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Abdullah Umair

Nosheen Nasir

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Clinical features and outcomes of critically ill patients with *Elizabethkingia meningoseptica*: an emerging pathogen

Abdullah Umair¹, Nosheen Nasir²

¹Medical College, Aga Khan University, Karachi; ²Section of Adult Infectious Diseases, Department of Medicine, Aga Khan University, Karachi, Pakistan

Background: *Elizabethkingia meningoseptica*, formerly known as *Chryseobacterium meningosepticum*, is a non-motile, non-fastidious, catalase and oxidase-positive, aerobic, glucose-non-fermentative, Gram-negative bacillus that was first defined by Elizabeth O. King in 1959. It has emerged as an opportunistic pathogen that has infected patients in extreme age groups and immunocompromised individuals, especially in intensive care settings. There has been an increased interest in this pathogen due to its increasing occurrence around the world, ubiquitous nature, and inherent capacity for antimicrobial resistance.

Methods: We describe an observational study at a tertiary care center in Karachi, Pakistan, based on patients admitted between January 2013 and December 2018, with *E. meningoseptica* infections. All patients were confirmed to have a positive clinical culture specimen for *E. meningoseptica* along with symptoms and signs consistent with infection. Data were collected on a structured proforma from the Hospital Information Management Systems.

Results: Sixteen patients with *E. meningoseptica* that met the criteria for infection were identified, 13 of whom required admission. Eight patients had bacteremia in addition to confirmed *E. meningoseptica* infection. Two of the isolates were multi-drug resistant and only sensitive to minocycline. Nine out of 13 patients that were admitted required intubation and mechanical ventilation. The median length of hospital stay was 13 days, and five out of the 13 patients died during the hospital stay.

Conclusion: This is the largest case series to date reporting *E. meningoseptica* infections and highlights the importance of this organism as an emerging nosocomial pathogen.

Key Words: *Chryseobacterium*; *Elizabethkingia meningoseptica*; Nosocomial infection

INTRODUCTION

Elizabethkingia meningoseptica, formerly known as *Chryseobacterium meningosepticum*, is a non-motile, non-fastidious, catalase and oxidase-positive, aerobic, glucose-non-fermentative, Gram-negative bacillus that was first defined by Elizabeth O. King in 1959 [1]. The *Elizabethkingia* genus has been noted due to the genetic makeup that facilitates a large degree of genetic variability and subsequent antimicrobial resistance. This, combined with lack of literature reports on the wide distribution in nature and of adequate treatment regimens have led to high mortality rates in hospital-settings, particularly in intensive care units (ICUs), since 2004 [2].

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Corresponding author

Nosheen Nasir
Section of Adult Infectious Diseases,
Department of Medicine, Aga Khan
University, Stadium Rd, Karachi
74800, Pakistan
Tel: +92-233-3213-3936
Fax: +92-21-3494-6623
E-mail: Nosheen.nasir@aku.edu

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E. meningoseptica is isolated most frequently from soil, salt-water, and freshwater and from dry and moist clinical environmental and equipment surfaces, intravenous lipid solutions, and municipal water supplies, including those adequately chlorinated [3]. Although nearly ubiquitous in nature, it is an uncommon human pathogen. *E. meningoseptica* predominantly causes outbreaks of meningitis in immunocompromised patients, particularly in premature newborns and infants in neonatal ICUs of developing countries [4]. The bacterium is a rare cause of nosocomial pneumonia, endocarditis, and meningitis in immunocompromised adults. More recently, in the past few years, it has been found to cause soft tissue infection and sepsis in immunocompetent adults [5].

In a study from Wisconsin, 48 cases of *Elizabethkingia* infection were reported during an outbreak, which resulted in 17 deaths in a 5-month period beginning in November 2015 [6]. Another case series showed that the yearly incidence of *E. meningoseptica* bacteremia increased substantially from 2002 to 2006 (from 6.8–13.1 to 26.6–39.9 per 100,000 admissions; $P=0.006$) [7].

Moreover, *Elizabethkingia*, similar to its genetic relative *Chryseobacterium* species, is inherently extensively drug resistant. It is resistant to a broad spectrum of antibiotic classes, including macrolides, tetracyclines, linezolid, polymyxin group, chloramphenicol, aminoglycosides, and beta-lactam drugs [8]. Vancomycin, rifampicin, new fluoroquinolones, piperacillin-tazobactam, and minocycline are the current preferred empirical choices for treating *E. meningoseptica* infections.

E. meningoseptica is an important emerging opportunistic bacterium that primarily occurs in nosocomial settings. It is unclear which treatment regimen is most effective and what factors are associated with adverse outcomes. The aim of this study is to describe the clinical features and outcomes of *E. meningoseptica* infections in a tertiary care center in Karachi, Pakistan.

MATERIALS AND METHODS

The study received an exemption from ethical approval from the Aga Khan University Ethics Review Committee (ERC #2019-1786-4439) and requirement of informed consent was waived due to retrospective nature of study. Data was anonymized and no personal identifiers were collected.

This was an observational study of patients admitted between January 2013 and December 2018, with *E. meningoseptica* infections. All patients were confirmed to have a positive clinical culture specimen for *E. meningoseptica* along with

KEY MESSAGES

- *Elizabethkingia meningoseptica* is an opportunistic pathogen infecting people in the extremes of age and the immunocompromised, especially in intensive care settings.
- We are describing the largest case series to date reporting *E. meningoseptica* infections.
- Our study found that *Chryseobacterium meningosepticum* is an emerging nosocomial pathogen causing mortality in patients requiring intensive care and outcomes are better if isolates are susceptible to quinolones.

signs and symptoms consistent with infection. All patients presumed to be colonized but not infected were excluded. Data were collected on a structured proforma from the Hospital Information Management Systems. Identification and susceptibility of *E. meningoseptica* isolated from cultures were performed by automated systems in accordance with Clinical Laboratory Standards Institute recommendations. Identification of *E. meningoseptica* was determined by a Vitek 2 system (bioMérieux, Marcy-l'Étoile, France).

Definitions

Infection was defined based on clinical presentation along with patient-related factors and microbiological diagnosis. The Center for disease control/National Healthcare Safety Network definitions [9] for specific types of infections were used. A multidisciplinary team of doctors including infectious disease consultants, pulmonologists, and intensivists was involved in case identification and management. Patients were considered to be colonized if they had positive culture results for the organism but no signs and symptoms to suggest active infection based on the primary physician evaluation and continued status of good health without treatment. Patients were considered to have co-infection if a clinically significant true pathogen was identified simultaneously from a culture specimen and the patient improved after corresponding treatment. Patients were considered to have co-colonization if the pathogen isolated was a known contaminant or did not produce signs and symptoms consistent with infection. Polymicrobial infection was defined as the presence of another bacteria or fungi in the same culture specimen. Multi-drug resistance was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [10]. Death was confirmed as all-cause mortality during hospitalization.

Statistical Analysis

Data were analyzed using IBM SPSS ver. 19 (IBM Corp., Armonk, NY, USA). Descriptive analysis was performed for demographic features with median and interquartile range values reported for quantitative variables such as age and length of hospital stay, and frequency (percentage) were reported for qualitative variables such as sex, comorbid conditions, mortality, and complications. A P-value ≤ 0.05 was considered statistically significant. Data were kept confidential, and no personal identifiers were used.

RESULTS

Sixteen patients with *E. meningoseptica* infections were identified between 2013 and 2018, 13 of whom required hospital admission, constituting an infection rate of 2.9 per 100,000

admissions. The median age was 29 years for six males and seven females, with ages ranging from 3 days to 83 years. The most common comorbid conditions were diabetes (5/13) and hypertension (5/13). The average Charlson's comorbidity index was 3.3. Three patients had underlying malignancy, and five patients had a history of repeated hospitalization. Eleven patients were admitted to the ICU. Eight of 13 patients had bacteremia with *E. meningosepticum*, and the most common source of bacteremia was central line-associated bloodstream infection in six patients. Among other sites of infection, one had urinary tract infection, two had meningitis, two had pneumonia, and one had infective endocarditis. Nine patients had mono-microbial growth, whereas four had polymicrobial growth in culture. Of 13 patients, eight required a Foley catheter and nine required a central venous catheter, endotracheal intubation, and mechanical ventilation. The clinical characteristics

Table 1. Summary of patients with *Elizabethkingia meningoseptica* infections

No.	Age/sex	Associated disease	Site of infection	Type of strain	Treatment	Outcome
1	Term baby at the 2nd day of life	None	Meningitis	Drug sensitive	Ciprofloxacin	Recovered
2	Preterm 33-week-baby girl brought to NICU at the 3rd day of life	Respiratory distress syndrome, bilateral intraventricular hemorrhage	Bloodstream infection (umbilical vein catheterization)	Drug sensitive	Minocycline	Recovered
3	5 day/F	Subglottic stenosis	Bloodstream infection (source unclear)	Drug sensitive	Levofloxacin	Recovered
4	19 yr/M	SLE, CKD	Central line-associated bloodstream infection	Drug sensitive	Cotrimoxazole	Recovered
5	22 yr/M	Status post-RTA with anoxic brain injury, craniotomy, tracheostomy, liver injury	Central line-associated bloodstream infection	Multi-drug resistant	Minocycline	Recovered
6	25 yr/F	Pregnancy induced hypertension, post-partum hemorrhage	Urinary tract infection	Drug sensitive	Cefixime	Recovered
7	29 yr/M	Dengue hemorrhagic fever	Central line-associated Bloodstream infection	Drug sensitive	Meropenem	Recovered
8	41 yr/F	DM, HTN, APLA syndrome, left MCA stroke	Bloodstream infection (infective endocarditis)	Multi-drug resistant	Minocycline	Death
9	54 yr/F	DM, HTN, esophageal carcinoma	Hospital-acquired pneumonia	Drug sensitive	Levofloxacin	Death
10	58 yr/M	DM, HTN, IHD	Hospital-acquired pneumonia	Drug resistant	Cotrimoxazole	Death
11	65 yr/F	DM, CLD, glioblastoma grade IV	Central line-associated bloodstream infection	Drug sensitive	Minocycline	Death
12	76 yr/F	DM, HTN, IHD, CKD	Meningitis	Drug sensitive	Levofloxacin+cotrimoxazole	Recovered
13	86 yr/M	DM, HTN, IHD	Central line-associated bloodstream infection	Drug sensitive	Levofloxacin	Death

NICU: neonatal intensive care unit; SLE: systemic lupus erythematosus; CKD: chronic kidney disease; RTA: road traffic accident; DM: diabetes mellitus; HTN: hypertension; APLA: anti-phospholipid antibody; MCA: middle cerebral artery; IHD: ischemic heart disease; CLD: chronic liver disease.

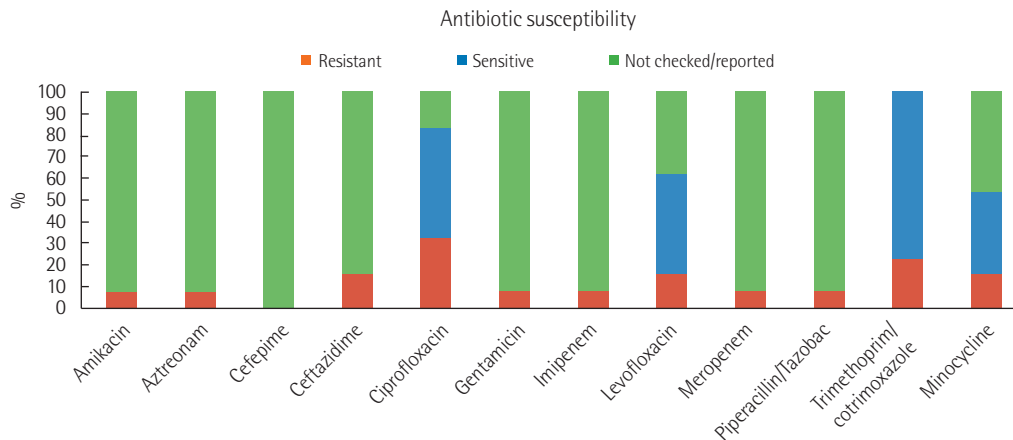


Figure 1. Antibiotic susceptibility of *Elizabethkingia meningoseptica* isolates.

Table 2. Summary of studies reporting *Elizabethkingia* infections and outcomes

Study	Sample size	Clinical diagnosis	Risk factor	Treatment	Outcome
Khan et al. [11] (2015)	4	Empyema, peritonitis, endocarditis, intra-abdominal sepsis	CKD, valvular heart disease, ruptured ectopic pregnancy	Cotrimoxazole-sensitive isolates	3 Survived; 1 died
Arbune et al. [12] (2018)	1	Meningitis	Preterm baby	Piperacillin, tazobactam, and Rifampin	Survived
Celik et al. [13] (2019)	3	Ventilator-associated pneumonia	Preterm infants	One baby treated with cefoperazone-sulbactam and 2 babies treated with ciprofloxacin	All survived
Hamza et al. [14] (2018)	4	Central line-associated bloodstream infection and hospital-acquired pneumonia	Pediatric patients requiring intensive care	Treatment details not available	All survived
Sahu et al. [15] (2019)	1	Ventilator-associated pneumonia	Five-month-old baby with congenital heart disease	Cotrimoxazole in combination with ciprofloxacin	Died
Raghavan et al. [16] (2017)	1	Urinary tract infection	Congestive heart failure	Minocycline	Survived
Dziuban et al. [17] (2018)	283 Pediatric cases from 28 countries (1944–2017)	Spine was the most common site of infection.	Infants	Treatment details and susceptibility patterns not available	138 Survived; 89 died ^a

CKD: chronic kidney disease.

^aThe outcome was unknown in 56 patients.

of all 13 patients are summarized in Table 1. *E. meningoseptica* was sensitive to quinolones in five of 13 isolates. Two of the *E. meningoseptica* isolates were multi-drug resistant with sensitivity only to minocycline, which was the drug used for definitive treatment. The susceptibility pattern of all isolates is summarized in Figure 1. Five of 13 patients were treated with a quinolone, four with cotrimoxazole, and four with minocycline. However, culture appropriate antibiotics were not initiated in two patients. The most common co-infection was with multi-drug resistant *Acinetobacter* (n=2) or *Pseudo-*

monas aeruginosa (n=2). Five of 13 patients died, two cases were referred for palliative care in view of advanced underlying malignancy, and the median length of hospital stay was 13 days. All five patients who died had a history of repeat hospitalization and significant comorbidities. All five of these patients were mechanically ventilated and underwent invasive catheterization. *E. meningoseptica* was isolated from the blood of three patients and from tracheal aspirate in one patient who had undergone esophagectomy, thoracotomy, and tracheostomy. Death could be attributed to *E. meningoseptica* infec-

tion in two of five patients. One patient had repeated isolation of the organism from blood cultures due to infective endocarditis, and the other had nosocomial pneumonia after prolonged hospitalization.

DISCUSSION

Our study identified and analyzed *Elizabeth meningoseptica* infections in patients with underlying comorbidities, particularly in patients that required frequent hospitalizations. While many isolated case reports and series have been reported [11-16], only a few [17] have included more than four *Elizabethkingia* cases (Table 2). There are no reports on *Elizabethkingia* cases from Pakistan. Our study identified 16 patients in the last six years with *Elizabethkingia meningosepticum* infections. Unlike other case series with predominantly neonatal cases [17], our patients had a median age of 29 years. Similar to other case reports, the infections were urinary tract infection and meningitis [11,16]. The outcomes have been variable, with significant mortality among neonates [17]. However, patients with isolates susceptible to quinolones and treated with Ciprofloxacin had better survival outcomes [14]. This result is similar to patients that of who were treated with a quinolone in our study.

E. meningosepticum is resistant to most commonly used antimicrobials; therefore, options for treatment are limited. Most studies have established that clinical isolates are resistant to aminoglycosides and beta lactams, with notable exception of piperacillin-tazobactam, and show sensitivities to fluoroquinolones and tetracyclines [15]. These patterns were consistent with the results of this study.

This study is a single-center case series with several inherent limitations such as the small sample size and unavailability of molecular testing and minimum inhibitory concentration data on all isolates. However, this study is the largest to date and the first from Pakistan, to report clinical features and treatment outcomes of *E. meningoseptica* infections. Moreover, it offers insight into the sensitivity pattern of this organism in our region. *E. meningosepticum* is an emerging nosocomial pathogen that causes mortality in patients requiring intensive care.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Abdullah Umair <https://orcid.org/0000-0002-8402-3087>
Nosheen Nasir <https://orcid.org/0000-0003-1610-8748>

AUTHOR CONTRIBUTIONS

Conceptualization: NN. Data curation: all authors. Formal analysis: NN. Methodology: AU. Writing–original draft: all authors. Writing–review & editing: all authors.

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