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Nocardia keratitis: Clinical course and effect of corticosteroids

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Abstract

Purpose—To compare the clinical course of *Nocardia* spp keratitis with keratitis due to other bacterial organisms, and to assess the effect of corticosteroids as adjunctive therapy using data collected from the Steroids for Corneal Ulcers Trial (SCUT).

Design—Sub-group analysis of a randomized controlled trial

Setting: Multicenter randomized controlled trial

Study Population: 500 patients with bacterial keratitis, randomized 1:1 to topical corticosteroid or placebo who had received at least 48 hours of topical moxifloxacin

Intervention/Observation Procedure: Topical prednisolone phosphate 1% or placebo; clinical course of *Nocardia* keratitis

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Conformity with Author Information: This research received prospective Institutional Review Board approval from the University of California, San Francisco Committee on Human Research, the Aravind Eye Hospital Institutional Review Board, and the Dartmouth University Committee for the Protection of Human Subjects. Informed consent was obtained from all participants. The study was HIPAA-compliant. The Steroids for Corneal Ulcers Trial is registered with clinicaltrials.gov, NCT #00324168.

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Main outcome measures: Best spectacle-corrected visual acuity and infiltrate/scar size at 3 months from enrollment

Results—Of 500 patients enrolled in the trial, 55 (11%) had a *Nocardia* corneal ulcer. Patients with *Nocardia* ulcers had better presentation visual acuity compared to non-*Nocardia* ulcers (median Snellen 20/45 compared to 20/145, $P<0.001$), and comparable 3-month visual acuity (median 20/25 versus 20/40, P=0.25). *Nocardia* ulcers had approximately 2 lines less improvement in visual acuity compared to non-*Nocardia* ulcers (0.21 logMAR, 95% CI 0.09 to 0.33 logMAR, $P=0.001$). This difference may reflect the better starting visual acuity in patients with *Nocardia* ulcers. In *Nocardia* ulcers, corticosteroids were associated with an average 0.4 mm increase in 3-month infiltrate/scar size (95% CI 0.03 to 0.77mm, $P=0.03$).

Conclusion—*Nocardia* ulcers responded well to treatment. They showed less overall improvement in visual acuity than non-*Nocardia* ulcers, but had better presentation acuity. Corticosteroids may be associated with worse outcomes.

INTRODUCTION

Nocardia spp is a common cause of infectious keratitis in South Asia, where it has been found to be ubiquitous in the soil.[1–3] Several large case series have shown that patients with *Nocardia* keratitis typically have good visual outcomes with appropriate diagnosis and therapy.[4,5] However, there is little evidence regarding outcomes of *Nocardia* keratitis compared to keratitis due to other bacterial organisms, and there is little information on the utility of topical corticosteroids as adjunctive therapy in these cases. Corticosteroids may reduce immune-mediated tissue damage in bacterial corneal ulcers and improve clinical outcomes, however case reports have suggested that topical corticosteroids may cause recurrent infection in *Nocardia* keratitis.[6,7] Additionally, the majority of prior reports have focused primarily on the use of amikacin in the treatment of *Nocardia* keratitis, but there are few reports on the clinical response to fluoroquinolones.[8] The Steroids for Corneal Ulcers Trial (SCUT) was a randomized controlled trial assessing clinical outcomes in patients with bacterial corneal ulcers who received adjunctive topical corticosteroids versus placebo.[9] Here, we report the clinical outcomes of *Nocardia* keratitis cases enrolled in the trial, the susceptibility and response of these cases to fluoroquinolones, and the effect of adjunctive topical corticosteroid therapy on clinical outcomes.

METHODS

SCUT was an NIH/NEI-funded, multicenter, randomized, placebo-controlled, double masked clinical trial comparing clinical outcomes in patients receiving topical corticosteroid or topical placebo as adjunctive therapy in the treatment of bacterial corneal ulcers. Detailed methods for the trial have been described previously.[9] In brief, 500 patients with culture-proven bacterial corneal ulcers were randomized to receive topical prednisolone phosphate (Bausch & Lomb Pharmaceuticals, Inc., Tama, FL) or topical placebo (0.9% NaCl and preservative, prepared by Leiter's Pharmacy, San Jose, CA) after they had received at least 48 hours of topical 0.5% moxifloxacin (Vigamox, Alcon, Fort Worth, TX). The corticosteroid and placebo regimens consisted of 1 drop applied topically 4 times per day for one week, and then twice a day for one week, and then once a day for one week. The moxifloxacin regimen for both arms consisted of 1 drop applied topically every hour while awake for the first 48 hours, then 1 drop applied every two hours until re-epithelialization, and then 4 times a day until 3 weeks from enrollment. Treating physicians were allowed to change or discontinue adjunctive medications and were allowed to discontinue the study medication if they felt it was medically necessary. Exclusion criteria included: evidence of fungus on KOH preparation, Giemsa stain, or culture; evidence of acanthamoeba by stain; evidence of herpetic keratitis by history or examination; use of a topical corticosteroid or

systemic prednisolone during the course of the present ulcer; and impending perforation. Enrollment centers included the Aravind Eye Care System (Madurai, Coimbatore, Tirunelveli), Dartmouth-Hitchcock Medical Center, and the Francis I. Proctor Foundation at the University of California, San Francisco.

The primary outcome for the trial was best spectacle-corrected visual acuity (BSCVA) at 3 months from enrollment. Secondary outcomes included infiltrate/scar size at 3 months from enrollment, time to re-epithelialization, and proportion of adverse events including corneal perforation in each arm. Patients were evaluated every 3 days +/− 1 day until re-epithelialization. Infiltrate/scar size and epithelial defect size were measured by slit lamp examination as the longest diameter by the longest perpendicular to that diameter. BSCVA was measured at enrollment and 3 months using an ETDRS “Tumbling E” chart. All measurements were performed by masked examiners certified for the study.

Corneal scraping was performed at presentation. Two scrapings were smeared for Gram stain and KOH wet mount. Three scrapings were inoculated onto sheeps' blood agar, chocolate agar, and potato dextrose agar or Sabouraud's agar. The criterion for a positive bacterial culture was growth of the organism on one solid medium at the site of inoculation, with the exception of diptheroids and coagulase-negative staphylococcus, where more stringent criteria were required.[10,11] Antibiotic susceptibility testing for moxifloxacin was performed using the Etest method (AB BIODISK, Solna, Sweden).[10,12] Kirby-Bauer disk diffusion (Hi-media, India) was used to test antibiotic susceptibility to amikacin, ciprofloxacin, ofloxacin, gatifloxacin and moxifloxacin, according to CLSI standards.[13] Patients with mixed infections were excluded from this ancillary study.

The *Nocardia* strains were speciated and subtyped by PCR and bi-directional sequencing using methods previously described.[14] The sequences obtained were then used to perform nucleotide-nucleotide searches utilizing the BLASTn database at the NCBI website (http://www.ncbi.nlm.nih.gov/BLAST/). BLAST outputs were sorted based on maximum identity, and identifications were made when BLAST searches yielded at least 85% and for closely related species >90% of query coverage.

Demographic and clinical characteristics across *Nocardia* species were analyzed with a Fisher's exact test for categorical variables or analysis of variance (ANOVA) for continuous variables. Comparisons of three-month BSCVA and infiltrate/scar size in *Nocardia* spp keratitis versus all other causative organisms were analyzed using multivariate linear regression with a dichotomous term for *Nocardia* spp versus other causative organisms, controlling for corticosteroid treatment and baseline characteristics (BSCVA or infiltrate scar/size, respectively). The effect of corticosteroid in *Nocardia* spp on BSCVA and infiltrate/scar size at 3 months was analyzed using a multivariate linear regression controlling for whether the patient had amikacin added to their treatment regimen and baseline BSCVA and infiltrate/scar size, respectively. A sensitivity analysis was performed on the entire dataset, using an interaction term for *Nocardia* spp by treatment arm (corticosteroid or placebo). A Cox proportional hazards model controlling for baseline epithelial defect size and addition of amikacin to the treatment regimen was used to assess time to re-epithelialization. The geometric mean of the two measurements obtained for infiltrate/scar and epithelial defect size was used in the analyses. Proportion of cases perforating was assessed using a Fisher's exact test. All analyses were performed in Stata 10.0 (StataCorp, College Station, TX).

RESULTS

Of the 500 corneal ulcers enrolled in the trial, 56 (11%) were identified as being due to *Nocardia* spp. All *Nocardia* cases were isolated in India. One patient had a mixed infection with *Nocardia* and was excluded. *Nocardia* spp was the third most commonly-isolated organism in the trial overall. Of the 55 enrolled *Nocardia* cases, 32 (58%) reported a history of trauma in the affected eye. Of these, 11 (34%) were due to vegetative matter injury. Nearly half (N=26, 47%) of the patients were agricultural workers. Median age at presentation was 48 years (interquartile range (IQR) 40 to 60 years). Thirty (55%) of the patients were male. The median duration of symptoms prior to presentation was 10 days (IQR 4 to 15 days).

Strain typing results were available for 52 of the 55 samples (95%). The most common species were *N. cyriacigeorgica* (N=18, 35%), *N. pneumoniae* (N=11, 21%), and *N. asteroides* (N=10, 19%) (Table 1). Ninety-eight percent of *Nocardia* spp were susceptible to amikacin. The fluoroquinolones tested by Etest and disk diffusion had variable activity against the *Nocardia* species, ranging from 45% of *N. pneumoniae* isolates susceptible to moxifloxacin and ciprofloxacin to 100% susceptibility against *N. farcinica*. There was no difference across *Nocardia* species in terms of history of trauma (P=0.88), agricultural work (P=0.43), age (P=0.38), gender (P=0.24), or duration of symptoms (P=0.50). *N. cyriacigeorgica* ulcers were associated with a vegetative matter injury (P=0.03). There were no contact lens wearers.

Nocardia spp cases had a median duration of symptoms of 10 days (IQR 4 to 15 days) versus 4 days (IQR 3 to 7 days) in non-*Nocardia* cases. Median enrollment BSCVA of *Nocardia* spp cases was 0.34 logMAR (approximate Snellen equivalent 20/45, IQR 0.1 to 1.2 logMAR (20/25 to 20/300)), compared to 0.86 logMAR (20/145, IQR 0.42 to 1.7 logMAR (20/50 to Count Fingers), P<0.001) in non-*Nocardia* cases. Median infiltrate/scar size at enrollment in *Nocardia* spp cases was 2.7 mm (IQR 1.9 to 4.1 mm), and 2.7 mm (IQR 1.9 to 4.0 mm, P=0.75) in non-*Nocardia* cases. Of the 55 *Nocardia* cases, 51 (93%) returned for their 3-month follow-up visit. At 3 months, median BSCVA in *Nocardia* keratitis cases was 0.12 logMAR (20/25, IQR 0.00 to 0.74 logMAR (20/20 to 20/100)), compared to 0.30 logMAR (20/40, IQR 0.06 to 0.68 logMAR (20/22 to 20/95), P=0.25) in all other organisms. Median infiltrate/scar size at 3 months was 2.7 mm (IQR 1.6 to 3.7 mm) in *Nocardia* cases, and 2.7 mm (IQR 1.8 to 3.9 mm, P=0.9) in non-*Nocardia* cases. Controlling for baseline characteristics, *Nocardia* spp ulcers were associated with 2 lines less improvement in 3-month BSCVA (0.21 logMAR, 95% CI 0.09 to 0.33 logMAR, P=0.001, Table 2) and 0.2 mm less improvement in infiltrate/scar size (95% CI 0.02 to 0.4 mm, P=0.03, Table 3) compared to other bacterial ulcers.

Median time to re-epithelialization in *Nocardia* ulcers was 5.5 days (IQR 2.5 to 14 days), compared to 7.5 days (IQR 2.5 to 16.5 days) in all other bacterial ulcers. There was no difference in time to re-epithelialization, adjusting for baseline epithelial defect size and treatment, between *Nocardia* spp and all other organisms (Hazards Ratio 0.82, 95% CI 0.60 to 1.12, P=0.21). One (2%) *Nocardia* spp case had a corneal perforation, compared to 14 of the remaining 445 other bacterial cases (3%, P>0.999). During the course of treatment, 18 patients (33%) with *Nocardia* keratitis had amikacin added to their treatment regimen. Of these, 9 were in the corticosteroid arm (29%) and 9 were in the placebo arm (38%, P=0.57). The median study day on which amikacin was added was 4.5 days after enrollment (IQR 1 to 9 days). Amikacin typically was added to cases that were severe. Median enrollment BSCVA was worse in patients who received amikacin, although this difference was not significant (0.46 logMAR versus 0.28 logMAR in the moxifloxacin-only group, P=0.43). Median 3-month BSCVA was worse in patients receiving amikacin (0.54 logMAR vs. 0.09

logMAR, *P*=0.01). Time to re-epithelialization was longer in cases that received amikacin versus those that did not (13 days versus 4 days, *P*=0.004). Patients who had amikacin added to their regimen had a higher median MIC to moxifloxacin than those who did not have amikacin added (12.0 μg/ml, IQR 1.50 μg/ml to 32 μg/ml versus 1.7 μg/ml, IQR 0.5 μg/ml to 4 μg/ml). Changes in medication were permitted by treated physicians by the SCUT protocol according to clinical parameters, not susceptibility.

Of the patients with *Nocardia* spp ulcers, 31 patients were randomized to receive topical corticosteroid and 24 were randomized to placebo (*P*=0.32, Fisher's exact test). At 3 months, 4 patients had been lost to follow-up, resulting in 28 patients from the corticosteroid arm and 23 patients from the placebo arm that were included. On average, the use of corticosteroids was associated with a 0.40 mm larger infiltrate/scar size at 3 months in *Nocardia* keratitis cases, with enrollment infiltrate/scar size and addition of amikacin as covariates (0.40 mm, 95% CI 0.03 to 0.77mm, *P*=0.03, Table 4). A sensitivity analysis using an interaction term (corticosteroid by *Nocardia* spp) did not change these results. There was no difference in 3-month BSCVA between corticosteroid and placebo arms, controlling for enrollment BSCVA and addition of amikacin (0.14 logMAR, 95% CI −0.085 to 0.37, *P*=0.21). There was no difference in time to re-epithelialization with the use of corticosteroids (HR 0.89, 95% CI 0.49 to 1.61, *P*=0.70). There was no difference in perforation between the two arms (*P*=1.0).

DISCUSSION

While *Nocardia* spp have historically been a relatively rare cause of bacterial keratitis, the incidence of *Nocardia* spp keratitis may be increasing, especially in India.[15] Previous case series from South India have shown that *Nocardia* spp were responsible for a small proportion of bacterial ulcers, however in SCUT, *Nocardia* was the third most commonly-isolated organism.[5,16] Prior reports have evaluated outcomes in *Nocardia* keratitis in a retrospective manner, and no information is available on the utility of corticosteroids for this type of keratitis. In this prospective subanalysis of a clinical trial, we found that *Nocardia* keratitis generally had good outcomes, but the use of corticosteroids resulted in larger infiltrate/scar sizes, suggesting they may not be appropriate for treating this disease. Additionally, treatment with fluoroquinolones as monotherapy in two-thirds of cases resulted in good median visual acuity (approximately 20/25), despite having variable *in vitro* susceptibility.

Overall, patients did not have a high degree of vision loss at enrollment (approximate Snellen equivalent 20/40), and outcome visual acuity was good (approximate Snellen equivalent 20/25). *Nocardia* keratitis cases had significantly less improvement at 3 months in visual outcomes and infiltrate/scar size than ulcers due to all other bacteria. This indicates that there may not have been room for dramatic improvement, as seen in ulcers of other etiologies.[11] We did not find any difference in baseline characteristics or clinical outcomes across species of *Nocardia*. Patients with *Nocardia* spp ulcers had a significantly delayed presentation compared to ulcers with non-*Nocardia* ulcers. Despite this, infiltrate/scar size was almost identical in ulcers due to *Nocardia* vs. other bacterial organisms, and visual acuity was significantly better at enrollment in *Nocardia* ulcers. It is possible that the scars of *Nocardia* spp ulcers may be less opaque or dense than non-Nocardia ulcers, but this was not assessed in this study.

The use of topical corticosteroids in bacterial corneal ulcers is controversial. Corticosteroids may reduce inflammation that can lead to ocular damage, however there is a risk that they may exacerbate the infection and cause corneal melting.[17–20] The primary SCUT analysis found no overall difference in safety and efficacy between adjunctive corticosteroid therapy and placebo.[16] The effect of topical corticosteroids on *Nocardia* spp ulcers has not been

previously well characterized. Case reports have suggested that topical corticosteroids may result in recurrence of the infection and prolonged healing time.[21] In this study, we found that the use of adjunctive corticosteroids was associated with significantly larger infiltrate/scar sizes at 3 months in *Nocardia* keratitis cases. There was no difference in visual acuity, time to re-epithelialization, or perforation between the corticosteroid and placebo arms. Epithelial healing may not be an appropriate indicator for improvement in *Nocardia* keratitis, because the disease can progress despite epithelial defect healing. However, these findings suggest that caution should be taken when treating patients with presumed *Nocardia* keratitis with corticosteroids.

There have been few reports in the literature about the response of *Nocardia* keratitis to fluoroquinolones. *In vitro* studies have shown that *Nocardia* isolated from keratitis has variable susceptibilities to fluoroquinolones[4,5], and in this study, gatifloxacin had the best activity, followed by moxifloxacin. Nearly all isolates were susceptible to amikacin. It is not clear how *Nocardia* keratitis responds clinically to treatment with fluoroquinolones. To date, studies of *Nocardia* keratitis *in vivo* have focused primarily on treatment with amikacin. In this study, all patients were started on moxifloxacin as the initial treatment per study protocol. Treating physicians were allowed to change or add antibiotics if they felt it was medically necessary. Approximately one third of patients had amikacin added to their moxifloxacin regimen, generally within the first week of treatment. Patients who had amikacin added to their treatment regimen had more severe ulcers at presentation, with worse visual acuity and larger infiltrate/scar sizes. They also had worse visual acuity outcomes, suggesting these are cases that were more difficult to treat. The cases that received only moxifloxacin steadily improved, but were less severe at presentation. These results suggest that for less severe Nocardia ulcers, moxifloxacin monotherapy may be a viable treatment option. However, no definitive conclusions about the efficacy of moxifloxacin for the treatment of *Nocardia* keratitis can be drawn from this study, as this study was not designed to compare the efficacies of amikacin and moxifloxacin.

This study must consider several limitations. While *Nocardia* spp was the third most commonly-isolated organism during the course of the trial, only 55 samples were isolated, resulting in a small study sample size. There was a relatively small number of each *Nocardia* species, making comparisons between species difficult. Due to the small sample size, we are unlikely to have detected even a moderate effect on visual acuity. However, we did find a difference in infiltrate/scar size, showing that we did have sufficient power to detect this difference. As a subanalysis of a larger clinical trial, this study may suffer a selection bias resulting from the clinical trial's exclusion criteria, such as the exclusion of ulcers with a descemetocoele. Some excluded patients may have been *Nocardia* spp cases; no information was collected on patients who were excluded. However, because this study was part of a prospective, randomized, controlled trial, all patients followed a standardized treatment protocol and had standardized study measurements of visual acuity, infiltrate/scar and epithelial defect size at pre-specified time points. This methodology improves our ability to make a direct comparison in this subgroup to ulcers from other organisms, and allows us to assess the utility of corticosteroids in a rigorous manner. Although the use of corticosteroids resulted in worse infiltrate scar, this did not appear to affect visual acuity. However, it is possible that high contrast acuity may not disclose an adverse effect on visual function that might be revealed by other measures such as contrast sensitivity.

In this study, *Nocardia* spp ulcers improved less over the course of treatment compared to ulcers of other etiologies, but *Nocardia* ulcers may have had less room for improvement given that they presented with better visual acuity. The use of corticosteroids was associated with a worse infiltrate/scar size at 3 months. The susceptibility of isolates to fluoroquinolones was variable; however, cases that were treated only with moxifloxacin,

which were in general less severe at presentation than those where amikacin was added, had good clinical outcomes, suggesting that moxifloxacin may be an acceptable treatment for such cases. Clinical outcomes in *Nocardia* keratitis generally are good, but there is no evidence that corticosteroids are of benefit in ulcers due to this organism, and in fact may result in worse outcomes.

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Biography

Prajna Lalitha, MD is currently the Chief of Ocular Microbiology Laboratory at Aravind Eye Hospital, Madurai, India. She is also a practicing Ophthalmologist at the same institute since 2002. She holds a dual degree in both Ophthalmology and Microbiology. Her main area of interest is in the field of infections of the eye. Her research focus is on understanding the host immune response in fungal corneal ulcers.

References

1. Khan Z, Neil L, Chandy R, et al. Nocardia asteroides in the soil of Kuwait. Mycopathologia. 1997; 137(3):159–163. [PubMed: 9424591]
2. Kurup P, Randhawa H, Sandhu R. A survey of *Nocardia asteroides, N. caviae* and *N. brasiliensis* occuring in soil in India. Sabouraudia. 1968; 6(3):260–266. [PubMed: 5679672]
3. Lalitha P. Nocardia keratitis. Curr Opin Ophthalmol. 2009; 20(4):318–323. [PubMed: 19387343]
4. DeCroos F, Garg P, Reddy A, et al. Optimizing diagnosis and management of *Nocardia* keratitis, scleritis, and endophthalmitis: 11-year microbial and clinical overview. Ophthalmology. 2011; 118(6):1193–1200. [PubMed: 21276615]
5. Lalitha P, Tiwari M, Prajna N, Gilpin C, Prakash K, Srinivasan M. Nocardia keratitis: species, drug sensitivities, and clinical correlation. Cornea. 2007; 26(3):255–259. [PubMed: 17413948]
6. Mizota A, Haki K, Shiina C, et al. The first case of keratitis caused by Nocardia exalbida. Int Ophthalmol. 2007; 27(5):333–336. [PubMed: 17476571]

7. Matsuka S, Rama P, Cavellero A, Paganoni G, Spinelli A, Brancato R. Nocardia keratitis: a case report. Eur J Ophthalmol. 2006; 16(1):164–167. [PubMed: 16496263]
8. Patel N, Reidy J, Gonzalez-Fernandez F. Nocardia keratitis after laser in situ keratomileusis: clinicopathologic correlation. J Cataract Refract Surg. 2005; 31(10):2012–2015. [PubMed: 16338576]
9. Srinivasan M, Mascarenhas J, Rajaraman R, et al. The Steroids for Corneal Ulcers Trial: Study Design and Baseline Characteristics. Arch Ophthalmol. 2012; 130(2):143–150. [PubMed: 21987582]
10. Lalitha P, Srinivasan M, Manikandan P, et al. Relationship of in vitro susceptibility to moxifloxacin and in vivo clinical outcome in bacterial keratitis. Clin Infect Dis. 2012; 54(10): 1381–1387. [PubMed: 22447793]
11. Sy A, Srinivasan M, Mascarenhas J, et al. Pseudomonas aeruginosa keratitis: Outcomes and response to corticosteroid treatment. Invest Ophthalmol Vis Sci. 2012; 53(1):267–272. [PubMed: 22159005]
12. Chen A, Prajna L, Srinivasan M, et al. Does in vitro susceptibility predict clinical outcome in bacterial keratitis? Am J Ophthalmol. 2008; 145(3):409–412. [PubMed: 18207124]
13. CLSI. M100-S22: Performance standards for antimicrobial susceptibility testing; twenty-first informational supplement. Clinical and Laboratory Standards Institute; Wayne, PA: 2011.
14. Rodriguez-Nava V, Couble A, Devulder G, Flandrois J, Boiron P, Laurent F. Use of PCR-restriction enzyme pattern analysis and sequencing database for hsp65 gene-based identification of *Nocardia* species. J Clin Microbiol. 2006; 44(2):536–546. [PubMed: 16455910]
15. Srinivasan M, Gonzales C, George C, et al. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, South India. Br J Ophthalmol. 1997; 81(11):965–971. [PubMed: 9505820]
16. Srinivasan M, Mascarenhas J, Rajaraman R, et al. Corticosteroids for Bacterial Keratitis: The Steroids for Corneal Ulcers Trial (SCUT). Arch Ophthalmol. 2012; 130(2):151–157. [PubMed: 21987581]
17. Cohen E. The case against the use of steroids in the treatment of bacterial keratitis. Arch Ophthalmol. 2009; 127(1):103–104. [PubMed: 19139349]
18. Engel L, Callegan M, Hobden J, Reidy J, Hill J, O'Callaghan R. Effectiveness of specific antibiotic/steroid combinations for therapy of experimental *Pseudomonas aeruginosa* keratitis. Curr Eye Res. 1995; 14(3):229–234. [PubMed: 7796606]
19. Ohadi C, Litwin K, Moreira H, et al. Anti-inflammatory therapy and outcome in a guinea pig model of *Pseudomonas* keratitis. Cornea. 1992; 11(5):398–403. [PubMed: 1424667]
20. Wilhelmus K. Indecision about corticosteroids for bacterial keratitis: an evidence-based update. Ophthalmology. 2002; 109(5):835–842. [PubMed: 11986084]
21. Rao S, Madhavan H, Sitalakshmi G, Padmanabhan P. Nocardia asteroides keratitis: report of seven patients and literature review. Indian J Ophthalmol. 2000; 48(3):217–221. [PubMed: 11217254]

Table 1

Nocardia keratitis isolate species and antibiotic susceptibilities

***Nocardia* spp strain**	**Total N (%)**	**Moxifloxacin MIC_{50} (μg/ml)**	**Susceptible isolates by disc diffusion (N, %)**				
			Moxifloxacin	**Amikacin**	**Ciprofloxacin**	**Gatifloxacin**	**Ofloxacin**
Nocardia cyriacigeorgica	18 (35%)	2.5	14 (78%)	18 (100%)	11 (65%)[a]	13 (72%)	11 (65%)**
Nocardia pneumoniae	11 (21%)	12	5 (45%)	10 (91%)	5 (45%)	6 (55%)	5 (45%)
Nocardia asteroides	10 (19%)	1	8 (80%)	10 (100%)	6 (60%)	9 (90%)	6 (60%)
Nocardia farcinica	5 (10%)	0.125	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)
Nocardia ignorata	3 (6%)	1.5	2 (66%)	3 (100%)	2 (67%)	2 (67%)	2 (67%)
Nocardia araoensis	2 (4%)	5.7	1 (50%)	2 (100%)	1 (50%)	2 (100%)	1 (50%)
Nocardia asiatica	1 (2%)	32	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Nocardia blacklockiae	1 (2%)	0.5	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Nocardia wallacei	1 (2%)	32	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Total	52	2	36 (69%)	51 (98%)	31 (61%)	38 (73%)	31 (61%)

[a]Susceptibility not done for one isolate

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Table 2

Comparison of 3-month best spectacle-corrected visual acuity (BSCVA) in *Nocardia* keratitis vs. non-*Nocardia* keratitis patients with a multivariate linear regression model

Covariate	Coefficient (logMAR)	95% CI	*P-value*
Nocardia spp (vs. all other organisms)	0.21	0.09 to 0.33	0.001
Corticosteroid (vs. placebo)	−0.02	−0.09 to 0.06	0.64
Enrollment BSCVA (logMAR)	0.64	0.58 to 0.70	<0.001

Table 3

Comparison of 3-month infiltrate/scar size (geometric mean in mm) in *Nocardia* keratitis vs. non-*Nocardia* keratitis patients with a multivariate linear regression model

Covariate	Coefficient (mm)	95% CI	*P-value*
Nocardia spp (vs. all other organisms)	0.20	0.02 to 0.39	0.03
Corticosteroid (vs. placebo)	0.06	−0.05 to 0.18	0.29
Enrollment infiltrate/scar size (geometric mean in mm)	0.91	0.88 to 0.95	<0.001

Table 4

Comparison of 3-month infiltrate/scar size (geometric mean in mm) in *Nocardia* keratitis patients receiving corticosteroid or placebo

Covariate	Coefficient (mm)	95% CI	*P-value*
Corticosteroid (vs. placebo)	0.40	0.03 to 0.77	0.03
Addition of amikacin to regimen (vs. not added)	0.38	−0.03 to 0.78	0.07
Enrollment infiltrate/scar size (geometric mean in mm)	1.00	0.90 to 1.12	<0.001