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Sina Rezaei

Daniel W. Steen

Sejal R. Amin

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Successful treatment of an extensively drug-resistant pseudomonal ulcer associated with contaminated artificial tears

Sina Rezaei *, Daniel Steen, Sejal Amin

Department of Ophthalmology, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202, USA

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ABSTRACT

Purpose: To report a case of bacterial keratitis caused by an extensively drug-resistant (XDR) *Pseudomonas aeruginosa* strain linked to contaminated artificial tears in the United States. The ulcer was successfully treated without perforation or extracorneal spread.

Observations: An 81-year-old patient presented with a corneal ulcer of the right eye. The patient had a notable complex ocular history including glaucoma and corneal edema from corneal decompensation after prolonged retained lens fragment. Despite starting hourly fortified tobramycin and vancomycin eye drops, the infiltrate grew significantly by the next day. Bacterial culture grew *Pseudomonas aeruginosa* that was resistant to all tested antibiotics except for intermediate susceptibility to colistin and susceptibility to cefiderocol. Tobramycin-soaked collagen shields were applied daily for three days, and the patient was started on fortified colistin eye drops. The ulcer improved and, after seven weeks of therapy, the infiltrate resolved and resulted in a large central corneal scar.

Conclusions and Importance: A combination of fortified colistin and tobramycin (administered via a combination of fortified eye drops and tobramycin-soaked collagen shields) appears to be an effective treatment option for extensively drug-resistant *Pseudomonas aeruginos*a corneal ulcers.

1. Introduction

Pseudomonas aeruginosa is one of the leading causes of bacterial keratitis and is associated with more severe infection compared to other pathogens.[1,2] Although ocular samples show relatively low rates of resistance in the United States, there have been growing reports of resistant *P. aeruginosa* associated keratitis cases, especially overseas.[3–6] Multidrug-resistant (MDR) *P. aeruginosa* keratitis portends a poorer prognosis than its drug sensitive counterparts, with approximately half of drug resistant cases resulting in corneal perforation, requiring cyanoacrylate glue, and/or requiring keratoplasty in a prior case-control study.[4]

Recent reports have emerged of a highly resistant strain of *Pseudomonas aeruginosa* linked to contaminated artificial tear drops. These strains of *P. aeruginosa* have $bla_{\text{VIM-80}}$ and $bla_{\text{GES-9}}$ resistance genes, the combination of which has not been previously reported in the United States.[7] Here, we report a case of infectious keratitis due to extensively drug-resistant (XDR) *Pseudomonas aeruginosa* linked to contaminated artificial tears that was successfully treated without corneal perforation or extracorneal spread.

2. Case report

An 81-year-old male presented with two days of progressive pain and redness of his right eye. Of note, the patient had cataract surgery nearly three years prior to this presentation. He developed subsequent recurrent iritis, and he was eventually found to have retained lens fragments in the angle and sulcus that had caused corneal edema and lens particle glaucoma. Six weeks earlier, the patient had undergone a successful removal of the lens fragments. In addition to his long-term therapy with brimonidine eye drops for glaucoma and sodium chloride ointment for corneal edema, he began using EzriCare Artificial Tears nine days prior to the onset of his symptoms. He did not have a history of contact lens wear, trauma, or known additional exposures to increase risk of bacterial infection.

On examination, the patient's visual acuity in the affected right eye was hand motion, down from a baseline of 20/200 after corneal decompensation from the prolonged lens fragments. The intraocular

* Corresponding author.
E-mail address: rezasin@med.umich.edu (S. Rezaei).

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pressure in the right eye was also notably elevated to 36 mmHg. Slit lamp examination revealed a corneal infiltrate inferior to the visual axis measuring approximately 2.0mm in diameter, and an overlying epithelial defect of equal size (Fig. 1). Additionally, the patient had a 1.0 mm inferiorly layered hypopyon within the anterior chamber. Though there was significant conjunctival injection, no evidence of infectious scleritis was clinically identified. The retina was unable to be examined due to corneal opacity, but a B-scan ultrasound was without visible vitritis or retinal detachment. The patient was promptly prescribed hourly fortified tobramycin (14mg/mL) and vancomycin (25 mg/mL) from a local compounding pharmacy. Aerobic, anaerobic, and fungal cultures were sent to microbiology for further investigation of the corneal infiltrate. Of note, the patient discontinued the use of his artificial tears and sodium chloride ointment at the time of antibiotic initiation.

The next day, the infiltrate had grown significantly to 3.3mm vertically by 4.1mm horizontally. The patient reported only a delay of a few hours from the time of clinical evaluation to acquisition and initiation of fortified antibiotic therapy. The aerobic culture resulted with *Pseudomonas aeruginosa* within the first 24 hours after culture. Given the rapidly increasing size of the corneal infiltrate, a dissolvable collagen shield soaked in 40mg/mL tobramycin for 10 minutes was subsequently applied to the eye. The eye was patched closed, and the patient was instructed to remove the patch and restart his fortified antibiotic eye drops after 4 hours. On day two following presentation, the ulcer appeared stable (Fig. 2), but susceptibility testing showed resistance to all antibiotics routinely tested at our laboratory, including tobramycin (Table 1). Infectious disease was consulted, and additional susceptibility testing was sent to an outside laboratory. Given the patient's severe infection and the encouraging clinical response to treatment despite the resistance profile, an additional tobramycin-soaked collagen shield was applied, and the patient was additionally initiated on ciprofloxacin while awaiting additional susceptibility results. The vancomycin drops were decreased and ultimately discontinued. Notably, on day four following presentation, there was new, fifteen to twenty percent thinning concerning for interval clinical worsening. Thus, the ciprofloxacin eye drops were discontinued and fortified colistin (0.19%) drops were initiated, using the same concentrations as previously reported by Jain et al.[5] An additional tobramycin collagen shield was applied, and the patient was also started on nightly neomycin-polymixin B-bacitracin ointment. Once the patient started fortified colistin drops, the stromal thinning stabilized, and the infiltrate began to clear over the course of several weeks. Additional testing ultimately revealed intermediate susceptibility to colistin and susceptibility to cefiderocol (Table 1).

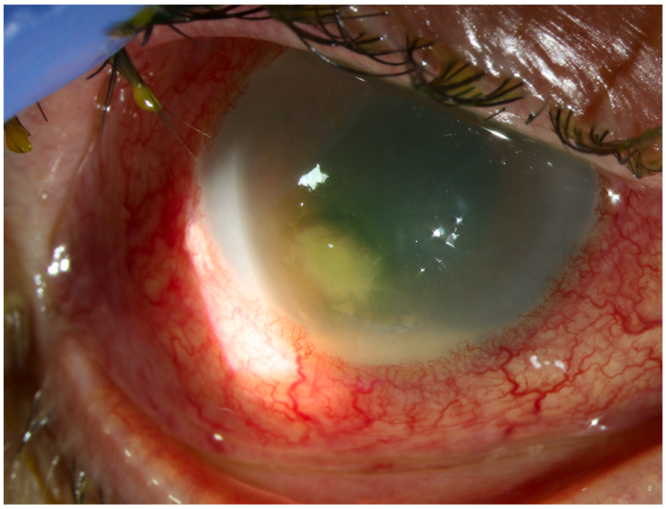

Fig. 1. Slit lamp photograph of corneal ulcer on day 1.

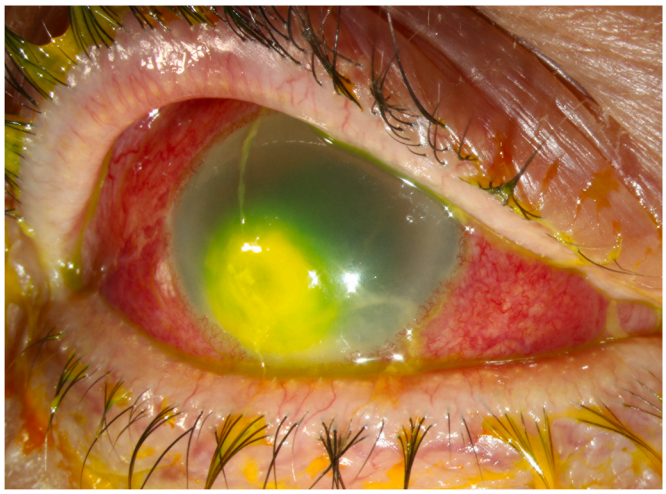

Fig. 2. Slit lamp photograph of corneal ulcer on day 3.

Table 1
Pseudomonas Aeruginosa susceptibility results.

Antibiotic	Susceptibility
Amikacin	Resistant
Cefepime	Resistant
Ciprofloxacin	Resistant
Gentamicin	Resistant
Meropenem	Resistant
Tobramycin	Resistant
Ceftolozane Tazobactam*	Resistant
Piperacillin Tazobactam*	Resistant
Ceftazadime Avibactam*	Resistant
Cefiderocol*	Susceptible
Colistin*	Intermediate

Susceptibility results were consistent with an extensively drug-resistant strain of *Pseudomonas aeruginosa*. Antibiotics with an asterisk were tested after the initial susceptibility results were found to be resistant. These results were not available during the initial management of the ulcer and were obtained to guide treatment.

Cefiderocol was investigated to potentially administer to the patient as a compounded ophthalmic solution, but the cost was greater than $2000 and prohibitive for the patient to obtain. Given the clinical improvement on his topical ophthalmic regimen with colistin drops and the inability to obtain cefiderocol for ophthalmic administration, his treatment was continued. He was monitored very closely over the next several weeks. Prednisolone acetate eye drops were started in week six to help reduce any residual inflammation in the setting of clinically resolved infection. Fortified colistin and tobramycin drops were gradually tapered and by week seven, antibiotics were discontinued. A slit lamp photograph of the corneal scar at week 9 is shown in Fig. 3.

3. Discussion

Given the high morbidity associated with extensively drug-resistant (XDR) *P. aeruginosa* infections, early and aggressive treatment is crucial to reduce the risk of complications such as loss of vision, the eye, or even life. In this case, the use of frequent fortified colistin and tobramycin along with the use of medicated collagen shields likely played a large role in controlling an aggressive and resistant strain of *P. aeruginosa*.

Colistin, also known as polymyxin E, is an antibiotic which fell out of favor for systemic use due to nephrotoxicity. It remains a useful tool, however, for topical ophthalmic use in cases of multidrug resistant (MDR) gram-negative rods. Colistin was likely the most efficacious agent used in this case given its intermediate susceptibility and the improved

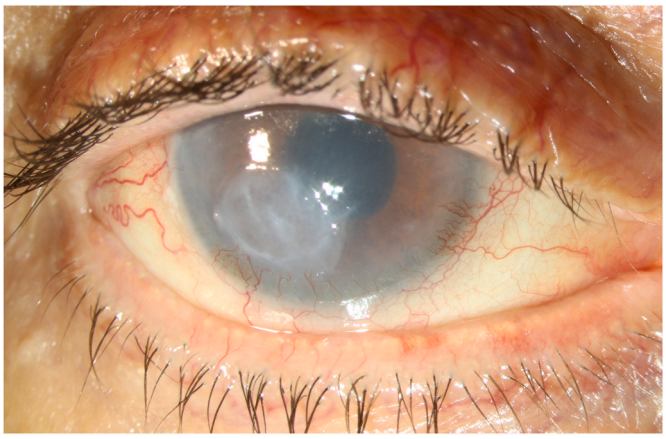

Fig. 3. Slit lamp photograph of resolved infectious corneal ulcer resulting in corneal scar at week 9.

clinical course following its addition. A previous case series also reported success when using colistin for MDR *Pseudomonas* keratitis.[5] We prepared colistin (0.19%) in the same manner as described in that case series through a local compounding pharmacy at a cost of $70 for a 15mL bottle. This compounded medication was prepared with less than a twenty-four-hour turnaround.

Although our lab was unable to test for susceptibility to neomycin or polymyxin B, neomycin-polymixin B-bacitracin ointment was utilized nightly to help promote epithelial healing and provide potentially beneficial antimicrobial coverage. Given its infrequent dosing, its role in controlling this patient's infection was likely limited.

Despite susceptibility testing showing resistance to tobramycin, the concentrations used in preparing the fortified tobramycin ophthalmic solution and collagen shields are significantly higher than the 16 μg/mL MIC level tested in our laboratory. The delivery of high-concentration tobramycin using a combination of fortified eye drops and collagen shields likely assisted in slowing the progression of the infiltrate prior to initiating colistin treatment. Notably, the infiltrate did increase in size after antibiotic initiation, but clinically stabilized for two days after the addition of a tobramycin-soaked collagen shield. A several-hour delay in acquiring the compounded fortified eye drops may have been a confounding factor resulting in growth of the infiltrate. Nevertheless, when used as a drug-delivery device, collagen shields may be helpful in delivering an increased antibiotic concentration at the site of infection and subsequently reducing bacterial load, especially when combined with topical therapy. Furthermore, collagen shields may promote corneal healing by neutralizing the collagenases released during infection, reducing corneal lysis, inflammation, and edema. In the setting of an XDR pathogen, the benefits may outweigh concerns of epithelial toxicity associated with the use of antibiotic-soaked collagen shields.[1,8]

The *P. aeruginosa* isolate in this case was ultimately found to be susceptible to cefiderocol, consistent with the other cases reported by the Centers for Disease Control and Prevention in this particular outbreak associated with contaminated artificial tears.[7] Though potentially beneficial, cefiderocol proved to be cost prohibitive to acquire through our local compounding pharmacy, and we were unable to find literature on its use as a compounded ophthalmic solution. Further research is necessary to determine its utility in treatment of bacterial keratitis.

4. Conclusions

This case demonstrates how fortified tobramycin, delivered through a combination of topical eye drops and antibiotic-soaked collagen shields, combined with colistin can be an effective treatment regimen for the treatment of infectious keratitis linked to a recent outbreak of extensively drug-resistant *Pseudomonas aeruginosa*.

Patient consent

Consent to publish the case report was obtained from the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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