

# Clinical Characteristics of Elizabethkingia meningoseptica Ophthalmic infections

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## Original research

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# Abstract

**Background:** *Elizabethkingia* is a Gram-negative, obligate aerobic, oxidase positive bacillus that is known to cause a variety of nosocomial infections and has emerged as an important pathogen because of multiple anti-microbial resistance. We present the first case series of *Elizabethkingia* ophthalmic infections, with specific emphasis on its clinical spectrum, risk factors, treatment and outcome.

**Method:** Microbiological specimens growing *Elizabethkingia* were reviewed retrospectively at a regional tertiary hospital from 2005-2019. Clinical manifestation, risk factors, treatment including types of antibiotics, treatment duration and clinical outcome were documented.

**Results:** Ten cases of culture positive *Elizabethkingia* ophthalmic infection were identified, which all cultured *E. meningoseptica*. Four cases of keratitis, three cases of conjunctivitis, two cases of blepharitis and one case of blepharitis-conjunctivitis were observed. Four cases were found to be associated with contact lens use and were discovered to colonize *E. meningoseptica*. One case of blepharitis was associated with an ocular prosthesis (scleral shell) in an eviscerated eye. Fluoroquinolone and chloramphenicol were most commonly used topical antibiotics for treatment. The mean treatment duration for all infections were averaged at 6.5 weeks.

**Conclusion:** *E. meningoseptica* is the predominant species that causes ophthalmological related *Elizabethkingia* infections and is found most frequently manifested on the ocular surface. Contact lens use and ocular prosthesis appears to be a risk factor for infection due to ocular surface barrier disruption and bacteria colonization. Combination of fluoroquinolone and chloramphenicol is a safe and effective treatment against *Elizabethkingia* ocular infections. Further studies are required to determine the susceptibility of commonly used topical anti-microbial agents to *Elizabethkingia* species.

## Introduction

*Elizabethkingia* is a Gram-negative, obligate aerobic, oxidase positive, non-glucose fermenting bacillus that is widely available in nature and is increasingly being identified to survive on hospital surfaces and medical equipment [1–4]. *Elizabethkingia* is known to cause a variety of nosocomial human infections and has emerged as a clinically important pathogen because of its resistance to multiple anti-microbial agents [4–7]. Ophthalmological related *Elizabethkingia* infections are increasingly being reported where use of contact lens, trauma, ocular surgery and ocular surface disorders were associated [8–11]. Standardized management, choice of anti-microbial treatment and prognosis of *Elizabethkingia* ocular infections are lacking due to paucity of cases. We present the first case series of *Elizabethkingia* induced ophthalmic infections, with specific emphasis on its clinical spectrum, risk factors, treatment and outcome.

## Materials And Methods

Microbiological specimens growing *Elizabethkingia* were reviewed retrospectively in a regional tertiary hospital from 2005-2019. Positive *Elizabethkingia* isolates from eye swabs, corneal scrapping and bacterial culture for contact lens in respective cases were retrieved from the hospital microbiological database. All clinical specimens were collected and handled according to standard protocols. *Elizabethkingia* was first identified by conventional phenotypic method. Gram-negative bacilli were initially recovered from the specimens. These isolates were incubated on sheep blood agar for 24 hours which gave rise to yellowish, semi-translucent, convex shaped small colonies. No growth was observed after incubation on MacConkey agar. Extracted non-motile Gram-negative rods were then examined biochemically that yielded catalase positivity and oxidase positivity, which were further characterized using VITEK GN (Gram-negative) card and matrix-assisted laser-desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) VITEK-2 system (Biomerieux Vitek, Hazelwood, MO, USA). Acanthamoeba and fungi were also tested on all cases using direct microscopy, polymerase chain reaction (PCR) and real-time PCR. Antibiotic susceptibility of the samples was not examined as VITEK-2 system Gram negative antibiotic testing card at the institution do not cover most of the topical antibiotics used in the study.

Clinical data and hospital charts were reviewed retrospectively. Patient demographics including age, gender and past medical history were recorded. Diagnosis were clinical and supplemented by microbiological finding. Treatment including types of antibiotics, total number of antibiotics used, treatment duration and clinical outcome were documented. The study has received approval from the hospital ethics committee and adhere to the principles of the Declaration of Helsinki.

## Results

Thirteen cases of culture positive *Elizabethkingia* species in ocular microbiological specimen were identified. Two cases were excluded because of lost to follow up. One case was excluded due to incomplete data. Six eye swab culture samples, four corneal scrapping samples and four bacterial culture samples for contact lens were obtained. The mean age of patients being infected by *Elizabethkingia* was 57 years old (age range 16 days old- 91 years old). The female to male ratio was 6:4. One patient had a history of underlying pancytopenia, bullous pemphigoid and pre-existing type 2 diabetes. Three other patients had co-existing type 2 diabetes and ischemic heart disease. No apparent immunosuppressive states were noted in others.

The findings were summarized in the Table 1. All ten cases have cultured *E. meningoseptica* and tested negative for fungal infection. Case 6 and 8 showed co-isolates of coagulase negative Staphylococcus. Four eyes resulted in keratitis, where three eyes were affected by conjunctivitis, two by blepharitis and one by concurrent blepharitis- conjunctivitis. Keratitis was typically observed to present clinically as a paracentral epithelial defect measuring between 0.5mm to 4mm. The borders were ill-defined and all cases were associated with localized corneal oedema, stromal infiltration, peripheral pannus formation and perilimbal injections. One case was complicated by development of corneal abscess, with deposition of puriform deposits deep in stroma. No associated hypopyon has been observed. Clinical characteristics of

*E. meningoseptica* induced conjunctivitis and blepharitis were characterized by marked conjunctival injection and mucopurulent discharges. Blepharitis was in addition characterized by erythema and swelling of eye lid margins, fine telangiectasia formation and tear film instability, without eyelash involvement.

Table 1 Summary of clinical syndrome associated with Elizabethkingia associated ocular infection and treatment outcome.

NUMBER OF PATIENTS	AGE (years)	GENDER	CULTURE	DIAGNOSIS	BACKGROUND	ANTIBIOTICS EYE DROP	ORAL ANTIBIOTICS
1	36	M	Elizabethkingia meningoseptica	Keratitis; Corneal abscess	Nil	Levofloxacin; ofloxacin; chloramphenicol	None
2	55	F	Elizabethkingia meningoseptica	Blepharitis	Eviscerated eye secondary to conjunctival tumor. Orbital prosthesis (scleral shell) in situ	Levofloxacin; chloramphenicol	Ciprofloxacin
3	32	M	Elizabethkingia meningoseptica	Keratitis	Nil	Chloramphenicol; levofloxacin; ofloxacin; gentamicin	Ciprofloxacin
4	45	F	Elizabethkingia meningoseptica	Keratitis	Nil	Moxifloxacin; ofloxacin; gentamicin; fusidic acid	Doxycycline
5	42	F	Elizabethkingia meningoseptica	Keratitis	Nil	Levofloxacin; ofloxacin	Clarithromycin; doxycycline
6	91	F	Elizabethkingia meningoseptica	Blepharitis- conjunctivitis	Type 2 diabetes; ischemic heart disease	Levofloxacin; fusidic acid	None
7	16 days	M	Elizabethkingia meningoseptica	Conjunctivitis	Nil	Chloramphenicol; neosporin	None
8	68	M	Elizabethkingia meningoseptica	Blepharitis	Pancytopenia; Type 2 diabetes; bullous pemphigoid	Levofloxacin; tobramycin	None
9	57	F	Elizabethkingia meningoseptica	Conjunctivitis	Type 2 diabetes; ischemic heart disease; heart failure;	Chloramphenicol; moxifloxacin	None
10	83	F	Elizabethkingia meningoseptica	Conjunctivitis	Type 2 diabetes; congestive heart failure	Chloramphenicol; fusidic acid	Nil

All four cases of keratitis were associated with contact lens use, with one case of keratitis complicated by development of corneal abscess secondary to trauma to the eye. Three blepharitis cases were recorded, where one case of blepharitis had a history of evisceration and an ocular prosthesis (scleral shell) in situ, one had a history of pancytopenia and bullous pemphigoid, whilst another one developed blepharitis six weeks after same eye cataract operation whilst using topical steroids for prolonged anterior chamber inflammation. Three cases of conjunctivitis were recorded, in which two cases had a background of type 2 diabetes and history of heart disease. No cases of conjunctivitis had reported use of contact lens or

trauma prior to infection. The clinical outcome of conjunctivitis and blepharitis were satisfactory with clinical resolution after treatment. All keratitis cases resulted in corneal scar.

Contact lens were also examined microbiologically in all respective cases. Four cases have cultured *E. meningoseptica*. Tests for fungal infection in all cases were negative.

All cases in the study were treated with topical medications in drop and ointment form. The average number of topical antibiotics class used were two (range 2-4). Fluoroquinolone (levofloxacin, moxifloxacin, ofloxacin) and chloramphenicol were most commonly used topical antibiotics for treatment. Topical Fusidic acid, Gentamicin and Neosporin were added in five other cases. Four cases of ocular infection included systemic oral antibiotics (ciprofloxacin, doxycycline and clarithromycin) as part of the treatment regime (three cases of keratitis, one case of blepharitis with ocular prosthesis in situ). The average duration of treatment were 6.5 weeks (range 4-12 weeks).

## Discussion

*Elizabethkingia* is an important saprophyte that has grown much attention in recent years due to its ability to cause clinically significant infections and resistance to multiple anti-microbial agents [1–4]. Limited cases of ocular *Elizabethkingia* infections have been reported, where contact lens use, trauma, previous ocular surgery and ocular surface disorders appeared to be important risk factors [8–12]. We present the largest series of *Elizabethkingia* infection that has manifested in eyes. The spectrum of *Elizabethkingia* ocular infections is wide and mostly confined to the ocular surface. In our series, 40% (4/10) of cases resulted in keratitis, whereas 30% (3/10) caused conjunctivitis, 20% blepharitis (2/10) and 10% as concurrent blepharitis- conjunctivitis (1/10). The clinical characteristics of *Elizabethkingia* echoed with previous reports and is found confined to the ocular surface. Previously reported *Elizabethkingia* induced endophthalmitis was not found in our series and no intraocular infections were identified [13, 14]. To date, six species of *Elizabethkingia* have been identified: *E. meningoseptica*, *E. miricola*, *E. anopheles*, *E. bruuniana*, *E. ursingii*, and *E. occultia* [15]. *E. anopheles* has traditionally been shown to be the predominant strain that causes life threatening bacteremia and neonatal meningitis, where *E. meningoseptica* and *E. miricola* are known to cause biliary tract infections [16]. In our series, *E. meningoseptica* has been established to be the major species that caused ocular infection. The reason for the “ophthalmic strain” and predominance is unknown and yet to be determined.

The association of *Elizabethkingia* induced keratitis and contact lens is demonstrated in our study. Contact lens predisposes the cornea to microtrauma and hypoxia which disrupted the corneal epithelium and barrier to bacterial binding. In addition, biofilm formation and pathogen colonization on contact lens also potentiated the infection. This is confirmed in our study, where respective contact lens has cultured the same pathogen. The ability of *Elizabethkingia* to attach on contact lens, cases and water supplies is an important factor for development of ocular infections [3, 4]. Mechanisms including substandard contact lens hygiene, extended wear and trauma may also play a role in the potentiating the infection.

The association between orbital surgery and *Elizabethkingia* infection are also being reported for the first time. Previous reports have documented *Elizabethkingia* infections to occur after intraocular surgeries e.g. penetrating and lamellar keratoplasty [17, 18]. The authors believed history of previous orbital surgeries may be linked with development of ocular surface *Elizabethkingia* infections. In one of our case, an ocular prosthesis (scleral shell) presents as a risk factor for development of blepharitis in an eviscerated eye, as *E. meningoseptica* may have colonized the foreign body and acted as a reservoir for the pathogen. We speculate that the uneven surface of the acrylic prosthesis allowed bacterial attachment and subsequent biofilm formation, which created a barrier against removal from normal cleansing and sterilization.

The use of topical steroids in the post-operative cataract period may also be linked to *E. meningoseptica* blepharitis. Prolonged topical steroid was prescribed in our case due to anterior chamber inflammation. We suspect that the treatment aggravated the development of *Elizabethkingia* blepharitis, as topical steroid has been shown to delay epithelial healing and inhibit neutrophil activation, which subsequently weakened the ocular surface protective barrier [19, 20]. While chronic co-morbidities have been shown to cause *Elizabethkingia* systemic infections, in our study we could not establish a strong relationship, with only 40% (4/10) of cases identified to have significant past medical histories [21].

Established reports of antibiotics susceptibility on *Elizabethkingia* species have shown resistance to ceftazidime, imipenem and aminoglycosides and susceptibility to ciprofloxacin, cefoperazone-sulbactam and vancomycin treatments [16, 22, 23]. The multiple anti-microbial resistance in *Elizabethkingia* is conferred in  $\beta$ -lactams as a result of possession of Ambler class A serine extended-spectrum  $\beta$ -lactamase (ESBL) gene  $bla_{CME}$  and Ambler class B metallo- $\beta$ -lactamase (MBL) genes  $bla_{BlaB}$  and  $bla_{GOB}$  [24, 25]. Resistance is also seen in quinolones secondary to genetic mutations in DNA gyrase and topoisomerase IV [26]. Empirical treatment using fluoroquinolone, glycopeptide and third-generation cephalosporin with  $\beta$ -lactamase inhibitor have been advocated for treating systemic infections [16, 22, 23].

There is currently no consensus on treatment for *Elizabethkingia* ophthalmic infections. Treatment of ocular infection frequently employ topical route of administration and susceptibility to commonly used topical antibiotics in ophthalmic practice, such as chloramphenicol and fusidic acid, have not been evaluated. Our series has demonstrated that combined use of 2 topical antibiotic, fluoroquinolone and chloramphenicol, could lead to safe and successful treatment of *E. meningoseptica* conjunctivitis, blepharitis and keratitis. The addition of systemic oral antibiotics such as oral quinolones, tetracycline or macrolide have shown to be effective. Levofloxacin, one of the commonly used topical fluoroquinolone in ophthalmological practice, contain a C-8 methoxy group that exert stronger antibacterial activity against fluoroquinolone-resistant bacteria that harbored QRDR mutations [27, 28]. Whether the single agent of topical fluoroquinolone alone enabled treatment success or combination with topical chloramphenicol is not determined. Further studies are required to determine the susceptibility of chloramphenicol to *Elizabethkingia* species. A longer period of treatment for *Elizabethkingia* ocular surface infections was also observed, which averaged at 6.5 weeks in our series. We speculate that this could be due to bacterial intracellular invasion, inability to break multicellular biofilm and ineffective ocular immunity [3, 29]. This

was reflected in the outcome, where conjunctivitis, blepharitis and conjunctivitis-blepharitis confer excellent clinical recovery where keratitis all resulted in corneal scarring.

## Conclusion

In summary, *Elizabethkingia* is an emerging organism that could manifest in eyes and is clinically challenging to treat due to its multiple anti-microbial resistance. Our study have demonstrated *E. meningoseptica* to be the predominant species that causes *Elizabethkingia* ophthalmic infection and is most frequently manifested on the ocular surface. Contact lens use and ocular prosthesis in situ appears to be a significant risk factor due to ocular surface barrier disruption and bacteria colonization. Contrary to previous beliefs, immunosuppressive state has not been shown to be a significant factor for ocular infections. Combination of topical fluoroquinolone and chloramphenicol is a safe and effective treatment regime for *Elizabethkingia* ocular infections. Further studies are required to establish the most effective treatment approach.

## Declarations

Ethics approval and consent to participate- not applicable

Consent for publication- not applicable

Availability of data and material- not applicable

Competing interest- The authors declare that they have no competing interests

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