

# Clinical Efficacy of Moxifloxacin in the Treatment of Bacterial Keratitis

## A Randomized Clinical Trial

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**Purpose:** To determine the clinical efficacy and safety of moxifloxacin (1.0%) in patients with bacterial keratitis compared with patients treated with ofloxacin (0.3%) or fortified tobramycin (1.33%)/cephazolin (5%).

**Design:** Prospective randomized trial.

**Participants:** A total of 229 patients diagnosed with bacterial keratitis were enrolled in the study; 78 patients were randomized to the fortified tobramycin/cephazolin group, 77 patients to the moxifloxacin group, and 74 patients to the ofloxacin group. A total of 225 patients were evaluable for safety and 198 patients were included in the efficacy analysis.

**Intervention:** After corneal specimens were obtained, the assigned study medication was instilled every hour, day and night, for 48 hours and on the third day, every hour by day and every 2 hours at night. For days 4 and 5, 1 drop every 2 hours by day and every 4 hours at night, and for days 6 and 7, 1 drop every 4 hours. After day 7, the antibiotic was tapered to every 6 hours and stopped when appropriate.

**Main Outcome Measures:** Resolution of keratitis and healing of ulcer, time to cure, mean time to discharge, clinical sign score, adverse reactions to study medication, and treatment failures.

**Results:** Of the 186 nonexiting patients, resolution of the keratitis and healing of the ulcer occurred in 175 (94%) nonexiting patients. In the 175 patients in whom the corneal ulcer was cured, there were no statistically significant differences between the treatment groups for the mean time to cure ( $P = 0.25$ ). There were no statistically significant differences between the 3 treatment groups in the various sign parameters including the sign score. A positive bacterial corneal culture was obtained in 190 (83%) of the 229 enrolled patients. The distribution of the species of bacterial organisms was similar in each treatment group and no significant difference in the percentage of isolates between the groups was observed. Twelve (5.2%) of the treated patients had serious complications (perforation or enucleation). No serious events attributable to therapy occurred during the study and all treatments were safe and well tolerated.

**Conclusion:** No difference in healing rate, cure rate, or complications between fortified cephalosporin and tobramycin, ofloxacin, or moxifloxacin was seen in this study. *Ophthalmology* 2007;114:1622–1629 © 2007 by the American Academy of Ophthalmology.

Bacterial keratitis is a serious ocular infectious disease that can lead to significant vision loss.<sup>1</sup> Any infectious process in the cornea producing a keratitis, mild or severe, requires prompt and vigorous treatment with an effective antimicro-

bials agent(s) to minimize corneal scarring and visual loss.<sup>1,2–6</sup>

The treatment regimen includes the frequent administration of topical ocular antibacterial agents (e.g., cephalosporins and aminoglycosides), often at concentrations higher (fortified) than those currently available in the market.<sup>3–8</sup> Sometimes these are used in conjunction with subconjunctival injections and/or systemic administration of antibiotics. The use of multiple antibiotics simultaneously and with frequent dosing may result in toxicity.<sup>9</sup> With the advent of fluoroquinolones, monotherapy has been established as an alternate paradigm in the treatment of bacterial keratitis.<sup>10–12</sup> This practice has been questioned with the increased detection of fluoroquinolone resistant bacterial strains.<sup>13,14</sup>

Bacterial keratitis accounts for approximately 65% to 90% of all microbial corneal infections.<sup>2,6,15–17</sup> Although these bacteria may vary in incidence according to geo-

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graphical locale,<sup>8</sup> the most common organisms include *Staphylococcus aureus*, *S. epidermis*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and other Gram-negative bacilli.<sup>1,5,8,18</sup> Of these, *S. aureus* is the predominant pathogen isolated from the majority of cases of keratitis,<sup>1,3,5,8,18</sup> but *P. aeruginosa*, a potentially devastating ocular pathogen, is the most common cause of hypopyon corneal ulcers,<sup>19</sup> ulcerative keratitis associated with contact lens wear,<sup>3,6,7,20–22</sup> and severe necrotic corneal ulceration.<sup>16</sup> The precise role of endogenous bacteria has not been ascertained, although some organisms considered normal flora of the eye can devastate the avascular cornea.<sup>5</sup> Polymicrobial keratitis has been reported in up to 12% of cases and can be difficult to treat.<sup>15</sup>

The use of fortified intensive antibiotics has practical limitations related to availability and cost. The effectiveness of multiple fortified antibiotics is limited further by variability in shelf life and the dissipation of 1 agent if a second agent is applied shortly thereafter.<sup>23</sup> The use of multiple antibiotics simultaneously and with frequent dosing may result in added toxicity and damage to the ocular surface epithelium, thereby impairing recovery.<sup>24,25</sup> Fluoroquinolones offer the advantages of good ocular penetration, demonstration of broad-spectrum efficacy, excellent safety pro-

files in ocular infections, and a distinct mode of resistance acquisition.

Moxifloxacin is a fourth-generation fluoroquinolone that exhibits a broad spectrum of bactericidal activity<sup>26–29</sup> against both Gram-positive and Gram-negative bacterial pathogens, including staphylococci, *S. pneumoniae*, members of the family enterobacteriaceae, *P. aeruginosa*, *H. influenzae*, and *Moraxella* species. Moxifloxacin has also been shown to have superior activity compared with ciprofloxacin against quinolone resistant strains of *S. aureus*.<sup>30</sup> Data also shows superior corneal and aqueous penetration of moxifloxacin (Solomon R, Donnenfeld E, et al. Penetration of topically applied gatifloxacin 0.3%, moxifloxacin 0.5% and ciprofloxacin 0.3% into the aqueous humor. Poster presented at: ARVO annual meeting, April 25–30 2004, Ft. Lauderdale, FL) and so higher therapeutic levels can be obtained, which should lead to more effective antimicrobials activity and hence better clinical outcomes.

We undertook a prospective, randomized study, to determine clinical efficacy and safety for moxifloxacin (1.0%) in patients with bacterial keratitis. A comparison was made to patients treated with ofloxacin (0.3%) or fortified tobramycin (1.33%)/cephazolin (5%).

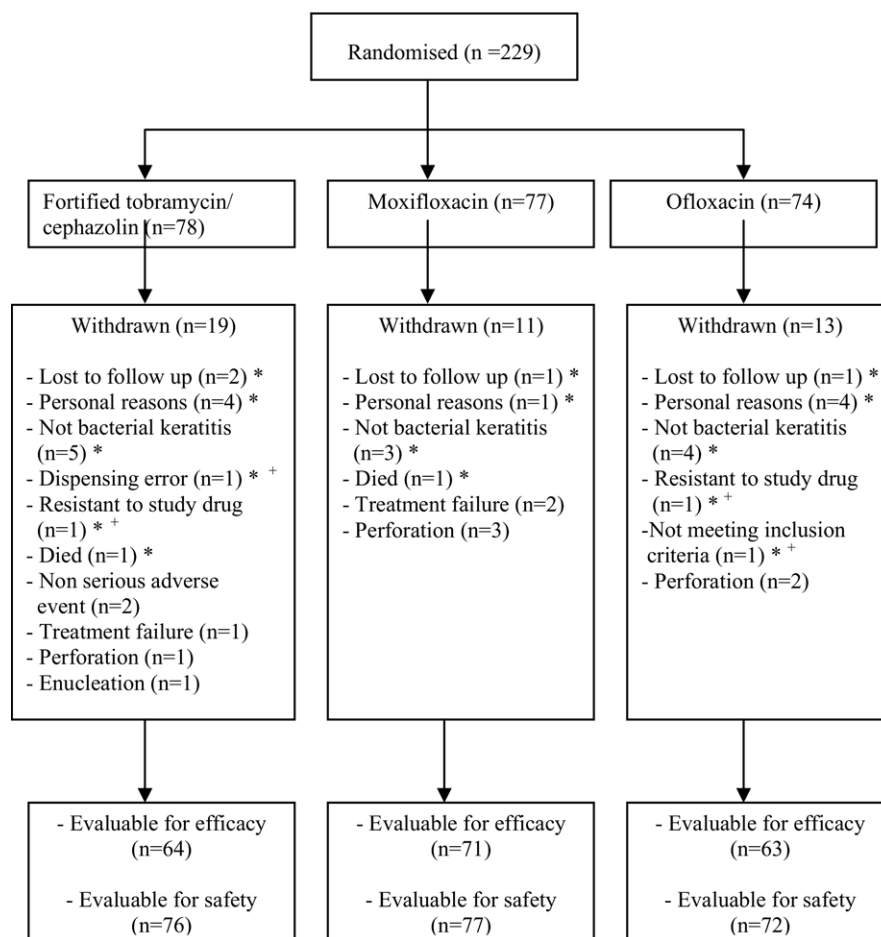


Figure 1. Trial profile. \*Not evaluable for efficacy. +Not evaluable for safety.

Table 1. Demographic and Baseline Characteristics

	Fortified Tobramycin/Cephazolin	Moxifloxacin	Ofloxacin	P Value
Number enrolled	78	77	74	
Age	64.9±20.5	65.9±19.6	66.0±20.8	0.94
Range (yrs)	12.5–93.1	19.1–98.8	6.3–97	
Symptoms duration (days)				0.99
Mean	9.2±27.4	8.9±20.2	9.4±16.2	
Median (range)	3.0	3.0	4.0	
Eye				0.35
Right	32 (41%)	35 (47%)	39 (53%)	
Left	46 (58%)	42 (53%)	35 (47%)	
Gender				0.75
Male	43 (55%)	46 (60%)	45 (61%)	
Female	35 (45%)	31 (40%)	29 (39%)	
Type of admission				0.03
Inpatient	56 (72%)	68 (88%)	56 (76%)	
Outpatient	22 (28%)	9 (12%)	18 (24%)	
Hypopyon size in day 1				0.60
Mean (n = 87)	1.6±1.6	1.3±0.75	1.5±1.4	
Number with positive hypopyon size > 0	32 (41%)	30 (39%)	25 (34%)	
Prescrape diameter of epithelial defect				0.24
Mean	2.9±2.0	3.2±2.2	3.6±2.5	
n	62	59	58	
Clinical sign score				0.99
Mean	11.3±4.1	11.2±3.3	11.3±4.1	
n	78	77	74	

## Materials and Methods

### Study Design

This is a prospective, randomized trial to determine the clinical efficacy and safety of moxifloxacin (1.0%) in patients with bacterial keratitis compared with patients treated with ofloxacin (0.3%) or fortified tobramycin (1.33%)/cephazolin(5%). This trial was single masked, except that a placebo treatment was not included in the 2 monotherapy arms, so there was the potential that patients could identify whether they were on combined fortified treatment or not.

### Patients

The Human Research Ethics Committee of the Royal Victorian Eye and Ear Hospital approved the study protocol. Patients of

either gender with a clinical diagnosis of severe bacterial keratitis who were willing to comply with the protocol and who provided informed consent were recruited from the Royal Victorian Eye and Ear Hospital Corneal Clinic. Written informed consent was obtained from all patients before the initiation of any study medication or study-related procedure.

Patients were excluded from the study if there was a known allergy to fluoroquinolones, aminoglycosides, penicillins, cephalosporins, or benzalkonium chloride. Patients with fungal, viral (e.g., herpes simplex) or acanthamoeba infection based on clinical evidence, patients to be treated with subconjunctival injection(s) of antibiotic(s) and/or with systemic antimicrobials and patients <1 year of age were excluded from the study. Pregnant and lactating women were also excluded. The trial medications were discontinued before the completion of the study if there were adverse events, protocol violations, lack of efficacy, or for personal reasons.

Table 2. Prestudy Pathology and Therapy before Bacterial Keratitis

Pathology/Therapy	Fortified Tobramycin/ Cephazolin	Moxifloxacin	Ofloxacin	P Value
None	11 (14%)	10 (13%)	16 (22%)	0.32
Dry eye	10 (13%)	10 (13%)	12 (16%)	
Corneal graft	11 (14%)	11 (14%)	5 (7%)	
Herpes simplex keratitis	6 (8%)	13 (17%)	3 (4%)	
Contact lens wear	9 (12%)	5 (6%)	4 (5%)	
Glaucoma	5 (6%)	3 (4%)	9 (12%)	
Trauma	6 (8%)	2 (3%)	4 (5%)	
Lagophthalmos	1 (1%)	2 (3%)	2 (3%)	
Chemical burn	0 (0%)	1 (1%)	0 (0%)	
Microbial keratitis	3 (4%)	1 (1%)	1 (1%)	
Bullous keratopathy	0 (0%)	2 (3%)	2 (3%)	
Other	16 (21%)	17 (22%)	16 (22%)	

Table 3. Preexisting Systemic Disease

Systemic Diseases	Fortified Tobramycin/ Cephazolin	Moxifloxacin	Ofloxacin	P Value
None	57 (73%)	47 (61%)	55 (74%)	0.17
Diabetes	6 (8%)	9 (12%)	5 (7%)	
Rheumatoid arthritis	4 (5%)	3 (4%)	3 (4%)	
Chronic neurologic abnormalities	0 (0%)	2 (3%)	2 (3%)	
Sjögren syndrome	3 (4%)	0 (0%)	0 (0%)	
Malnutrition	0 (0%)	0 (0%)	2 (3%)	
Systemic immunosuppression	0 (0%)	1 (1%)	1 (1%)	
Alcoholism	0 (0%)	1 (1%)	0 (0%)	
Other	8 (10%)	14 (18%)	6 (8%)	

Table 4. Bacterial Isolates

Isolate	Fortified			Total
	Tobramycin/Cephalosporin	Moxifloxacin	Ofloxacin	
<i>Staphylococcus aureus</i>	16 (25%)	11 (17%)	19 (32%)	46 (24%)
<i>Staphylococcus epidermidis</i>	6 (9%)	9 (14%)	5 (8%)	20 (11%)
<i>Staphylococcus</i> sp., coagulase negative	12 (18%)	13 (20%)	12 (20%)	37 (19%)
<i>Pseudomonas aeruginosa</i>	6 (9%)	3 (5%)	5 (8%)	14 (7%)
<i>Moraxella</i> species	4 (6%)	8 (12%)	4 (7%)	16 (8%)
<i>Corynebacterium</i> sp.	5 (8%)	4 (6%)	3 (5%)	12 (6%)
<i>Streptococcus pneumoniae</i>	3 (5%)	4 (6%)	3 (5%)	10 (5%)
<i>Serratia</i> sp.	1 (2%)	2 (3%)	3 (5%)	6 (3%)
Other <i>Streptococcus</i> sp.	3 (5%)	1 (2%)	1 (2%)	5 (3%)
<i>Klebsiella</i> sp.	2 (3%)	3 (5%)	0 (0%)	5 (3%)
<i>Haemophilus influenzae</i>	1 (2%)	0 (0%)	1 (2%)	2 (1%)
<i>Bacillus</i> sp. (not <i>B. cereus</i> )	2 (3%)	0 (0%)	0 (0%)	2 (1%)
<i>Propionibacterium</i> sp.	3 (5%)	6 (9%)	2 (3%)	11 (6%)
<i>Micrococcus</i> sp.	0 (0%)	0 (0%)	1 (2%)	1 (1%)
<i>Mycobacterium chelonae</i>	1 (2%)	0 (0%)	1 (2%)	2 (1%)
<i>Proteus mirabilis</i>	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Total	65	65	60	190

## Study Protocol

Patients were randomly assigned to 1 of 3 treatment groups to receive moxifloxacin, ofloxacin, or fortified tobramycin/cephazolin. A predetermined randomization list generated by computer was used. All the patients underwent a complete initial ocular examination including measurement of visual acuity, anterior segment biomicroscopy with assessment of ulcer size, depth, location, anterior chamber reaction, and the presence and height of any hypopyon. The size of the ulcer was measured after fluorescein staining.

The diagnosis of bacterial corneal ulcer was based on supportive clinical findings confirmed by microbiology (stain and culture). A standard protocol was used for the initial microbiological investigation of all patients with keratitis. On presentation, corneal specimens from scrapings were submitted for staining with Gram's and Blankophor and cultures on blood agar, chocolate agar, Sabouraud's dextrose agar, and thioglycolate broth. Patients with negative cultures from initial specimens who had demonstrated clinical progression of their corneal infection underwent repeat cultures. The Sabouraud's agar was kept at ambient temperature and the other media were incubated at 37 °C. The fungal cultures were followed for 4 weeks before a negative result was declared and the slopes were discarded. A swab for herpes simplex DNA detection by polymerase chain reaction was also taken in all cases. All of the corneal specimens were submitted to the Microbiology Department, St. Vincent's Hospital (Melbourne).

After the corneal specimens were obtained, the patient was commenced on the study medication. The initial assigned drug instillation protocol was 1 drop of the drug instilled every hour, day and night, for 48 hours. If the patient was assigned to the fortified tobramycin/cephazolin group, then the second medication was instilled 2 to 5 minutes after the first. A second placebo drop was not used in the other 2 groups. This time lapse was repeated between drugs throughout treatment. On the third day, 1 drop was instilled every hour by day and every 2 hours at night. For days 4 and 5, 1 drop was instilled every 2 hours by day and every 4 hours at night and for days 6 and 7, one drop was used every 4 hours. After day 7, the antibiotic was tapered to every 6 hours and stopped when clinically appropriate. If epithelial healing had not occurred, a preservative-free prophylactic antibiotic (chloramphenicol ointment) was used for the second week of treatment. Additional supportive treatment included vitamins, topical steroids, and cycloplegic and antiglaucoma therapy.

Examination findings were recorded on days 2, 4, 7, 14, and >16. A final follow-up examination was scheduled for between 2 and 3 months after commencement of treatment. Each follow-up examination included visual acuity testing, biomicroscopy to evaluate the progress (cured, improved, resolving, unchanged, or worse) and the degree of change from the initial baseline visit in fluorescein staining and infiltrate, clinical evaluation by the physicians of the progress of the ocular infection, evaluation of symptoms, monitor for adverse events and replacement of medication. If the patient did not respond to the assigned therapy (no clinical response to the medication or worsening of signs and symptoms), they were considered a treatment failure, study medications were discontinued, and alternative treatments were introduced. Treatment failures were not classified as adverse events.

## Data Analysis and Statistical Methods

Sample size calculation has considered efficacy and safety endpoints. Based on an estimated difference of >15% in response rate between fluoroquinolones and fortified tobramycin/cephazolin, with an overall response rate of >85%, a total of 231 patients (77 per treatment group) gave an 85% probability of detecting a similar difference with a 2-sided  $\alpha$  of 0.05. There is sufficient power to detect differences in other parameters of efficacy endpoints such as duration of therapy and length of hospital stay, based on results from our previous retrospective study.<sup>31</sup> However, given the numbers we have in each group, we cannot exclude the possibility of rare adverse events that can occur with one or the other treatment.

A patient was evaluated for efficacy if they completed the study as planned (treated for the length of time necessary for the ulcer to heal) or if they are considered a treatment failure. A patient was defined as a treatment failure if their corneal ulcer did not respond, necessitating a change in therapy. Patient data were also eligible for analysis of efficacy if the study eye had a culture positive for bacterial organisms at the initial visit. Fungal, viral, and acanthamoeba infections were not evaluated for efficacy. These cases were evaluated for safety only.

The primary objective of this study was to assess the treatment failures between the 3 treatment arms. The secondary efficacy variables included the number of days of therapy required, required healing time and clinical signs. A clinical sign score<sup>32-34</sup> summarizing the key signs from the biomicroscopic examination

Table 5. Antibiotic Sensitivity

Bacteria	Chloramphenicol	Cephazolin	Tobramycin	Ciprofloxacin
<i>Staphylococcus aureus</i>	40/44 (91%)	45/46 (98%)		43/43 (100%)
<i>Staphylococcus epidermidis</i>	18/21 (86%)	13/21 (62%)	1/1 (100%)	16/19 (84%)
<i>Staphylococci</i> (coagulase negative)	13/20 (65%)	15/18 (83%)	2/2 (100%)	15/15 (100%)
<i>Streptococcus pneumoniae</i>	10/11 (91%)	11/11 (100%)		
Other <i>Streptococcus</i> sp.	5/5 (100%)	3/3 (100%)		
<i>Pseudomonas aeruginosa</i>	1/14 (7%)		15/15 (100%)	15/15 (100%)
<i>Moraxella</i> sp.	18/18 (100%)	18/18 (100%)	15/15 (100%)	19/19 (100%)
<i>Corynebacterium</i> sp.	10/11 (91%)	11/11 (100%)	11/11 (100%)	7/7 (100%)
<i>Haemophilus influenzae</i>	4/4 (100%)	1/1 (100%)		2/2 (100%)
<i>Proteus mirabilis</i>	5/6 (83%)	6/6 (100%)	5/5 (100%)	6/6 (100%)
Enterobacteriaceae	1/1 (100%)			
<i>Klebsiella</i> sp.	5/5 (100%)	4/5 (80%)	5/5 (100%)	5/5 (100%)
<i>Serratia</i> sp.	7/7 (100%)	0/7	6/7 (86%)	7/7 (100%)
<i>Bacillus</i> sp. (not <i>B. cereus</i> )	2/2 (100%)	0/2	2/2 (100%)	2/2 (100%)
<i>Enterococcus faecalis</i>	2/2 (100%)			
<i>Mycobacterium chelonae</i>				0/1
Total number tested	171	149	63	141

MIC = minimum inhibitory concentration.

Data are presented as number sensitive/number tested (% sensitive).

was used as a secondary measure of efficacy. The sign score was the sum of the severity grading (0, 1, 2, or 3) of the following features: erythema swelling, conjunctival discharge, bulbar conjunctival injection, superficial punctate keratopathy, intensity of infiltration, maximal depth of stromal loss, and anterior chamber reaction (cells and flare).

Comparison was made using the chi-square test for nominal measures and a test for trend in proportion for ordinal measures. Analysis of variance was used for comparison of mean age, duration of disease, and duration of hospital stay. The time to cure of the epithelial defect was estimated using the Kaplan–Meier survival curves and the Wilcoxon test. Cured was defined as no evidence of active bacterial infection, wound healing (reepithelialization) complete (i.e., absence of macropunctate staining), and inflammation resolved.

Multivariate logistic regression was performed to evaluate the risk of complications by the treatment group controlling for other confounding variables.

## Results

A total of 229 patients diagnosed with bacterial keratitis were enrolled in the study; 78 patients were randomized to the fortified tobramycin/cephazolin group, 77 patients to the moxifloxacin group, and 74 patients to the ofloxacin group. A total of 225 patients were evaluable for safety and 198 patients were used in the efficacy analysis (Fig 1). There were 186 nonexiting patients and 43 did not complete the study.

There were no statistically significant differences between the 3 study arms for any of the demographic or baseline characteristics, except for type of admission (Table 1). No clinically or statistically significant differences were found between the treatment groups in the prestudy pathology or the presence of associated eye conditions or predisposing factors (Table 2). Of the 229 episodes, 59 (26%) were associated with  $\geq 1$  prestudy pathology.

Preexisting systemic disease was not significantly different between the 3 study groups (Table 3). Of the 229 episodes, ten (4%) were associated with  $\geq 1$  systemic disease. There was no

significant correlation between systemic risk factors and the severity of the clinical presentation. A hypopyon was present in 87 (38%) patients and no significant difference in frequency was noted between the groups.

## Microbiological Analysis

Laboratory data were available for all 229 study ulcers. Of 229 Gram stain specimens, organisms were seen in 83 (36%). Of these, 35 (42.7%) were gram-positive cocci and 31 (37.8%) were gram-negative rods, 10 (12.2%) were gram-positive rods, 3 (3.7%) were gram-positive coccobacilli, and 1 (1.2%) was gram-negative coccobacilli. Two (2.4%) specimens showed fungal elements.

A positive bacterial corneal culture was obtained in 190 (83%) of the 229 enrolled patients (Table 4). Of these 190 positive isolates, 166 (72%) had 1 bacterial isolate and 24 (10.5%) out of the 166 had an additional bacterial isolate. Gram-positive bacteria constituted 76.2% of the initial bacterial isolates and 23.8% of the initial gram-negative isolates. The distribution of species of bacterial organisms was similar in each treatment group and no significant difference in percentage of isolates between the groups was observed (Table 4). Four patients had a positive fungal culture. These patients were excluded from the study and treated with antifungal agents.

All isolated bacteria were tested for sensitivity to antibiotics currently used in topical preparations. The results of bacterial in vitro tests are shown in Table 5.

Of strains tested, 17.5% were resistant to chloramphenicol, 14.8% to cephazolin, 2.8% to ciprofloxacin, 2.5% to ofloxacin, and 1.6% to tobramycin. Only 1 isolate with *Serratia* sp. was resistant to the combination cephazolin and tobramycin. For an isolate to be deemed susceptible to moxifloxacin the minimum inhibitory concentration was to be  $\leq 2$   $\mu\text{g/ml}$ .<sup>29,35</sup> Among the 162 organisms tested for susceptibility to moxifloxacin, none were resistant.

## Outcomes

After treatment, of the 186 nonexiting patients, resolution of keratitis and healing of ulcer occurred in 175 (94%) nonexiting patients. In the 175 nonexiting patients that the corneal ulcer cured,

for Isolated Organisms

Ofloxacin	Moxifloxacin (MIC ≤ 2 µg/mL)	Cloxacillin	Neomycin	Vancomycin
43/43 (100%)	42/42 (100%)	45/46 (98%)	44/45 (98%)	42/42 (100%)
16/19 (84%)	20/20 (100%)	12/20 (60%)	16/20 (80%)	17/17 (100%)
16/16 (100%)	20/20 (100%)	12/15 (80%)	14/17 (82%)	14/14 (100%)
9/9 (100%)	11/11 (100%)		1/10 (10%)	9/9 (100%)
4/5 (80%)	3/3 (100%)		1/3 (33%)	4/4 (100%)
15/15 (100%)	13/13 (100%)		1/14 (7%)	
18/18 (100%)	17/17 (100%)	1/1 (100%)	14/14 (100%)	1/1 (100%)
8/8 (100%)	10/10 (100%)	1/1 (100%)	11/11 (100%)	
4/4 (100%)	4/4 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
6/6 (100%)	6/6 (100%)	1/1 (100%)	4/6 (67%)	1/1 (100%)
1/1 (100%)	1/1 (100%)		0/1	1/1 (100%)
5/5 (100%)	5/5 (100%)		2/5 (40%)	
7/7 (100%)	6/6 (100%)		6/6 (100%)	
2/2 (100%)	2/2 (100%)		2/2 (100%)	1/1 (100%)
1/1 (100%)	2/2 (100%)		0/2	2/2 (100%)
159	162	85	157	93

there were no statistically significant differences between the treatment groups for the mean time to cure ( $P = 0.25$ ; Table 6) or with the survival analysis (data not presented). Total duration to cure and mean time to discharge (hospital stay) were also without any significant differences ( $P = 0.27$  and  $P = 0.25$  respectively). Eleven (5.9%) infections were not cured by the final follow-up at 2 to 3 months. Recurrent bacterial keratitis was noted in 5 patients, with 4 in the moxifloxacin group and 1 in the ofloxacin group. Three patients required therapeutic keratoplasty (2 in the moxifloxacin group and 1 in the ofloxacin group). One patient in the moxifloxacin treatment group had a failing graft at the final follow visit. The corneal ulcer of 2 patients in the ofloxacin group had a persistent epithelial defect.

Twelve (5.2%) of the patients treated had serious complications (perforation or enucleation; Table 7). Of the 11 ulcers that perforated, 7 had to be treated with glue and a bandage contact lens to

provide tectonic support, 4 were treated with corneal grafting, and 1 graft required resuturing.

Over the period studied, there was no statistically significant difference between the 3 treatment groups in the sign score. The sign score was similarly distributed between the 3 treatment groups at baseline and decreased in a similar fashion during follow-up (Table 8).

No serious events directly attributable to therapy were reported during the study. Two (0.9%) patients, both in the fortified treatment group, reported ocular discomfort (stinging). One patient in the fortified treatment group developed ulceration of the inferior bulbar conjunctiva, which may have been related to antibiotic toxicity. Another patient in the fortified group developed allergic conjunctivitis, which was most likely related to cessation of the patient's allergy medications. Two patients enrolled in the trial

Table 6. Outcomes

	Fortified Tobramycin/Cephazolin	Moxifloxacin	Ofloxacin	Total	P Value
Nonexiting patients (n = 186)					
Cured	59	59	57	175	
Not cured	0	7	4	11	
Recurrent keratitis	0	4	1	5	
Graft	0	2	1	3	
Failed graft	0	1	0	1	
Persistent epithelial defect	0	0	2	2	
Total	59	66	61	186	0.13
Time to cure of nonexiting patients (days)					
Mean (95% CI)	38.2 (29.7–46.8)	36.4 (27.8–44.9)	46.2 (37.5–54.9)		0.25
Mean (SD)	38.2 (33.7)	36.4 (28.6)	46.2 (37.2)		
n	59	59	57		
Time to discharge (days)					
Mean discharge of inpatients	5.5±3.4	5.6±4.0	8.2±16.6	180	0.25
Outpatients (n)	22	9	18	49	

CI = confidence interval; SD = standard deviation.

Table 7. Serious Complications (Days 1 to  $\geq 16$ )

	Fortified			Total
	Tobramycin/Cephazolin	Moxifloxacin	Ofloxacin	
Perforation treated with glue and bandage contact lens	2 (2.6%)	4 (5.2%)	1 (1.4%)	7 (3.1%)
Perforation treated with corneal grafting	1 (1.3%)	1 (1.3%)	1 (1.4%)	3 (1.3%)
Perforation requiring resuturing	0 (0%)	0 (0%)	1 (1.4%)	1 (0.4%)
Enucleation	1 (1.3%)	0 (0%)	0 (0%)	1 (0.4%)
Total	4 (5.1%)	5 (6.5%)	3 (4.1%)	12 (5.2%)

died while on treatment, but the cause of death was unrelated to the study drug in both cases.

## Discussion

All 3 antibiotic treatments were equally effective against a wide range of ocular isolates in the treatment of severe bacterial keratitis. Outcomes measured included resolution of keratitis and healing of ulcer as well as time to cure and mean time to discharge. There was no statistically significant difference between the 3 treatment groups with regard to the various secondary outcomes measured.

The patients were randomized after diagnosis but before entry in the study. There was no statistically significant difference between the 3 study arms with regard to baseline demographic characteristics. The study also looked at complications from treatment such as nonhealing epithelial defects, perforation, and enucleation. Again, there was no significant difference between the 3 groups.

Other prospective randomized control trials have examined the efficacy of second-generation fluoroquinolones such as ofloxacin and ciprofloxacin compared with traditional combined fortified antibiotics in the treatment of bacterial keratitis.<sup>10,11,36</sup> These studies showed similar efficacy between the treatment groups. Given the difficulty in demonstrating superiority of fluoroquinolone treatment in previous studies,<sup>10,11,36</sup> it is perhaps not surprising that this study failed to show clear superiority of one of the treatment alternatives. The dosage regimens used lead to extremely high tissue and aqueous levels of antibiotic, well above the 90% minimum inhibitory concentration of most of the organisms in the study. Given the resistance patterns of the organisms encountered, high cure rates would be expected. There was also excellent compliance with the hospital in-

patients receiving the study drug. If we had a decrease in compliance, it is possible a difference may have been seen.

The spectrum of organisms encountered was similar to those seen in other studies from urban communities in temperate climatic zones. Gram-positive organisms (such as staphylococcal species) made up a slightly higher proportion of cases and gram-negative species (especially *Pseudomonas*) were less common than in other published series. *Pseudomonas* infection is well known to cause severe keratitis; poor outcomes and levels of resistance to fluoroquinolones have been observed in some communities. Another small but important subgroup is streptococcal infection, which can cause severe progressive keratitis and is theoretically less susceptible to second-generation fluoroquinolones. The resistance data of our study patients revealed *Pseudomonas* species were 100% sensitive to tobramycin, ciprofloxacin, ofloxacin, and moxifloxacin, but not to chloramphenicol. In fact, there was no evidence of moxifloxacin resistance with any of the organisms isolated. Ciprofloxacin had a low degree of resistance (2.8%), whereas nearly 14.8% of cultured species were resistant to cephazolin, although only 1.6% were resistant to tobramycin. Many of the isolates that were resistant to cephazolin were *S. epidermidis*.

Resistance data are based on concentrations of antibiotic achieved in the serum and may not be directly applicable to microbial keratitis in which much higher tissue levels are achieved through direct application of drops. Penetration may be further enhanced by the presence of an epithelial defect. Emerging fluoroquinolone resistance, particularly among *Pseudomonas* species, has been reported in the United States and India.<sup>1</sup> Methicillin-resistant *S. aureus* species have developed patterns of resistance to antibiotics, particularly fluoroquinolones, and may prove problematic in the future.<sup>1</sup> Antibiotic resistance has been shown to slow both healing rates and cure rates in bacterial keratitis despite the overwhelming concentrations of drugs that can be obtained.<sup>10</sup>

The other major finding of this study was the similarity in the safety profiles of the 3 treatments. No statistically significant difference was found between the treatment groups; all seemed safe and well tolerated. No serious events directly attributable to therapy observed during the study. There was no difference in healing rate or incidence of serious complications such as perforation or enucleation. This is in contrast to previous studies that have shown delayed epithelial healing and toxicity from continued use of intensive tobramycin or gentamicin. This may be due to our treatment paradigm in which intensive, around-the-clock treatment was rapidly tapered after 48 hours. In most cases, the initial therapy was ceased at 1 week and a preservative-free prophylactic antibiotic (chloro-

Table 8. Clinical Sign Score

Day	Fortified			P Value
	Tobramycin/Cephazolin	Moxifloxacin	Ofloxacin	
1	11.3 (10.4–2.2)	11.2 (10.4–2.1)	11.3 (10.4–12.2)	1.0
2	9.9 (9.0–10.8)	9.7 (8.8–10.6)	10.4 (9.5–11.3)	0.58
4	8.1 (7.3–9.0)	7.6 (6.8–8.5)	8.1 (7.2–8.9)	0.69
7	6.2 (5.3–7.0)	5.8 (5.0–6.6)	5.6 (4.9–6.6)	0.74
14	5.0 (4.1–5.9)	4.8 (4.1–5.6)	4.6 (3.8–5.3)	0.75

Data are presented as mean values (95% confidence intervals).

mycetin ointment) was used subsequently if required. This may have reduced toxicity significantly and allowed more rapid healing of the epithelium. The previously noted increased perforation rate with ofloxacin<sup>31</sup> was not seen in this prospective randomized study, highlighting the limitations of historical controls and revealing the benefits of randomized controlled trials. Even at this high concentration of moxifloxacin (1%) corneal precipitates were not detected unlike ciprofloxacin.<sup>23</sup>

In conclusion, no significant difference in healing rate, cure rate, or complications between traditional fortified cephalosporin and tobramycin, ofloxacin alone, or moxifloxacin alone was seen in this study. The regimen of intensive, around-the-clock antibiotics for 48 hours leading to rapid sterilization followed by a rapid taper of antibiotics over the following week was validated as effective and safe. Resolution of keratitis and healing of the ulcer occurred in 94% of nonexiting patients.

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