Title

Tube-shunt related, non-tuberculosis Mycobacterial endophthalmitis: A case series and review of the literature

Journal

INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, 65(7)

ISSN

0146-0404

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Publication Date

2024

Peer reviewed

Journal of VitreoRetinal Diseases

Three Cases of Mycobacteria Endophthalmitis Associated With Exposed Tube Shunts

Journal:	*Journal of VitreoRetinal Diseases*
Manuscript ID	JVRD-24-0255
Manuscript Type:	Case Report
Date Submitted by the Author:	07-Dec-2024
Complete List of Authors:	Pandey, Bhagyashri; The University of Texas Southwestern Medical Center, Ophthalmology Chernyak , Michelle ; UCI Medical Center, Ophthalmology Huang, Jennifer ; UCI Medical Center, Ophthalmology He, Yu-Guang; The University of Texas Southwestern Medical Center, Ophthalmology Kuppermann, Baruch; UCI Medical Center, Ophthalmology Mehta , Mitul ; UCI Medical Center, Ophthalmology Wang, Angeline; The University of Texas Southwestern Medical Center, Ophthalmology
Keywords:	non-tuberculosis mycobacteria, Endophthalmitis, exposed tube shunts, case series
Abstract:	Purpose: To describe the clinical course of patients who developed non-tuberculosis mycobacteria endophthalmitis (NTME) associated with exposed glaucoma tube shunts. Methods: Retrospective, noncomparative case series of patients from two institutions. Results: Three patients (59M, 71M, and 79F) were identified to have glaucoma tube shunt-related NTME. Patients presented with persistent inflammation, which progressed to hypopyon and/or fibrinous intraocular white strands. Endophthalmitis was diagnosed 177, 24, and 204 days from presentation. Patients received 16, 3, and 3 intravitreal amikacin injections and required definitive therapy with pars plana vitrectomy (PPV), glaucoma device explanation, and intraocular lens removal. Despite aggressive interventions, follow-up visual acuity ranged from counting fingers to no light perception. Conclusions: Providers should have a high degree of suspicion of NTME in patients with complicated ocular histories, multiple intraocular surgeries

	and persistent intraocular inflammation. Diagnosis should be expeditiously followed by targeted intravitreal antibiotic injections, PPV, and/or removal of culpable intraocular implants.

Three Cases of Mycobacteria Endophthalmitis Associated With Exposed Tube Shunts

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: Research to Prevent Blindness Challenge Grant.

Ethical Approval

This case series was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed with HIPAA (Health Insurance Portability and Accountability Act) compliance.

Statement of Informed Consent

Informed consent was performed prior to performing all procedures or surgeries. Informed consent was obtained from one patient for inclusion in the case series; the other two patients had relocated and could not be contacted despite multiple attempts.

Abstract

Purpose

To describe the clinical course of patients who developed non-tuberculosis mycobacteria endophthalmitis (NTME) associated with exposed glaucoma tube shunts.

Methods

Retrospective, noncomparative case series of patients from two institutions.

Results

Three patients (59M, 71M, and 79F) were identified to have glaucoma tube shunt-related NTME. Patients presented with persistent inflammation, which progressed to hypopyon and/or fibrinous intraocular white strands. Endophthalmitis was diagnosed 177, 24, and 204 days from presentation. Patients received 16, 3, and 3 intravitreal amikacin injections and required definitive therapy with pars plana vitrectomy (PPV), glaucoma device explanation, and intraocular lens removal. Despite aggressive interventions, follow-up visual acuity ranged from counting fingers to no light perception.

Conclusions

Providers should have a high degree of suspicion of NTME in patients with complicated ocular histories, multiple intraocular surgeries, and persistent intraocular inflammation. Diagnosis should be expeditiously followed by targeted intravitreal antibiotic injections, PPV, and/or removal of culpable intraocular implants.

Introduction

Mycobacterium chelonae, a type of non-tuberculosis mycobacteria (NTM), is recognized as a culprit of infectious keratitis, scleritis, chronic uveitis, and endophthalmitis[1–5] . Risk factors for non-tuberculosis mycobacterial endophthalmitis (NTME) include multiple intraocular surgeries, penetrating ocular trauma, immunosuppressive therapy, ocular surface disease, and corneal transplantation[2,6]. The highest incidence of exogenous NTME is seen following cataract extraction and intraocular lens (IOL) implantation although keratoprosthesis and corneal transplant have also been noted to precede NTME [2,3,6–11]. Treatment typically requires intravitreal amikacin, pars plana vitrectomy (PPV), systemic antibiotic therapy, and removal of the IOL, the lens capsule complex, and infected grafts[3,7–9].

There are limited reports of glaucoma drainage implants associated with NTME[4,12,13]. This study reports three patients who developed NTME secondary to exposed or eroded tube shunts. This case series seeks to highlight clinical presentations, risk factors, diagnostic modalities, and therapeutic strategies with suggestions for improvement and standardization of care for these patients.

Methods

This is a retrospective chart review of three patients diagnosed with NTME between 2017 and 2019 who were treated at the University of California Irvine Medical Center and University of Texas Southwestern Medical Center.

Case Descriptions

Case 1

A 59-year-old man with a history of pseudophakia, glaucoma tube shunt surgery and penetrating keratoplasty presented with blurry vision, photophobia, and pain of the right eye. VA was 20/50, and the patient was noted to have mild anterior chamber (AC) cell. The patient was initially treated for corneal graft rejection with prednisolone drops. After one month, VA decreased to 20/200; exam showed exposure of the tube shunt at the limbus, leading to subsequent tube shunt revision. The patient's post-operative course was complicated by persistent scleritis, keratic precipitates, AC cell, vitreous cell, and cystoid macular edema (CME). Treatment with difluprednate drops resulted in improvement in inflammation.

Five months after tube shunt revision, the patient presented without bleb leak but with clumps of white material on the corneal endothelium thought to be an early hypopyon [Figure 1A], purulent debris surrounding the tube in the anterior chamber angle, and vitritis. The patient underwent vitreous aspiration and intravitreal injection of vancomycin and ceftazidime for empiric treatment of endophthalmitis. No growth was detected from the vitreous specimen. Addition of oral steroids improved inflammation and hypopyon but worsened CME. Intravitreal dexamethasone injection was performed to improve CME but resulted in worsening of AC and vitreous inflammation. The patient was diagnosed with chronic endophthalmitis associated with the existing tube shunt. Repeat vitreous aspiration and intravitreal injection with vancomycin and ceftazidime was performed followed by PPV, dexamethasone implant removal, and glaucoma tube shunt removal. The vitreous fluid and glaucoma shunt were sent for culture, which showed no growth, but PCR of vitreous fluid detected *M. chelonae* DNA.

Further treatment included a series of intravitreal amikacin 400 mcg/0.1 mL injections (16 total) and oral clarithromycin 500 mg daily for two months. The patient had resolution of

inflammation but continued to have CME. After one year, the patient was noted to have worsened AC inflammation with concerns for recurrent *M. chelonae* infection but subsequent cultures and PCR testing were negative. The IOL complex was suspected as a potential source of chronic infection, so the patient underwent intraocular lens removal (IOL-R). Vision progressed to no light perception (NLP) secondary to persistently elevated intraocular pressure.

Case 2

This 71-year-old man had an extensive preceding ocular history including ocular surface reconstruction, secondary scleral-fixed IOL, and Baerveldt glaucoma drainage device placement (Johnson & Johnson Surgical Vision, Jacksonville, FL) in the left eye following an alkali chemical injury. The course was further complicated by exposure keratoconjunctivitis and recurrent epithelial defects necessitating bilateral tarsoconjunctival onlay flaps, a keratolimbal allograft of the left eye, and penetrating keratoplasty of the left eye. The patient was placed on mycophenolate mofetil and prednisolone drops to prevent rejection in addition to maximum medical therapy for intraocular pressure management. Baseline VA was counting fingers left eye.

While the patient was being treated for recurrent corneal epithelial defects, he presented with decreased vision to hand motion. This was thought to be due to corneal graft rejection as the patient had corneal graft haze with a large epithelial defect. Two weeks later, examination showed large white adherent strands in the AC [Figure 1C] and exposure of the glaucoma tube shunt. B-scan ultrasound demonstrated vitritis and extensive vitreous membranes. The patient received urgent vitreous aspiration and intravitreal injection of empiric intravitreal vancomycin, ceftazidime, and amphotericin B. He was continued on prednisolone drops and mycophenolate.

Fungal cultures grew *M. chelonae*. The patient received two doses of intravitreal amikacin 0.4mg/0.1mL followed by pars plana vitrectomy, glaucoma tube shunt removal, tractional retinal detachment repair [Figure 1D] with use of temporary keratoprosthesis, and an additional amikacin injection intraoperatively. The patient was treated with a short course of intravenous tobramycin, oral levofloxacin, and oral clarithromycin for 3 months. Post-operatively, the patient progressed to NLP.

[insert Figure 1.]

Case 3

A 79-year-old female presented with a history of pseudophakia, glaucoma with tube shunt placement, and recurrent anterior uveitis that started one year after placement of the tube. On presentation, the patient had 20/100 VA in the right eye with keratic precipitates, AC cell, and vitreous cell and haze. Uveitis work-up was unremarkable. Pre-existing difluprednate drops were increased in frequency and valacyclovir 1 gram twice daily was added for empiric viral coverage. The patient showed improvement in inflammation.

Two months later, exam revealed erosion of her glaucoma tube, so she underwent tube revision. Post-operatively, she had recurrence of inflammation with significant AC cell. This was initially responsive to difluprednate and subtenon's Kenalog injection but then worsened with development of small hypopyon, for which oral prednisone was started. The inflammation continued to worsen, and the patient was treated with a series of three injections of intravitreal vancomycin and ceftazidime weekly.

Anaerobic and fungal cultures speciated *Propionibacterium acnes* and *M. chelonae*. Subsequent surgical intervention [Figure 1B] included PPV, AC washout, glaucoma tube shunt removal, IOL-R, and intraoperative intravitreal vancomycin and amikacin. Specimens from the periocular fluid, anterior chamber fibrin, glaucoma implant, and vitreous washings confirmed *M. chelonae* endophthalmitis. Patient underwent two additional intravitreal amikacin and vancomycin injections. Visual acuity at last follow-up was counting fingers with no inflammation. Table 1 further summarizes and describes the three cases.

[insert Table 1.]

Discussion

Endophthalmitis is a rare, devastating event that can follow intraocular surgery. Although infection rates have decreased over the past decade, postoperative endophthalmitis is still estimated to occur at a rate of about 1.36 per 1000 cataract surgeries with concomitant retinal and glaucoma surgeries conferring a 2.60 and 1.40 increase in odds of endophthalmitis respectively[14]. Although uncommon, tube shunt exposures confer considerable risk of endophthalmitis. The rate of tube exposure varied from 0 to 12% in a meta-analysis of 3105 glaucoma patients who underwent tube shunt implantations[15,16]. Another study of 702 patients undergoing tube shunt implantation reported an exposure rate of 5.8% (n=41) which resulted in intraocular infections in 16.3% of exposures[15].

Amongst cases of tube shunt related endophthalmitis, NTM infections are even rarer and pose unique challenges for diagnosis and treatment. This case series describes three such cases of

NTME. We identified and summarized other case reports of tube shunt related NTME with *M. chelonae*, *M. fortuitum*, and *M. haeophilumin* sub-species [Table 2].

[insert Table 2.]

Patients with NTME may present with eye pain, redness and decreased vision[6,17–19]. Previous reports suggest that NTME presents at an average of 11.5 weeks from initial surgery with an upper limit of 16 months [19,20]. Presentation can include conjunctival injection, corneal edema, keratic precipitates, cell, flare, hypopyon, or scleral melt [6,17,18,21,22]. Early in the infection, intraocular inflammation can mimic chronic uveitis or persistent post-operative inflammation. Fluffy endo-exudates and white opacifications within the capsular bag or anterior vitreous often prompt an investigation for fungal, *Propionibacterium acnes,* or other causes of bacterial endophthalmitis[6,8,9,17,18,21,23,24]. Delay to final diagnosis has been reported to be a median of 18 days but up to one year[6].

Laboratory diagnosis of NTM infections can be challenging. Literature has shown multiple initial negative cultures in cases where NTME was only confirmed after histologic examination of tissue retrieved from the eye during surgical interventions[9,21,24]. Acid-fast bacilli are fastidious organisms, requiring careful specimen processing, optimal temperatures, specialized reagents such as Lowenstein-Jensen media, and prolonged colony growth for up to 6 weeks[25]. Rapidly growing mycobacteria, such as *M. chelonae*, should grow on conventional media within 7 days; infection by slow growers is more likely to be missed as culture plates are commonly disposed after a week[18]. In two of our cases, *M. chelonae* grew in fungal cultures on days 10 and 13 (AFB cultures were not sent at NTM was not initially suspected). Based on our

experience, in cases where NTME is suspected, we recommend communicating with the lab to keep the culture plates longer than the standard period.

Negative culture does not always correlate with absence of NTM infection. In our first case, the initial vitreous specimen was negative on infectious testing. In that case, broad range or universal PCR testing offered through the University of Washington (*Nontuberculous Mycobacteria DNA Detection panel*) was critical in diagnosis; the results were available on day 5, faster than typical culture results. Multiple molecular methods such as quantitative PCR (q-PCR), arbitrarily primed PCR (AP-PCR), reverse-transcription PCR (RT-PCR), PCR restriction fragment analysis, 16S rRNA gene sequencing, rpoB identification, and *hsp65* gene sequencing could help to rapidly identify mycobacterial species[15,25–32].

Intravitreal amikacin injections, systemic antibiotics, and removal of implants in the affected eye are the mainstays of therapy. Mycobacterial endophthalmitis requires high concentrations of antibiotics within the vitreous humor, which can be difficult to maintain[21,33]. The average number of intravitreal amikacin injections given to patients in one study was 9.9 injections over an average of 3.3 months[17].

Within NTMs, the *M. chelonae-abscessus* group is capable of biofilm formation, causing high rates of antibiotic resistance[6,19,33–37]. Combined PPV, IOL-R, and tube shunt removal may help prevent recurrence by removing biofilms[4,9,17,26,38,39]. Barkmeier et al. presented a patient with NTME who had intractable inflammation despite removal of the exposed glaucoma implant, vitrectomy, systemic antibiotic therapy, and 20+ amikacin injections[3]. A lens capsular complex remnant was found on ultrasound; after removal with vitrectomy and an additional 6 months of oral clarithromycin, visual acuity improved to 20/80[3]. This suggests complete IOL-R with removal of the capsule is needed to eliminate infection[4,7].

Systemic regimens for NTME in literature consist of a combination of oral antibiotics such as macrolides, fluoroquinolones, and aminoglycosides for at least 3 months and up to 1 year[4,6,26,38]. In some cases, intravitreal amikacin was used for rapid intraocular therapy followed by intravenous amikacin acting as maintenance therapy[4,26,38].

In our patients, prior extensive corticosteroids use could explain the lengthy course of treatment and poor visual outcomes despite aggressive interventions. According to Kheir et al.'s review of 174 NTM ocular infections, eyes that were exposed to steroids prior to exact diagnosis had a 3 times increased likelihood of a prolonged course of infection, reduced response to medical intervention, and decreased possibility for resolution[17,20].

Visual outcomes in NTME are typically poor due to delayed diagnoses and difficulty in clearing the infection. Out of 15 patients reviewed between eight different case reports including this one [Table 2], three patients had visual acuity better than 20/200.

Conclusion

NTME represents a small number of tube shunt related infections with devastating outcomes and often irreversible vision loss. Through our case series and literature review, we suggest a high degree of suspicion for NTME when observing patients with persistent intraocular inflammation, history of multiple intraocular surgeries, device implantation, and immunodeficiency. In patients with glaucoma drainage implants, providers should thoroughly examine the tube shunts and overlying conjunctiva for possible erosion. For diagnosis and differentiation of NTM species, we recommend a combination of PCR testing and culture with maintenance of culture plates for an extended duration to detect slower-growing NTM. To clear the infection and prevent recurrence, we recommend complete surgical debridement, frequent intravitreal amikacin injections, and prolonged systemic antibiotics.

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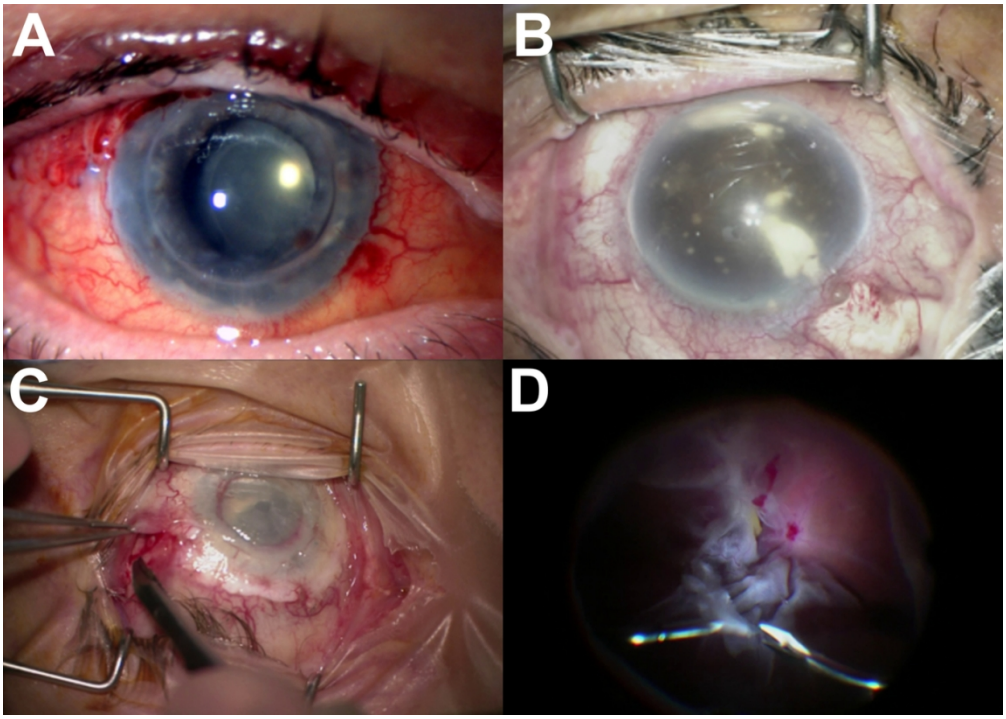

Figure 1: Clinical Photographs of Mycobacteria Endophthalmitis Patients.
A. Slit lamp photo of case 1 showing early hypopyon formation. B. Surgical video screenshot of case 3 demonstrating thick iris membrane and white purulent material in the anterior chamber. C and D. Surgical video screenshots of case 2 showing opacified cornea and white infectious material in the anterior chamber and tractional retinal detachment.

117x83mm (300 x 300 DPI)

Case Number	1	2	3
Age/Gender/Laterality	59/M/OD	71/M/OS	79/F/OD
Systemic Disease	Arthritis, gout	Type II diabetes, hypertension, hyperlipidemia, chronic kidney disease	Ventriculoperitoneal shunt for normal pressure hydrocephalus
Ocular History	Epiretinal membrane, pseudophakia, keratoconus, PKP, secondary glaucoma with tube shunt	Alkali chemical injury with corneal perforation, globe repair, PKP, limbal stem cell deficiency, non-healing epithelial defects, scleral-fixed IOL, exposure keratoconjunctivitis, secondary glaucoma with tube shunt	Steroid-responsive anterior uveitis, pseudophakia, primary glaucoma with tube shunt
Immunosuppression	Difluprednate, prednisolone, dexamethasone intravitreal implant, oral prednisone	Mycophenolate mofetil, prednisolone, oral prednisone	Difluprednate, subtenon Kenalog, oral prednisone
Symptoms	Decreased vision, photophobia, pain	Decreased vision, absent pain	Decreased vision, absent pain, absent redness
Initial VA	20/50	HM	20/100
Exam findings	AC cell and flare, keratic precipitates, vitritis, scleritis, CME	Large white adherent strands in the AC, vitritis and membranes on B-scan ultrasound	Keratic precipitates, AC cell, vitritis with vitreous clumps and haze
Presence of hypopyon	Yes	No	Yes
Confirmatory lab test/source	PCR/vitreous tap	Fungal culture/vitreous tap	Fungal culture/vitreous tap
Time until positive result	5 days	13 days	10 days
Type of IAI (number)	A (16), V + C (3), Dx (1)	A (3), V + C + amphotericin B (1)	A + V (3), V + C (2)
Interval between presentation and diagnosis of endophthalmitis	177	24	204
Interval between presentation and first PPV (days)/total # of PPV	225/2	26/1	218/1
Interval between presentation and tube shunt removal (days)	225	26	218

Interval between presentation and IOL-R (days)	460	26	218
Medical management	Oral clarithromycin	IV tobramycin, oral levofloxacin, oral clarithromycin	—
Duration of systemic antibiotics (months)	2	3	—
Complications	—	Tractional retinal detachment	Co-morbid P. acnes endophthalmitis
Other surgical interventions	—	RD repair with silicone oil insertion, temporary keratoprosthesis, PKP	—
Final VA	NLP	NLP	CF

Table 1: Description of three non-tuberculosis Mycobacterial endophthalmitis cases.
M=Male, F=Female, PKP=Penetrating keratoplasty, IOL=Intraocular lens, AC=Anterior chamber, CME=Cystoid macular edema, A=Intravitreal amikacin, V=Intravitreal vancomycin, C=Intravitreal ceftazidime, IV=Intravenous, PPV=Pars plana vitrectomy, LP=Light perception, NLP=No light perception, CF=Counting fingers.

Source	Age/Sex	Ocular history	Initial visual acuity	Final visual acuity	Organism (Source)	Primary Treatment	Implant removal	Number of intravitreal Amikacin	Systemic therapy
Huang et al, 2024	59M	Post-GDI exposure (BV), keratoconus, PKP, CEIOL	20/50	NLP	M chelonae (Vit)	PPV + GDI-R + IOL-R + (A + V + C + Dx)	GDI-R + IOL-R	16	Oral clarithromycin (8 weeks)
	71M	Post-GDI exposure (BV), alkali injury, LSCD, scleral-fixed IOL, PKP	HM	NLP	M chelonae (Vit)	PPV + GDI-R + IOL+R + PKP + IOAB (A + V+ C + AmpB)	GDI-R + IOL-R	3	Intravenous tobramycin (8 weeks); oral levofloxacin, clarithromycin (6 months)
	79F	Post-GDI exposure (BV), CEIOL, anterior uveitis	20/100	CF	M chelonae, P acnes (Vit)	PPV + CDI-R + IOL-R + IOAB (A + V + C)	GDI-R + IOL-R	3	None
Sevcik KM et al, 2022	73F	Post-GDI exposure (Ahmed)	---	---	M chelonae (Vit)	PPV + GDI-R + IOAB (V + C + Vo)	GDI-R	0	None
Pinitpuwadol et al, 2020	61M	Post-GDI exposure (BV), trabeculectomy (4)	20/100	20/60	M fortuitum (Vit)	PPV + GDI-R + IOAB (V + C)	GDI-R	>1	Intravenous amikacin, cefoxitin, levofloxacin; oral clarithromycin, levofloxacin (6 months)
Xin C et al ,2020	45M	Post-GDI exposure (Ahmed)	NLP	---	M houstonense (Enucleation)	Enucleation	GDI-R	0	Intravenous clindamycin (10 days), intravenous amikacin (1 week), oral levofloxacin (40 days)
Shah et al, 2016	68F	Post-GDI, PKP	HM	3/200	M chelonae (Vit)	PPV + Capsulectomy	IOL-R	0	None

						+ IOAB (V + Dx)			
	76F	Post-GDI	20/100	HM	M chelonae (AC)	GDI-R + IOAB (V + A)	GDI-R	24	Oral clarithromycin (4 weeks)
	23M	Post-GDI	2/200	20/300	M chelonae (Vit)	GDI-R + AC tap	GDI-R	3	Oral clarithromycin (1 week)
	65M	Post-GDI	HM	HM	M chelonae (Vit)	GDI-R + AC tap + IOAB (V + C + Dx)	GDI-R	2	None
	35F	Post-GDI	HM	20/60	M fortuitum (Vit)	GDI-R + IOL-R + Vitreous tap + IOAB (V + C + Dx)	GDI-R + IOL-R	4	Oral ciprofloxacin (2 weeks)
	86M	Post-GDI	HM	HM	M fortuitum (AC)	GDI-R + IOAB (V + C + Dx)	GDI-R + IOL-R	1	Intravenous levofloxacin (1 week)
Barkmeir AJ et al, 2013	72F	Post-GDI exposure, aphakia	HM	20/100	M chelonae (Vit)	PPV (2) + GDI-R + IOAB (A)	GDI-R	>20	Intravenous tigecycline, oral azithromycin, oral clarithromycin (6 months)
Rao A, et al 2013	13M	Post-GDI exposure with AMT (Ahmed)	HM	CF	M fortuitum, S pneumoniae (Vit)	GDI-R + Vitreous tap + IOAB (Cf + A)	GDI-R	1	None
Scott IU et al, 2003	70F	Post-GDI exposure (2) (BV), ACIOL with pseudophakic bullous keratopathy, PKP (2)	HM	3/200	M chelonae (Vit)	GDI-R + Anterior vitrectomy + IOAB (Cf + C + Dx)	GDI-R	0	Oral clarithromycin (8 weeks)

Table 2: Summary of case reports from 2000 - 2023, adapted from *Shah et al*, 2016.
M=Male, F=Female, GDI=Glaucoma drainage implant, GDI-R=Glaucoma drainage implant removal, BV= Baerveldt, PKP=penetrating keratoplasty, IOL=Intraocular lens, IOL-R=Intraocular lens removal, LSCD=Limbal stem cell deficiency, CEIOL=Cataract extraction and intraocular lens placement, Vit=Vitreous, ACIOL=Anterior chamber intraocular lens, AC=anterior chamber, CME=cystoid macular edema, IOAB=Intraocular antibiotic, A=Intravitreal amikacin, V=Intravitreal vancomycin, C=Intravitreal ceftazidime, Dx=Intravitreal dexamethasone, Cf=Intravitreal cefazolin, Vo=Intravitreal voriconazole, IV=Intravenous, PPV=Pars plana vitrectomy, LP=Light perception, NLP=No light perception, CF=Count fingers.