Intrastromal Antibiotic Injection in Polymicrobial Keratitis: Case Report and Literature Review

Clara M. Pak  Daniel E. Savage  Ronald Plotnik  Rachel A.F. Wozniak

Department of Ophthalmology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Keywords
Polymicrobial keratitis · Intrastromal injections · Intrastromal antibiotics · Case report

Abstract
Bacterial keratitis (corneal infection) caused by more than one organism is rare and exceedingly difficult to treat due to variable antibiotic susceptibilities. Intrastromal injections of antibiotics may be necessary to achieve higher drug concentrations at the site of infection, particularly in the case of deep stromal disease refractory to topical therapy. However, while this approach is increasingly used for fungal keratitis, there is a paucity of the literature regarding the use of intrastromal antibiotics bacterial keratitis. In the current case, an 86-year-old patient presented with a left corneal ulcer with corresponding microbiologic cultures positive for Staphylococcus epidermidis, Staphylococcus aureus, and Achromobacter species. The ulcer continued to progress despite maximal topical antibiotic treatment yet demonstrated marked improvement after two intrastromal injections of moxifloxacin administered 2 weeks apart. Polymicrobial keratitis can be particularly challenging to eradicate despite maximal topical antibiotic therapeutics. Intrastromal corneal injections provide a mechanism for drug delivery directly to the site of infection and thus may represent an important alternative in refractory cases.

Introduction
Polymicrobial keratitis, an infection of the cornea caused by more than one organism, is rare, with an incidence reported between 1 and 8% of all keratitis cases [1–3]. These types of complex infections are challenging to eradicate, often requiring multiple antimicrobial agents...
and frequent follow-up. Further complicating its management, significant antimicrobial resistance is often identified among one or more of the causative organisms [2]. While intrastromal injection of antimicrobial agents has garnered increased attention in the treatment of fungal keratitis refractory to topical therapy [4–7], the utility of this approach is still uncertain [8, 9], and intrastromal antibiotic injection to treat bacterial keratitis is even less well established. To the best knowledge of the authors, examples of successful treatment of bacterial keratitis with intrastromal antibiotic injection in the literature are limited to a handful of case reports [10–14]. Furthermore, there are no reports of intrastromal moxifloxacin injection or antibiotic stromal injection in the case of known triple-organism polymicrobial keratitis. Herein, we report for the first time in the literature a case of polymicrobial keratitis refractory to topical therapy successfully treated by intrastromal injection of moxifloxacin.

**Case Presentation**

An 86-year-old female with a 7-year history of recurrent left neurotrophic corneal ulcers secondary to a prior varicella zoster infection presented to our center’s Cornea Clinic with 3 days of foreign-body sensation in the left eye. Ophthalmic history was also notable for glaucoma and remote cataract removal with posterior-chamber intraocular lens placement bilaterally. Her medication list prior to presentation included oral famciclovir 250 mg twice daily, topical loteprednol 0.5% three times daily, and topical tobramycin 0.3% three times daily in the left eye for infection prophylaxis, given her extensive neurotrophic keratitis history.

On initial examination, BCVA was 20/40 in the right eye and hand motion only in the left eye. Intraocular pressures were measured with a handheld tonometer with the noninfected right eye evaluated first and found to be 13 mm Hg and 11 mm Hg in the right and left eyes, respectively. Pupillary examination and visual fields were within normal limits in the right eye, but examination was obscured by corneal opacity in the left eye. The left anterior segment exam was notable for 2+ scleral injection, stromal corneal edema, peripheral corneal neovascularization, endothelial plaque, and a 1.0 mm × 0.9 mm epithelial defect overlying a dense stromal infiltrate measuring 1.5 mm × 1.3 mm. The left anterior chamber also had 1+ cell and flare, but no hypopyon was noted. The corneal ulcer was swabbed for aerobic, anaerobic, and fungal cultures. Given the patient’s prior history of contact lens dependence, a silicone hydrogel lens was placed for comfort and to promote topical drop absorption. Additionally, given clinical concern for polymicrobial infection, broad-spectrum topical antimicrobial coverage was initiated, including hourly fortified vancomycin 25 mg/mL, tobramycin 14 mg/mL, and voriconazole 1%.

The patient was unable to return until 5 days later. At this visit, she reported worsening pain in the left eye, and her left BCVA was light perception only. The slit-lamp examination was notable for the presence of a new 3-mm hypopyon and 4+ cell and flare in the anterior chamber. The corneal cultures returned pan-sensitive *Staphylococcus epidermidis*, penicillin-resistant *Staphylococcus aureus*, and *Achromobacter* spp. with unknown susceptibilities. Given that two of the three isolated organisms demonstrated susceptibility to fluoroquinolones, as well as some evidence in the literature of successful moxifloxacin use in the treatment of *Achromobacter* keratitis [15, 16], hourly topical 0.5% moxifloxacin (commercially available) was added to the intensive three antibiotic regimen. Although the cultures did not demonstrate fungal involvement, antifungal therapy was continued at this time in the setting of a worsening ophthalmic exam.

A week after initial presentation, despite intensive topical therapy, the patient presented with worsening symptoms and deterioration of the clinical exam with increased corneal
thinning and surrounding infiltrate, as well as persistent intraocular inflammation. In an attempt to stabilize the cornea, an intrastromal injection of 0.2 mL of 0.5% moxifloxacin (standard commercial preparation) was administered, directed at the edge of the infiltrate. Topical vancomycin, tobramycin, and moxifloxacin were continued, in addition to a therapeutic bandage contact lens as before. At 5 days after the first injection, the patient showed significant improvement. The hypopyon was noted to be resolved, and the stromal infiltrate and endothelial plaque demonstrated signs of consolidation. Two weeks after the first injection, because there was still a significant ulcer present despite improved consolidation of the infiltrate and plaque, she received a second 0.2 mL intrastromal injection of 0.5% moxifloxacin. At that time, antibiotic drops were reduced to 2 times per day for an extended taper. Three days after the second injection, the patient reported no pain or discomfort in the affected eye, and corneal examination revealed complete resolution of the epithelial defect (Fig. 1). At 3-month follow-up, the left eye remained stable with no signs of recurrent infection. Unfortunately, due to significant stromal thinning, corneal scarring, and inferonasal corneal neovascularization, BCVA remained hand motion only in the left eye. Given her previous ophthalmic history, the patient was advised to continue loteprednol drops 4 times daily, moxifloxacin daily, and oral famciclovir twice daily.

Discussion

Intrastromal injection of antimicrobials is an increasingly utilized technique to treat corneal infections with a known or suspected fungal etiology [4]. This is because fungal infections are more often deep stromal infections, and oral and topical antifungal agents typically have poor corneal penetration due to their larger molecular structures [17]. In contrast, topical antibiotic drops typically have good penetration and can reach concentrations above the minimum inhibitory concentration in the corneal stroma, thereby achieving optimal drug levels at the site of the infection [18, 19]. However, in the case of deep stromal infections involving biofilm-forming bacteria, topical antibiotics may not provide adequate efficacy. For example, bacterial biofilm structures have been identified in patients with infectious crystalline keratopathy, a deep corneal infection caused by viridans streptococci, that are often recalcitrant to topical antibiotic therapies [20, 21].

In the present case, microbiologic cultures suggested a triple-bacterial keratitis involving pan-sensitive \textit{S. epidermidis}, penicillin-resistant \textit{S. aureus} as well as an \textit{Achromobacter} species with unknown antibiotic sensitivities. \textit{Achromobacter} is a Gram-negative, water-borne bacteria that readily forms biofilms, and a rare cause of keratitis has been associated with contact lens use, healthcare settings, and an immunocompromized state [15, 16, 22]. In our patient, the initial lack of clinical improvement with topical antimicrobial therapy was surprising, given that our corneal cultures found fluoroquinolone susceptibility for both \textit{S. epidermidis}

![Fig. 1. Slit-lamp photography of the patient’s left cornea following two intrastromal injections of moxifloxacin. Corneal examination was notable for resolution of the epithelial defect. However, there was resulting 60% stromal thinning at the ulcer site, corneal scarring, and neovascularization.](image-url)
and *S. aureus* and previous literature suggesting the successful treatment of *Achromobacter* keratitis with moxifloxacin, a fourth-generation fluoroquinolone. Interestingly, however, there was rapid resolution of the corneal ulcer following intrastromal moxifloxacin injection, raising the likelihood that either the infection was deeply embedded or the topical antibiotic drops had poor penetration secondary to local microscopic biofilm formation or both.

To the best knowledge of the authors, though intrastromal antibiotic injections may be increasingly more common in practice, only a small number of cases utilizing intrastromal antibiotic injections have been reported in the literature. The first report of intrastromal antibiotic injection for the treatment of bacterial keratitis was in 2010 by Khan and colleagues [10] in which 1 mL of intrastromal cefuroxime was used to successfully treat a recalcitrant *Streptococcus mitis* ulcer. In 2011, Liang and Lee [11] used intrastromal injection of tobramycin to successfully treat a resistant, undifferentiated ulcer that was believed to be bacterial, and in 2015, Agahan and Regalado [12] utilized intrastromal injection of 0.1 mL moxifloxacin to successfully treat keratitis caused by unknown pleomorphic Gram-positive bacilli believed to be diphtheroid species.

Our case reports for the first time intrastromal injection of moxifloxacin to successfully treat a triple-organism polymicrobial keratitis. Although intrastromal injection carries inherent risks, there were no complications noted in this case. Risks of injection include limited data on minimum effective intrastromal antibiotic dosing, mechanical damage to surrounding structures, bacterial seeding from inadvertent intracameral injection, and drug-specific adverse effects (e.g., macrocrystalline deposits with fluoroquinolone use) [11]. For example, in cases of accidental injection of antibiotics into the corneal stroma, corneal edema, transient Descemet’s membrane detachment, and a decrease in endothelial cell count have been reported [13, 14]. Ultimately, as a single intrastromal agent (moxifloxacin) was utilized in this case based on available culture data; additional publications regarding the preparation and minimum effective dosages of various ophthalmic intrastromal antibiotics as well as potential side effects are needed given the scarcity of the literature addressing this topic.

In conclusion, it is possible that intrastromal injection of antibiotic agents may be uniquely advantageous in certain cases of bacterial keratitis. Intrastromal antibiotics may be best suited in cases of deep stromal bacterial infections, infections with biofilm-forming bacteria, or other cases in which it is suspected that topical antibiotics have poor penetration to the site of infection. Moreover, while this case report presents the application of intrastromal antibiotic treatment of a polymicrobial infection, this technique may also be appropriate for infections that meet the above criteria but are thought to be caused by a single microorganism or in cases of unknown etiology. Clinicians should particularly consider intrastromal antibiotics prior to penetrating keratoplasty in cases of keratitis refractive to topical therapy.

**Statement of Ethics**

This retrospective review of patient data did not require ethical approval in accordance with the University of Rochester Research Subjects Review Board. Written informed consent was obtained by the next of kin as the patient is deceased at the time of writing, for publication of the details of their medical case and any accompanying images.

**Conflict of Interest Statement**

The authors have no financial disclosures or conflicts of interest to report.
Funding Sources

Rachel A.F. Wozniak, MD, PhD, Clara M. Pak, Daniel E. Savage, MD, and Ronald Plotnik, MD, were supported in part by an unrestricted departmental grant from the Research to Prevent Blindness for data collection and research; Rachel A.F. Wozniak, MD, PhD, was also supported by a career development award from the Research to Prevent Blindness for data collection, research, and writing the manuscript and also NIH K08 EYE29012 for data collection, research, and writing the manuscript.

Author Contributions

Clara M. Pak conducted a literature review and wrote the manuscript. Daniel E. Savage, MD, also conducted a literature review and provided manuscript editing. Ronald Plotnik, MD, provided manuscript editing and direct care of this patient. Rachel A.F. Wozniak provided oversight and manuscript editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Bourcier T, Thomas F, Borderie V, Chaumeil C, Larroche L. Bacterial keratitis: predisposing factors, clinical and microbiological review of 300 cases. Br J Ophthalmol. 2003;87(7):834–8.
2 Lim NCS, Lim DKA, Ray M. Polymicrobial versus monomicrobial keratitis: a retrospective comparative study. Eye Contact Lens. 2013;39(5):348–54.
3 Jones DB. Polymicrobial keratitis. Trans Am Ophthalmol Soc. 1981;79:153–67.
4 Robaei D, Carn T, Watson E. Established and emerging ancillary techniques in management of microbial keratitis: a review. Br J Ophthalmol. 2016;100(9):1163–70.
5 Prakash G, Sharma N, Goel M, Titiyal JS, Vajpayee RB. Evaluation of intrastromal injection of voriconazole as a therapeutic adjunctive for the management of deep recalcitrant fungal keratitis. Am J Ophthalmol. 2008;146(1):56–9. e2.
6 Nada WM, Al Aswad MA, El-Haig WM. Combined intrastromal injection of amphotericin B and topical fluconazole in the treatment of resistant cases of keratomycosis: a retrospective study. Clin Ophthalmol. 2017;11:871–4.
7 Maniam A, Yuen GS. Intrastromal antifungal injection as a successful modality of treatment for fungal keratitis: a case series. 2019.
8 Sharma N, Chacko J, Velpandian T, Titiyal JS, Sinha R, Satpathy G, et al. Comparative evaluation of topical versus intrastromal voriconazole as an adjunct to natamycin in recalcitrant fungal keratitis. Ophthalmology. 2013;120(4):677–81.
9 Narayana S, Krishnan T, Ramakrishnan S, Samantaray PP, Austin A, Pickel J, et al. Mycotic antimicrobial localized injection: a randomized clinical trial evaluating intrastromal injection of voriconazole. Ophthalmology. 2019;126(9):1004–9.
10 Khan IJ, Hamada S, Rauz S. Infectious crystalline keratopathy treated with intrastromal antibiotics. Cornea. 2010;29(10):1186–8.
11 Liang SYW, Lee GA. Intrastromal injection of antibiotic agent in the management of recalcitrant bacterial keratitis. J Cataract Refract Surg. 2011;37(5):960–2.
12 Agahan ALD, Regalado RNC. Infectious crystalline keratopathy caused by diphtheroids treated with intrastromal antibiotics in a post-corneal transplant patient. Ophthalmol Res. 2016(2):1–5.
13 Ha BJ, Lee SH, Kim YM, Kwon HS, Chu YK, Seo KY, et al. A case of inadvertent anterior chamber and corneal stromal injection with antibiotics during cataract operation. Korean J Ophthalmol. 2006;20(4):241.
14 Bhattacharjee K, Bhattacharjee H, Medhi J, Altaf A. Descemet’s membrane detachment caused by inadvertent vancomycin injection. Indian J Ophthalmol. 2008;56(3):241.
15 Almenara Micheleña C, Del Buey MÁ, Acsaso FJ, Cristóbal JÁ. Keratitis due to achromobacter xylosoxidans in a contact lens user. Eye Contact Lenses. 2018;44(5):S348–S351.
16 Reddy AK, Garg P, Shah V, Gopinathan U. Clinical, microbiological profile and treatment outcome of ocular infections caused by Achromobacter xylosoxidans. Cornea. 2009;28(10):1100–3.
17 Heralgi MM, Badami A, Voluda H, Venkatachalam K. An update on voriconazole in ophthalmology. Official Sci J Delhi Ophthalmol Soc. 2016;27(1):9–15.
18 Healy DP, Holland EJ, Nordlund ML, Dunn S, Chow C, Lindstrom RL, et al. Concentrations of levofloxacin, ofloxacin, and ciprofloxacin in human corneal stromal tissue and aqueous humor after topical administration. Cornea. 2004;23(3):255–63.
19 Holland EJ, Lane SS, Kim T, Raizman M, Dunn S. Ocular penetration and pharmacokinetics of topical gatifloxacin 0.3% and moxifloxacin 0.5% ophthalmic solutions after keratoplasty. Cornea. 2008;27(3):314–9.
20 Fulcher TP, Dart JK, McLaughlin-Borlace L, Howes R, Matheson M, Cree I, et al. Demonstration of biofilm in infectious crystalline keratopathy using ruthenium red and electron microscopy. Ophthalmology. 2001;108(6):1088–92.
21 Bispo PJ, Haas W, Gilmore MS. Biofilms in infections of the eye. Pathogens. 2015;4(1):111–36.
22 Lee B, Cai CX, Srikumaran D, Woreta FA. Severe achromobacter xylosoxidans keratitis with deep corneal involvement. Am J Ophthalmol case Rep. 2018;11:128–30.