthalmol* 2005;15:23–6.
7 Laspina F, Samudio M, Cibils D, *et al*. Epidemiological characteristics of microbiological results on patients with infectious corneal ulcers: a 13-year survey in Paraguay. *Graefes Arch Clin Exp Ophthalmol* 2004;242:204–9.
8 Sirikul T, Prabriputaloong T, Smathivat A, *et al*. Predisposing factors and etiologic diagnosis of ulcerative keratitis. *Cornea* 2008;27:283–7.
9 Leck AK, Thomas PA, Hagan M, *et al*. Aetiology of suppurative corneal ulcers in Ghana and south India, and epidemiology of fungal keratitis. *Br J Ophthalmol* 2002;86:1211–15.
10 Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). Chichester: John Wiley & Sons Ltd, 2011.
11 RevMan. Review Manager. 4.3 edn. Copenhagen: The Nordic Cochrane, The Cochrane Collaboration, 2006.
12 Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley & Sons Ltd, 2011. [cited 2013 March 12]; Version 5.1.0 [updated March 2011]:[Cochrane Collaboration, 2011]. http://www.cochrane-handbook.org
13 Laird NM, Mosteller F. Some statistical methods for combining experimental results. *Int J Technol Assess Health Care* 1990;6:5–30.
14 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719–48.
15 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ*. 1999;319:1492–5.
16 Booranapong W, Kosrirukvongs P, Prabhasawat P, *et al*. Comparison of topical lomefloxacin 0.3 per cent versus topical ciprofloxacin 0.3 per cent for the treatment of presumed bacterial corneal ulcers. *J Med Assoc Thai* 2004;87:246–54.
17 Constantinou M, Daniell M, Snibson GR, *et al*. Clinical efficacy of moxifloxacin in the treatment of bacterial keratitis: a randomized clinical trial. *Ophthalmology* 2007;114:1622–9.
18 Dehghani A, Fazel F, Akhlagi M, *et al*. Cefazolin-gentamicin versus vancomycin-ceftazidime eye drops for bacterial corneal ulcers; a randomized clinical trial. *J Opthal Vis Res* 2009;4:19–23.
19 Erjongmanee S, Kasetsuwan N, Phusitphoykai N, *et al*. Clinical evaluation of ophthalmic lomefloxacin 0.3% in comparison with fortified cefazolin and gentamicin ophthalmic solutions in the treatment of presumed bacterial keratitis. *J Med Assoc Thai* 2004;87(Suppl 2):S83–90.
20 Hyndiuk RA, Eiferman RA, Caldwell DR, *et al*. Comparison of ciprofloxacin ophthalmic solution 0.3% to fortified tobramycin-cefazolin in treating bacterial corneal ulcers. Ciprofloxacin Bacterial Keratitis Study Group. *Ophthalmology* 1996;103:1854–62.
21 Kasetsuwan N, Tanthuvanit P, Reinprayoon U. The efficiacy and safety of 0.5% levofloxacin versus fortified cefazolin and amikacin ophthalmic solution for the treatment of suspected and culture proven cases of infectious bacterial keratitis: a comparative study. *Asian Biomed* 2011;5:77–83.
22 Kosrirukvongs P, Buranapongs W. Topical ciprofloxacin for bacterial corneal ulcer. *J Med Assoc Thai* 2000;83:776–82.
23 O'Brien TP, Maguire MG, Fink NE, *et al*. Efficacy of ofloxacin vs cefazolin and tobramycin in the therapy for bacterial keratitis. Report from the Bacterial Keratitis Study Research Group. *Arch Ophthalmol* 1995;113:1257–65.
24 Panda A, Ahuja R, Sastry SS. Comparison of topical 0.3% ofloxacin with fortified tobramycin plus cefazolin in the treatment of bacterial keratitis. *Eye (Lond)* 1999;13:(Pt 6):744–7.
25 Parmar P, Salman A, Kalavathy CM, *et al*. Comparison of topical gatifloxacin 0.3% and ciprofloxacin 0.3% for the treatment of bacterial keratitis. *Am J Ophthalmol* 2006;141:282–6.
26 Pavesio C, Morlet N, Allan B, *et al*. Ofloxacin monotherapy for the primary treatment of microbial keratitis—a double-masked, randomized, controlled trial with conventional dual therapy. *Ophthalmology* 1997;104:1902–9.
27 Prajna NV, George C, Selvaraj S, *et al*. Bacteriologic and clinical efficacy of ofloxacin 0.3% versus ciprofloxacin 0.3% ophthalmic solutions in the treatment of patients with culture-positive bacterial keratitis. *Cornea* 2001;20:175–8.
28 Shah VM, Tandon R, Satpathy G, *et al*. Randomized clinical study for comparative evaluation of fourth-generation fluoroquinolones with the combination of fortified antibiotics in the treatment of bacterial corneal ulcers. *Cornea* 2010;29:751–7.
29 Zhang M, Hu Y, Chen F. [Clinical investigation of 0.3% levofloxacin eyedrops on the treatment of cases with acute bacterial conjunctivitis and bacterial keratitis]. *Yan Ke Xue Bao* 2000;16:146–8.
30 Sampaio C, Alves M, Jose N, *et al*. Clinical evaluation of ciprofloxacin 0.3% ophthalmic solution for treatment of bacterial keratitis [Avaliação clínica do tratamento tópico das úlceras de córnea bacterianas com ciprofloxacina a 0,3 por cento]. *Arq Bras Oftal* 1994;57:329–32.
31 Sharma N, Goel M, Bansal S, *et al*. Evaluation of moxifloxacin 0.5% in treatment of nonperforated bacterial corneal ulcers: a randomized controlled trial. *Ophthalmology* 2013;120:1173–8.
32 Willcox MD. Review of resistance of ocular isolates of Pseudomonas aeruginosa and staphylococci from keratitis to ciprofloxacin, gentamicin and cephalosporins. *Clin Exp Optom* 2011;94:161–8.
33 Garg P, Sharma S, Rao GN. Ciprofloxacin-resistant Pseudomonas keratitis. *Ophthalmology* 1999;106:1319–23.
34 Bezwada P, Clark LA, Schneider S. Intrinsic cytotoxic effects of fluoroquinolones on human corneal keratocytes and endothelial cells. *Curr Med Res Opin* 2008;24:419–24.
35 Vemuganti GK, Reddy K, Iftekhar G, *et al*. Keratocyte loss in corneal infection through apoptosis: a histologic study of 59 cases. *BMC Ophthalmol* 2004;4:16.
36 Lin CP, Boehnke M. Effect of fortified antibiotic solutions on corneal epithelial wound healing. *Cornea* 2000;19:204–6.
37 Chiquet C, Romanet JP. [Prescribing fortified eye drops]. *J Fr Ophtalmol* 2007;30:423–30.
38 Nelson JD, Silverman V, Lima PH, *et al*. Corneal epithelial wound healing: a tissue culture assay on the effect of antibiotics. *Curr Eye Res* 1990;9:277–85.

39 Stern GA, Schemmer GB, Farber RD, *et al*. Effect of topical antibiotic solutions on corneal epithelial wound healing. *Arch Ophthalmol* 1983;101:644–7.
40 Madhavan HN, Rao SK, Joseph PR, *et al*. Antibacterial activity of the white precipitate formed on the corneal surface after treatment with ciprofloxacin ophthalmic solution. *Cornea* 1999;18:549–52.
41 Moreira LB, Lee RF, de Oliveira C, *et al*. Effect of topical fluoroquinolones on corneal re-epithelialization after excimer laser keratectomy. *J Cataract Refract Surg* 1997;23:845–8.
42 Tsai AC, Tseng MC, Chang SW, *et al*. Clinical evaluation of ciprofloxacin ophthalmic solution in the treatment of refractory bacterial keratitis. *J Formos Med Assoc* 1995;94:760–4.
43 Wilhelmus KR, Abshire RL. Corneal ciprofloxacin precipitation during bacterial keratitis. *Am J Ophthalmol* 2003;136:1032–7.
44 Wilhelmus KR, Hyndiuk RA, Caldwell DR, *et al*. 0.3% ciprofloxacin ophthalmic ointment in the treatment of bacterial keratitis. The Ciprofloxacin Ointment/Bacterial Keratitis Study Group. *Arch Ophthalmol* 1993;111:1210–18.
45 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62: e1–34.

Topical antibiotics for the management of bacterial keratitis: an evidence-based review of high quality randomised controlled trials

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