RECALCITRANT MULTIDRUG-RESISTANT PSEUDOMONAS KERATITIS WITH SUBSEQUENT TRIPLE PROCEDURE

Eriks Elksnis¹, Eva Elksne¹, Olita Lüse¹, Juris Vanags², and Guna Laganovska²

¹Riga Stradins University
²Paul Stradins Clinical University Hospital

September 26, 2023

RECALCITRANT MULTIDRUG-RESISTANT PSEUDOMONAS KERATITIS WITH SUBSEQUENT TRIPLE PROCEDURE

Authors: Eriks Elksnis¹,²,⁴, Eva Elksne¹,³, Olita Lüse¹,², Juris Vanags¹,⁴, Guna Laganovska¹,⁴

Affiliations:
1. Riga Stradins University, Riga, Latvia
2. Latvian American Eye Center
3. Children’s Clinical University Hospital, Riga, Latvia
4. Pauls Stradins Clinical University Hospital

Correspondence to: Eriks Elksnis. ORCID 0000-0002-7899-8224
Riga Stradins University, Dzirciema street 16, Riga, Latvia. LV1007.

Data availability statement: We hereby transfer, assign, or otherwise convey all copyright ownership, including any and all rights incidental thereto, exclusively to the journal, in the event that such work is published by the journal.

Conflict of interest disclosure: Authors declare no potential conflicts of interest.

Ethics approval statement: All procedures performed involving this case were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent statement: Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

KEY CLINICAL MESSAGE
Recalcitrant Pseudomonas aeruginosa keratitis is a challenging case in ophthalmology and can lead to irreversible blindness if not treated properly and in time.

KEYWORDS: Pseudomonas aeruginosa, recalcitrant keratitis, penetrating keratoplasty.

INTRODUCTION
Corneal opacity is the 5th leading cause of blindness and visual impairment, affecting approximately 6 million people worldwide; additionally, it is responsible for 1.5–2.0 million new cases of monocular blindness per year. Among all etiologies (such as infection, trauma, and inflammation), infectious keratitis (IK) is the main cause
of corneal blindness, with an estimated incidence ranging from 2.5–799 per 100,000 population years (Ting et al. 2021).

*Pseudomonas aeruginosa* (*P. aeruginosa*) is a gram-negative aerobic pathogen that can cause a wide range of infections and is one of the main causative pathogens of bacterial keratitis, especially in contact lens-associated keratitis, potentially leading to sight-threatening complications if not appropriately treated (Hilliam, Kaye & Winstanley 2020).

A particular characteristic of multidrug resistant *Pseudomonas* keratitis is its rapid progression, in which corneal destruction can be completed within 24–48 hours in some of the more virulent bacterial strains (Reynolds & Kollef 2021). Therefore, *P. aeruginosa*-caused keratitis is often associated with a high-cost long treatment period and poor visual outcomes (Hilliam, Kaye & Winstanley 2020).

**CASE PRESENTATION**

A 60-year-old female presented to a tertiary medical center in May 2021 with progressive vision loss, purulent discharge, photophobia, foreign body sensation, and pain in the left eye (LE).

Three weeks prior, the patient developed a foreign body sensation in her LE due to contact lenses remaining unremoved for one night. She had visited her local ophthalmologist and been prescribed topical tobramycin/dexamethasone 3 mg/mL four times daily, cyclopentolate 10 mg/mL twice daily, and dexamethasone once daily before bedtime. There was clinical improvement during the first 5 days of therapy; however, severe clinical worsening followed. The patient returned to the outpatient department 8 days after the first consultation, and treatment was changed to topical chloramphenicol/dexamethasone 1 mg/2 mg/mL six times daily, cyclopentolate 10 mg/mL twice daily and oral doxycycline 100 mg twice daily. Despite treatment, the symptoms worsened in the following week.

On the presenting day at the tertiary medical center, the best corrected visual acuity (BCVA) was 20/25 in the right eye (RE) and hand-motion (HM) vision in the LE. The RE was unremarkable on initial examination, whereas slit-lamp examination of the LE revealed a massive amount of purulent discharge in the conjunctival fornixes and intense mixed conjunctival injection. A large epithelial defect in the cornea was present, associated with a ring-like stromal infiltrate 3.1 mm in height, which was “soupy” in appearance owing to stromal necrosis. A hypopyon 3.2 mm in height was observed (Figure 1A). Both the lids were swollen and erythematous. As the posterior segment could not be visualized, B-scan ultrasonography of the LE was performed and confirmed a flat retina with no vitritis.

Corneal scrapings and cultures were obtained from LE. Cultures were acquired using a sterile cotton-tipped swab and placed in transport medium. The scrapings were placed on a glass slide and, together with the culture, forwarded to a microbiology laboratory.

Topical chloramphenicol/dexamethasone was discontinued, and levofloxacin 5 mg/mL eyedrops were initially administered every hour. Additionally, cyclopentolate 10 mg/mL was administered twice daily to control pain and prevent synechia, artificial tear drops were administered to aid wound healing, and oral doxycycline 100 mg twice daily was administered to prevent keratolysis.

After 12 hours, the condition worsened; discharge remained in the same amount, however, the hypopyon increased to 5.4 mm in height, with an infiltration spread 360° around the limbus and significant corneal edema (Figure 1B).

Levofloxacin was switched to moxifloxacin 5 mg/mL eye drops every hour. As a result, the amount of purulent discharge reduced, yet the central corneal infiltrate and ulcer remained unchanged, with remarkable stromal necrosis and corneal thinning in the nasal limbs (Figure 1C).

On the fourth day from admission, multidrug resistant *P. aeruginosa* was isolated from the culture. (Table 1). Based on these results, and after consultation with an infectologist, moxifloxacin was changed to fortified piperacillin 1.5 mg/mL/tazobactam 12 mg/mL eye drops every hour.
<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Susceptibility profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/tazobactam</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Imipinem</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>

Table 1. Susceptibility profile of the *Pseudomonaaeruginosa* isolated from the corneal lesion.

To achieve a therapeutic level in the corneal stroma, piperacillin 1.5 mg/mL/tazobactam 12 mg/mL was administered every hour for three days, then every awake hour for three days, followed by 4 times a day for one month. Regression of hypopyon and ciliary injection occurred, as well as corneal ulcer re-epithelization, which were documented during the following month (Figure 2).

The patient was finally discharged from the hospital after one month. Her vision was light perception in the LE and slit-lamp examination revealed diffuse, non-transparent corneal opacity, scarring, and marginal ulcers.

Six months after (December 7, 2021) a triple procedure was performed, i.e., combined cataract extraction and intraocular lens (IOL) implantation with penetrating keratoplasty (Figure 3A). Before the surgery, the IOL was calculated for the RE. Trepan 8.5 mm was used for the donor cornea, and trepan 8.0 mm for the recipient cornea. After dissection of the recipient cornea, a connective inflammatory membrane was observed in the anterior chamber, in conjunction with the iris (Figure 3B). After inspection, the fibrotic tissue and part of the iris were removed (Figure 3C). The next step was an open-sky extracapsular cataract extraction while maintaining the capsular bag and posterior capsule intact. An IOL was implanted in the bag and, after successful implantation, the donor cornea was sutured with 16 interrupted sutures of 10-0 Nylon. Suturing was the most challenging part of the procedure, owing to the change in thickness of the scarred recipient cornea. After the operation, topical dexamethasone/levofloxacin (1 mg/mL / 5 mg/mL) was administered 6 times daily and gradually tapered until the end of the first postoperative month, along with cyclopentolate twice a day. Dexamethasone eye drops were administered twice daily until the sutures were removed.

**THE OUTCOME**

More than 24 months after the penetrating keratoplasty and suture removal, the BCVA with myopic shift was 20/150 and the intraocular pressure was 8 mmHg. Slit-lamp examination revealed no signs of active inflammation. A thin sclera was observed around the limbus, along with transparent donor corneal tissue with clear margins, a deep anterior chamber with an irregular mydriatic pupil, and an IOL located in the capsular bag (Figure 4). Fundoscopy revealed no pathological changes in the optic disc or macula. However, notable destruction of the vitreous body was observed. The affected eye presented a considerable myopic shift, with an axial length almost 5 mm longer (32.09 mm) than in the RE (27.29 mm); the myopic shift and axial length extension occurred after infectious keratitis.

**DISCUSSION**

This case report highlights that extended contact lens use allows the adhesion of *P. aeruginosa* to their surface and subsequently to the cornea. *P. aeruginosa* possesses specific virulence factors, including pili, glyocalyx, and exotoxins, which allow for adherence and invasion of the cornea (Dart & Seal 1988). Additionally, *P. aeruginosa* has developed resistance mechanisms, such as a protective outer membrane of lipopolysaccharides, tendency to colonize in biofilm form, and presence of antibiotic-resistant plasmids (Shrestha et al. 2021). These attributes allow bacteria to be virulent, highly destructive, and to develop multidrug resistance (Hilliam, Kaye & Winstanley 2020).
This clinical case reminds us that bacterial keratitis associated with contact lenses is a sight-threatening condition, requiring immediate and appropriate treatment to improve outcomes. (Austin, Lietman & Rose-Nussbaumer 2017). Pseudomonas is the leading gram-negative in bacterial keratitis, and one of the most common agents of bacterial keratitis overall. In a meta-analysis, the prevalence of *P. aeruginosa* isolates in bacterial keratitis ranged from 6.8–55% (Teweldemedhin et al. 2017). Pseudomonas keratitis is strongly associated with the use of contact lenses. In one study, the incidence of Pseudomonas keratitis was 2.76 cases per 10000 individuals per year, yet rose to 13.04 cases per 10000 individuals when only contact lens wearers were considered; in the same study, 55% of Pseudomonas keratitis cases were associated with contact lens use (Jeng 2010).

Recalcitrant keratitis caused by *P. aeruginosa* is a serious and potentially blinding condition. The aggressive nature of the organism coupled with its evolving multidrug resistance is an important cause of ocular morbidity (Chan et al. 2021). This case report illustrates the importance of the initial treatment in bacterial keratitis. The reported patient received dexamethasone and chloramphenicol as initial treatment, which was one of the main factors leading to advanced stromal necrosis and corneal scarring. *P. aeruginosa* is usually intrinsically resistant to chloramphenicol, and the addition of corticosteroids as an initial treatment for infectious keratitis impairs the body’s ability to fight the infection, which may prove catastrophic if an appropriate antibiotic is not administered, as in this case (Morita et al. 2001)(Aberdein & Singer 2006). Broad-spectrum topical antibiotics are the first-line empirical treatment in such cases of unknown etiology. Topical corticosteroids can be considered and cautiously introduced 24–48 hours after initiation of topical antibiotics if the causative organism is identified or if a demonstrated response to topical antibiotics is observed (Ray et al. 2014). The main goal of corticosteroids is to reduce the morbidity associated with uncontrolled inflammation and decrease permanent corneal scarring (Al-Shehri, Jastaneiah & Wagoner 2009). In contrast, the adjunctive therapeutic results of corticosteroids for infectious keratitis reported in different studies are controversial (Sy et al. 2012).

Pseudomonas keratitis is treated with intensive topical antibiotic therapy with fluoroquinolones or fortified gram-negative targeted antibiotics, including aminoglycosides (e.g., tobramycin), cephalosporins (e.g., cefazidime), and synthetic penicillins (e.g., carbenicillin). The microbiological response is usually rapid, with stabilization of the growth of stromal infiltrates and halt of further stromal necrosis and thinning within 24–48 hours (Al-Shehri, Jastaneiah & Wagoner 2009). Few studies have reported recalcitrant multidrug-resistant Pseudomonas keratitis that responded to alternative antibiotic choices, such as piperacillin/tazobactam (Chew et al. 2010), colistin (Chatterjee & Agrawal 2016), meropenem (Chatterjee & Agrawal 2016), and imipenem (Fernandes et al. 2016).

Chew et al. (Chew et al. 2010) described three cases that did not respond to various antimicrobials, except piperacillin/tazobactam, with no adverse side effects noted; each case showed good resolution after a month of instillation with a slow taper. These three cases also presented pan-sensitivity on antibiotic sensitivity testing, yet showed significant clinical drug resistance, which was similar to our experience in the current case. Such disparity could be due to the degree of corneal drug penetration, increasing use of fluoroquinolones with an associated increase in resistance, and different minimum inhibitory concentrations of antibiotics in the cornea (Chew et al. 2010). The treatment of Pseudomonas keratitis is becoming increasingly challenging owing to the evolving drug resistance of this pathogen.

Although progression to endophthalmitis is rare, Pseudomonas is commonly cited as the causative pathogen of microbial keratitis leading to endophthalmitis, resulting in evisceration or enucleation (Stevenson et al. 2020). Despite the destructive nature and rapid course of the described keratitis with late but appropriate treatment, progression ceased. The patient underwent a penetrating keratoplasty with IOL implantation to prevent corneal blindness. Vazirani et al. described 23 cases of multidrug-resistant *P. aeruginosa* in a retrospective case-control study, in which 12 eyes were complicated by corneal perforation and 11 required keratoplasty. The incidence of corneal perforation and keratoplasty need was significantly higher than that in the control group of drug-sensitive *P. aeruginosa* keratitis (Vazirani, Wurity & Ali 2015). The evidence in the literature and the case described in this report conclude that multidrug-resistant Pseudomonas keratitis...
is extremely difficult to treat, and accompany a high risk of requiring surgical intervention to restore vision and avoid blindness.

The triple procedure was the only option for the patient to regain eyesight; however, significant corneal opacity developed, including scarring in the anterior chamber as well as changes in the lens due to inflammation. The advantages of the triple procedure were the following: the possibility of performing lens extraction at the time of surgery would allow preservation of endothelial cells of the donor’s cornea from phacoemulsification in the future; and significant visual improvement was possible immediately after a single-step surgical intervention under general anesthesia with fewer follow-ups. However, the potential risks of the triple procedure should be considered like vitreous loss, IOL decentration or dislocation intraoperatively, as well as secondary glaucoma and graft rejection postoperatively. (Al-Mohaimeed 2013).

Unfortunately, lens extraction and IOL implantation as separate procedures before penetrating keratoplasty were not possible in this case because of significant corneal opacity. The only feasible approach would be to perform penetrating keratoplasty followed by lens extraction and IOL implantation in other surgical interventions, putting the endothelial cells at risk. However, in this case, keratometry data would be available for IOL calculation.

Predicting the value of the IOL in a triple procedure is challenging. Unacceptable refractive errors can significantly affect the patient and surgeon satisfaction. For the precise calculation of IOL biometric data, the corneal curvature, anterior chamber depth, and axial length are relevant. However, these parameters can change significantly postoperatively. The BCVA of our patient after surgery was 20/150. The patient presented a significant increase in axial length comparing to the opposite eye. This could be explained by scleral degenerative changes due to inflammation and surgically-induced changes in axial length. Previous studies have reported a BCVA of >20/40 in at least 38% of all cases after the triple procedure (Javadi, Feizi & Moein 2013). Although the macula and optic disc were unaltered, the current patient presented a significant myopic shift (-20.0 D), surgery-induced astigmatism, destructive changes in the vitreous, and an iris defect that could affect the visual potential. According to the literature, 26–68% of eyes achieved ±2 D of target refraction after the triple procedure (Javadi, Feizi & Moein 2013). Our data reflected worse refractive outcomes even though the triple procedure was performed successfully. Refractive error correction with spectacles achieved a BCVA of solely 20/150. The patient refused contact lenses, including scleral contact lenses, which could have provided better BCVA.

In ophthalmic surgery, the main factors that reflects patient satisfaction with treatment are visual outcomes and eyeball preservation in complicated cases. However, aesthetic reasons, such as the appearance of the eye, played a main role in the patient’s satisfaction in this case report, in addition to the low visual acuity after surgery.

CONCLUSION

Pseudomonous keratitis remains one of the most important potential complications of contact lens use. With this in mind, early diagnosis and treatment are key to minimizing the visually threatening sequelae. Moreover, close follow-up, attention to laboratory data, and changing antibiotics in case of no evident clinical improvement are important factors for a successful outcome. The evidence in the literature and the case described in this report indicate that multidrug-resistant Pseudomonas keratitis is exceptionally difficult to treat, and a high risk exists of requiring surgical intervention to restore vision and avoid blindness.

PATIENT CONSENT STATEMENT:

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has/have given his/her consent for his/her images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

AUTHOR CONTRIBUTIONS:
REFERENCES


FIGURE LEGENDS

Figure 1. (A) Ring-like stromal infiltrate, “soupy” in appearance due to stromal necrosis, with hypopyon present in the anterior chamber. (B) Spreading of stromal infiltration 360° around the limbus with corneal edema and increase of hypopyon 12 hours after hospitalization. (C) Stromal necrosis of the nasal limbus.

Figure 2. The dynamics of the corneal reepithelization during one month of hospitalization after starting treatment with piperacillin/tazobactam.

Figure 3. (A) Corneal scar with neovascularization and scleral thinning 6 months after acute keratitis. (B) Connective inflammatory membrane, probably remnants of the anterior chamber abscess, in conjunction with the iris. (C) Occluded pupil with iatrogenic damage after removal of the connective tissue.

Figure 4. More than 24 months after keratitis onset, the patient presented a transparent donor cornea, a thin, translucent sclera in the upper hemisphere, an IOL in the bag, and a clear red fundus reflex.