INTRODUCTION

Multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) keratitis presents a therapeutic challenge due to severe limitation of adequate antimicrobials, resulting in higher rates of corneal perforation and portending a poorer visual prognosis compared to drug-sensitive *Pseudomonas* keratitis (Vazirani, Wurity, and Ali 2015). Sequential endophthalmitis occurring from progression of infectious keratitis is relatively uncommon, but occurs more frequently in patients with patients with risk factors such as a unicameral eye and topical corticosteroid use (Henry et al. 2012).

We report the clinical course and treatment strategies employed in management of a case of MDR-PA keratitis...
progressing to endophthalmitis in a patient with no apparent risk factors for multidrug-resistant infection. After several weeks of intensive treatment, the patient began to show gradual signs of clinical improvement and was also informed that his case was discovered to be part of a cluster outbreak of MDR-PA ocular infections across the country that were traced to EzriCare Artificial Tears as the source of infection.

CASE REPORT

A 57-year-old male patient was referred to our institution by a local corneal specialist, who had been treating him for 5 weeks for a severe Pseudomonas corneal ulcer in the right eye that was recalcitrant to standard antibiotic therapy. He had a history of Descemet stripping automated endothelial keratoplasty (DSAEK) more than 5 years prior to presentation, with a good surgical outcome and stable postoperative course. He had no prior contact lens use or any ocular trauma, and his systemic medical history was unremarkable. Preceding our evaluation, the patient had been treated with topical moxifloxacin for 5 weeks and topical fortified tobramycin and vancomycin for 1.5 weeks, as well as topical prednisolone acetate four times a day. He had also undergone a vitreous tap and intravitreal injection of vancomycin and ceftazidine for suspected endophthalmitis in the week prior to presentation to our institution.

At initial presentation to our institution, the patient had a best-corrected visual acuity of counting fingers in the right eye. Initial examination of the right eye revealed multifocal areas of corneal infiltrate and a temporal 1 x 2 mm area of 80% corneal thinning (Figure 1).

No hypopyon was observed. Repeat cultures were obtained to rule out persistent infection and cyanoacrylate glue was applied to the area of temporal thinning. Considering his use of frequent moxifloxacin, fortified vancomycin and tobramycin eyedrops over the past several weeks, there was concern for toxicity. The expired fortified drops were stopped, and moxifloxacin was decreased to 4 times a day while awaiting cultures. His prednisolone acetate was decreased from 4 times a day to once daily, and he was started on oral doxycycline 100mg twice a day and vitamin C 1g three times a day. He followed up with his outside provider in 2 days and appeared stable. Culture results revealed growth of only rare Propionibacterium acnes.

One week later, he re-presented to our institution with a visual acuity of light perception in the right eye. Examination revealed a rapidly progressing limbus-to-limbus corneal ulcer and melt with diffuse severe thinning and an area of 1mm x 1mm perforation superiorly with iris plugging (Figure 2A). A B-scan ultrasound evaluation of the right eye showed findings suggestive of hemorrhagic choroidals; no clear vitritis was seen (Figure 2B).

Repeat cultures were obtained, and the patient was started on topical fortified vancomycin every 1 hour alternating with tobramycin every 1 hour around the clock and oral levofloxacin 750mg daily.

The patient underwent a limbus-to-limbus therapeutic penetrating keratoplasty (TPK), preserving the arrow, iris and intraocular lens. On post-operative day 1, his examination was remarkable for a clear graft with no epithelial defect, a 3.5mm mixed hypopyon and heme, and a dense pupillary membrane which was presumed to be inflammatory (Figure 3).

Alarming, his repeat cultures prior to surgery revealed multidrug-resistant Pseudomonas aeruginosa with resistance to fluoroquinolones, aminoglycosides, cephalosporins, and carbapenems, and only intermediate susceptibility to piperacillin/tazobactam (Figure 4).

There was also identification of VIM carbapenemase production on immunoassay. The patient was started on topical chlorhexidine 0.02% alternating with topical polymyxin B/trimethoprim every 1 hour around the clock, topical prednisolone acetate four times a day, atropine twice a day, and oral trimethoprim-sulfamethoxazole (80mg/400mg) twice a day for a 14-day course. He was in-

Figure 1. Slit-lamp microscopy image of the right eye at initial presentation, showing multifocal areas of corneal infiltrate and a temporal 1 x 2 mm area of 80% corneal thinning.

Figure 2. A: Slit-lamp microscopy image of the right eye a week after initial presentation, showing limbus-to-limbus corneal ulcer and melt with diffuse severe thinning and an area of 1mm x 1mm perforation superiorly with iris plugging. B: B-scan ultrasound evaluation showing findings suggestive of hemorrhagic choroidals.
Examination of the patient’s right eye the following week, which was post-operative week 1 after PPV and post-operative week 2 after TPK, revealed a 3mm hypHEMA in the anterior chamber as well as corneal edema with Descemet folds and an epithelial defect covering roughly 75 percent of the cornea inferiorly. Magnetic resonance imaging (MRI) of the brain confirmed no post-septal extension of inflammation. He underwent 2 additional intravitreal injections of 225 µg/0.1 mL piperacillin/tazobactam spaced apart by 48 hours. Over the next few days, tobramycin was discontinued and chlorhexidine and polymyxin B/trimethoprim drops were gradually reduced without recurrence of infiltrate. His eye pain also improved.

On follow-up examination 6 weeks after TPK and 5 weeks after PPV with anterior chamber washout and intravitreal injections of 225 µg/0.1 mL piperacillin/tazobactam, examination of the patient’s right eye showed signs of gradual clinical improvement (Figure 5).

His visual acuity, which had remained stable at light perception from his initial presentation through his clinical course to date, improved to hand motion. He had no evidence of recurrent infection, and his epithelial defect had resolved with a bandage contact lens (BCL). The patient remains stable on polymyxin B/trimethoprim (given the use of a BCL) and prednisolone acetate 4 times a day.

On January 20, 2023, the American Academy of Ophthalmology published an urgent press release notifying providers of an update from the Centers for Disease Control and Prevention (CDC) investigation of a multi-state cluster of VIM-producing carbapenem-resistant *Pseudomonas aeruginosa* ocular infections that found epidemiology and laboratory evidence linking these infections to use of EzriCare-brand artificial tears. The local department of public health contacted our patient, who confirmed that he had indeed purchased and used EzriCare artificial tears prior to onset of his corneal ulcer.

Figure 3. Slit-lamp microscopy image of the right eye on post-operative day 1 after therapeutic penetrating keratoplasty, showing a clear graft, a 3.5mm mixed hypopyon and heme, and a dense inflammatory pupillary membrane.

Figure 4. Susceptibility results from the patient’s initial corneal cultures.
CASE REPORT: Multidrug-resistant Pseudomonas keratitis and sequential endophthalmitis treated with chlorhexidine and

Chlorhexidine is an antiseptic biocidal agent that kills microbial organisms via disruption of cell membranes (McDonnell and Russell 1999), a non-selective mechanism of action that prevents the development of antimicrobial resistance ("More Antisepsis, Less Antibiotics Whenever Possible: The Asia-Pacific Journal of Ophthalmology" n.d.). While chlorhexidine is typically used in ophthalmology as a preservative in eye drops as well as an agent in the treatment of *Acanthamoeba* keratitis (typically at 0.02% concentration) (Dart, Saw, and Kilvington 2009), there have been reports of chlorhexidine as an effective therapy in vivo against fungal isolates (Martin et al. 1995) as well as for the treatment of *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections (Bu et al. 2007). Chlorhexidine is generally well-tolerated, inexpensive, and easy to formulate, making it a satisfactory antimicrobial agent for consideration in cases of severe recalcitrant infectious keratitis. Prolonged treatment with higher concentrations of chlorhexidine, however, can cause toxicity to corneal epithelial cells and keratocytes (Mathers 2006); thus, we prudently decreased the frequency of our patient’s chlorhexidine use as soon as he showed signs of clinical improvement and corneal epithelial healing. Polymyxin B/trimethoprim, commonly used for the treatment of bacterial conjunctivitis, was also employed as a key topical agent for our patient, based on inherently low levels of resistance of *P. aeruginosa* against polymyxin B (Granet et al. 2008) and its availability as a topical ophthalmic antibiotic.

Our patient developed endophthalmitis that was presumed to also be due to MDR-PA given perforation of his corneal ulcer. Piperacillin-tazobactam, a combination of a beta-lactam antibiotic agent and a beta-lactamase inhibitor, is effective for broad-spectrum antibiotic coverage against gram-positive, gram-negative, and anaerobic bacteria (Young and Plosker 2001). Intravitreal administration of piperacillin-tazobactam at a dose of 225 µg/0.1 mL has been performed as a nonconventional therapeutic option in a small number of cases of MDR-PA endophthalmitis in the literature, with reported success as a safe and effective alternative in the management of MDR-PA endophthalmitis (Pathengay et al. 2010; Suganeswari, Shah, and Anand 2020; Singh et al. 2007). Informed by prior case studies (Pathengay et al. 2010), we performed intravitreal injections of piperacillin-tazobactam at a dose of 225 µg/0.1 mL every 48 to 72 hours until our patient showed signs of clinical improvement, with resolution of hypopyon and regression of inflammation.

Our patient was one of several who suffered severe vision loss due to MDR-PA ocular infections that were eventually traced to use of EzriCare Artificial Tears prior to infection, as revealed through investigation by the Centers for Disease Control and Prevention (CDC) (American Academy of Ophthalmology 2023). As our patient had no systemic or underlying risk factors for developing a multidrug-resistant infection, the report of the CDC outbreak investigation conclusively brought to light the source for our patient’s infection. The highly drug-resistant strain of *Pseudomonas aeruginosa* that was isolated from our patient’s corneal cultures, as well as in opened bottles of EzriCare eye drops col-

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**DISCUSSION**

MDR-PA keratitis remains relatively uncommon, though clinical evidence shows increasing drug resistance among *Pseudomonas aeruginosa* keratitis isolates over the past 2 decades (Garg, Sharma, and Rao 1999; Oldenburg et al. 2013). Due to the severe limitation of adequate therapeutic options, outcomes of multidrug-resistant ocular infections are typically poor even with prompt administration of with appropriate medications (Vazirani, Wurity, and Ali 2015). The emergence of multidrug-resistant strains of *Pseudomonas aeruginosa* is facilitated by several intrinsic drug resistance mechanisms such as production metallo-beta-lactamases (which was positive in our patient’s isolate), as well as an ability to acquire exogenous genes encoding drug resistance, resulting in the emergence of strains resistant to fluoroquinolones, aminoglycosides, carbapenems, and other classes (Miyoishi-Akiyama et al. 2017; Hancock and Speert 2000; Livermore 2002; Chen and Lo 2005).

Our patient had severe infectious keratitis that was complicated by perforation necessitating a therapeutic penetrating keratoplasty, and then experienced progression of his infection to endophthalmitis. The causative organism in his case was a strain of *Pseudomonas aeruginosa* that was resistant to fluoroquinolones, aminoglycosides, cephalosporins (3rd, 4th, and 5th-generation), monobactams, and even carbapenems. Management of his ocular infection necessitated consideration of nonconventional therapeutic agents and strategies, including an intensive course of topical chlorhexidine and polymyxin B/trimethoprim for his keratitis and repeated intravitreal injections of compounded piperacillin-tazobactam for his endophthalmitis.

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**Figure 5.** Slit-lamp microscopy image of the right eye at 6 weeks post-therapeutic penetrating keratoplasty and 5 weeks post-pars plana vitrectomy, showing no evidence of recurrent infection and resolved epithelial defect.
lected from patients in the investigation, had never been identified in the United States prior to the current multi-state cluster outbreak (Holpuch 2023). While Global Pharma, the company based in India that manufactured the EzriCare artificial tears, has halted further distribution and recalled the eye drops in response to the investigation, clinicians and patients must be informed of the potential of EzriCare Artificial Tears to cause MDR-PA ocular infection. Furthermore, the artificial tears were marketed as being preservative-free but came in 15mL bottles rather than sterile single-use vials. Patients should be informed that preservative-free eye drops should be contained in individual, single-use formulations.

CONCLUSIONS

We describe a case of MDR-PA keratitis progressing to endophthalmitis that required consideration of nonconventional antimicrobial agents and experimental therapeutic alternatives. The patient necessitated a therapeutic penetrating keratoplasty, after which an intensive regimen of topical chlorhexidine and polymyxin-B/trimethoprim appeared to be efficacious in treating the recalcitrant keratitis and healing the ocular surface, while repeated injections of intravitreal piperacillin-tazobactam was well-tolerated and effective in treating the patient’s sequential endophthalmitis.
REFERENCES


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