

Multidrug resistant *Elizabethkingia meningoseptica* bacteremia – Experience from a level 1 trauma centre in India

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Summary

Elizabethkingia meningoseptica (*E. meningoseptica*) is a non-fermenting gram negative organism that is commonly detected in the soil and water but is rarely reported to cause human infection. However it is emerging as a nosocomial pathogen in patients admitted in intensive care units (ICUs). Infections caused by this organism have a high mortality rate due to lack of effective therapeutic regimens and its intrinsic resistance to multiple antibiotics. We report our experience in managing *Elizabethkingia meningoseptica* (*E. meningoseptica*) septicemia in our ICU patients with septic shock during prolonged intensive care management. Over a two year period four cases were admitted into the polytrauma ICU developed sepsis due to *E. meningoseptica*. All these patients were on mechanical ventilation, had central venous catheter (CVC) and were exposed to various broad spectrum antibiotics. Of the four patients, three died and one recovered. *E. meningoseptica* infection should be considered as a possible etiological agent of sepsis in patients who do not respond to empirical therapy, as this results in an inappropriate choice of antimicrobial therapy, leading to increased morbidity and mortality of patients. Its unusual resistance pattern along with inherent resistance to colistin makes this organism difficult to treat unless susceptibility patterns are available.

Keywords: *Elizabethkingia meningoseptica* (*E. meningoseptica*), septicaemia, Intensive Care Unit (ICU), multi-drug resistance

1. Introduction

Elizabethkingia species are gram negative bacilli which are aerobic, oxidase positive, indole positive, non-motile bacilli and does not ferment glucose. They can be found commonly in freshwater, saltwater, soil and in hospital environments (1). They do not normally exist in the human body, but have been reported to cause various invasive infections like meningitis, pneumonia, endocarditis, and bacteremia in adults and neonates in association with severe underlying illness (2). The risk factors associated with acquisition of

this infection include immunosuppression, underlying medical diseases, prolonged hospital stay, prior use of higher antibiotics, indwelling central venous catheter and other invasive devices (3). This organism is resistant to many antibiotics like beta-lactam antibiotics, aminoglycosides, tetracyclines, and chloramphenicol. However, it is susceptible to some agents used to treat Gram-positive bacteria like erythromycin, clindamycin, rifampicin, trimethoprim-sulfamethoxazole, quinolones and vancomycin (4). Selecting appropriate antimicrobial agents for patients infected with *E. meningoseptica* is difficult due to lack of data on clinical response to different treatments and also due to multiple drug resistance. In this report, we describe a series of four cases with *E. meningoseptica* bacteraemia and septic shock admitted to the ICUs of our level 1 Trauma Centre.

2. Patients and Methods

This is a retrospective study conducted over a two

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year period from June 2016 - May 2018 at our level 1 Trauma Centre. During the above time frame, four cases admitted in the polytrauma ICU developed sepsis due to *Elizabethkingia meningoseptica*. Blood cultures of these patients grew *E. meningoseptica* which were identified up to the species level by VITEK 2 GN card (version 7.02, BioMérieux, Inc. Durham, USA). Antimicrobial susceptibility testing was performed by Kirby-Bauer disc diffusion method on Muller Hinton agar and by Vitek 2 (BioMérieux) system. The MICs were interpreted based on the Clinical and Laboratory Standard Institute (CLSI) criteria for other non-*Enterobacteriaceae*. Patient's details and clinical data included sex, age, diagnosis at admission, presence of central venous catheter, dates and dosages of antibiotic drug administration, dates of catheter removal, and outcome of bacteraemia were recorded. The reports of culture of other samples were also recorded.

2.1. Case 1

A 54 year old male patient admitted with history of Road Traffic Accident (RTA), presented with loss of consciousness during admission. On examination, the patient was intubated from an outside hospital, stable haemodynamically, the Glasgow Coma Scale (GCS) being E4VTM5. The case was suspected to have head injury with chest trauma, abdominal injury and pelvic fracture along with fracture of long bones (Polytrauma). On local examination of the right leg, the patient had swelling, tenderness and deformity. X-ray finding revealed intertrochanteric fracture of femur following which the patient was started on intravenous (IV) augmentin 1.2 gram and injection metrogyl 750mg IV stat and operated on an emergency basis and was shifted to polytrauma ICU. On 3rd post-operative day in the ICU, the patient developed high grade fever along with pus from the operated site. The pus culture grew *Acinetobacter baumannii* sensitive to colistin and tigecycline. Based on the culture reports,

the patient was started on colistin 4.5 million IU IV BD and meropenem 1gram IV TDS for 14 days. Despite two weeks of antibiotic treatment, the patient still had persistent fever. The antibiotic was changed to IV tigecycline 50 mg BD. Total leucocyte count (TLC) was 13,350 cells/mm³ (4,500 - 11,000), hemoglobin 9.5 g/dL (13 - 15), sodium 136 meq/L (145 - 150), potassium 4.8 meq/L (3.5 - 5.5) and chlorides were 105 meq/L (96 - 106). The symptoms persisted with increasing TLC counts, thrombocytopenia and raised procalcitonin levels 2.53 ng/mL (normal < 0.15) suggestive of sepsis. Two sets of blood cultures were sent, one from central line and one from peripheral line. Both the cultures grew *E. meningoseptica* which was resistant to most of the antibiotics. The MICs of various antibiotics are shown in Table 1. The patient was started on IV levofloxacin and inotropic support. Despite all possible resuscitative measures the patient had a fatal outcome on the 42nd day of hospitalization.

2.2. Case 2

A 30 year old female was admitted in our emergency department following history of fall due to which she had sustained injury on the right side of the hip. On local examination there was tenderness, swelling, painful and restricted movements. X-ray revealed intertrochanteric fracture with proximal femoral nail (PFNA) in situ. The patient was started on injection cefoperazone/sulbactam 2 gm IV BD, injection levofloxacin 750 gm IV OD. She was operated on an elective basis and shifted to the orthopaedic ward. During the 14th postoperative day, the patient developed fever, hypotension, and generalised edema with tachycardia and was shifted to the ICU. In the ICU, the antibiotics were escalated to injection colistin 1 million units IV TDS and injection meropenem 1 gm IV TDS. Multiple blood cultures were sent. The blood culture sent on the 13th day of ICU stay grew *E. meningoseptica* sensitive to cefepime-tazobactam and piperacillin-

Table 1. Antimicrobial susceptibility profile of *E. meningoseptica* isolated from four cases

Antibiotics	Minimum Inhibitory concentration (MIC)			
	Isolate 1	Isolate 2	Isolate 3	Isolate 4
Amikacin	≥ 64(R)	≥ 64(R)	≥ 64(R)	≥ 64(R)
Gentamicin	≥ 16(R)	≥ 16(R)	≥ 16(R)	≥ 32(R)
Cefepime	≥ 64(R)	≥ 32(R)	≥ 64(R)	≥ 64(R)
Cefoperazone	≥ 64(R)	≥ 64(R)	≥ 32(I)	≥ 64(R)
Ceftazidime	≥ 32(R)	≥ 64(R)	≥ 64(R)	≥ 64(R)
Ciprofloxacin	≥ 4(R)	≥ 4(R)	≥ 4(R)	0.5 (S)
Levofloxacin	≥ 4(I)	≥ 8(R)	≥ 8(R)	0.5 (S)
Imipenem	≥ 16(R)	≥ 16(R)	≥ 16(R)	≥ 16(R)
Meropenam	≥ 16(R)	≥ 16(R)	≥ 16(R)	≥ 16(R)
Piperacillin	≥ 128(R)	≥ 64(I)	≥ 128(R)	≥ 128(R)
Piperacillin/Tazobactam	≥ 128(R)	≤ 16(S)	≥ 128(R)	≥ 128(R)
Ticarcillin/Clavulanic acid	≥ 128(R)	≥ 128(R)	≤ 16(S)	≥ 128(R)
Trimethoprim/Sulphamethoxazole	≥ 320(R)	≥ 160(R)	≥ 160(R)	≤ 2(S)

tazobactam. The antibiotic was changed to piperacillin-tazobactam based on the susceptibility report. On the 19th day of ICU stay, the patient again had an episode of fever, hypotension and also sustained a cardiac arrest. The patient was started on multiple inotropes, but could not be revived.

2.3. Case 3

A 76 year old female had a history of fall following which she sustained injury to the left hip. She was admitted to our emergency department. Local examination revealed pain, swelling and deformity of the left thigh. X-ray revealed sub trochanteric fracture of left femur. The patient was a known case of hypertension and Type 2 diabetes mellitus and had deranged kidney and cardiac parameters and was investigated for surgical clearance. Following surgical clearance the patient was operated on and owing to high risk and underlying illness, she was shifted to the ICU. On the 5th postoperative day, she developed high grade fever and the blood cultures grew *Escherichia coli* sensitive to tigecycline and colistin. The patient was started on the above antibiotics as per the culture report. Despite these antibiotics the patient continued to have fever and the blood cultures sent on the 15th day of ICU stay grew *Enterococcus faecium* sensitive to ampicillin-sulbactam, vancomycin, teicoplanin and linezolid. The patient was started on linezolid 600 mg IV BD. The patient still persisted to have fever on and off. The blood cultures sent on the 31st day of hospitalisation grew *E. meningoseptica* sensitive to cefepime-tazobactam, cefoperazone-sulbactam, piperacillin-tazobactam and ticarcillin-clavulanate. The patient was started on cefepime-tazobactam. Despite all the efforts the patient succumbed to death on the 47th day of ICU stay.

2.4. Case 4

A 16 year old male was admitted with a history of RTA following which he presented with loss of

consciousness and vomiting. He was suspected to have head injury. The CT scan revealed left temporal and occipital contusion with mass effect and midline shift. The patient was started on augmentin 1.2 mg IV stat. An emergency decompressive craniectomy was done and he was shifted to the ICU. Post operatively, the patient was started on injection cefoperazone-sulbactam 1 gm IV BD and injection netilmicin 200 mg IV OD and was kept under observation in the ICU. On the 5th postoperative day the patient developed fever along with chest infiltrates, following which endotracheal aspirate (ETA) sample was sent to the lab. The ETA grew *Pseudomonas aeruginosa* which was sensitive only to colistin. The patient was then started on IV colistin. The patient still continued to have fever with increasing TLC counts. Multiple blood culture samples were sent. The blood sample sent on the 9th day of ICU stay grew *Elizabethkingia meningoseptica* sensitive to ciprofloxacin, levofloxacin and trimethoprim/sulphamethoxazole. The MIC values of the antibiotics are shown in Table 1. Prompt treatment with ciprofloxacin led to improvement of the patient.

3. Results and Discussion

Four cases of *E. meningoseptica* infections were reported in our ICU from June 2016 - May 2018. All four patients blood samples grew *E. meningoseptica*. The colony morphology of *E. meningoseptica* was smooth circular 1-2 mm colonies with entire edges and regular margins with a slight yellow pigmentation on nutrient agar after 24 hours incubation. The growth on blood agar showed 1-2 mm smooth, circular, greyish-white non-hemolytic colonies. There was no growth on MacConkey agar. All isolates grew at a temperature of 37°C.

Among the four patients, three patients were immunocompetent, one was immunocompromised with underlying illness. The mean age of the patients was 43.7 years. Two were males and two were females. The median time from admission to isolation of *E. meningoseptica* was 12 days range (10-25 days). Two of them had long bone fracture, one had multiple rib

Tables 2. Summary of patients with *Elizabethkingia meningoseptica* infections

Case	Age	Sex	Diagnosis	Underlying illness	Length of stay	Previous antibiotic exposure	Antibiotic treatment	Outcome
1	53	M	Hemopneumothorax with septic shock	Nil	42	Meropenam, Tigecycline Colistin,	Levofloxacin	Death
2	30	F	Intertrochanteric fracture femur with septic shock	Nil	55	Cefepirazole sulbactam, Levofloxacin, Meropenam Colistin,	Piperazillin/Tazobactam	Death
3	76	F	Subtrochanteric fracture femur with sepsis	HT, Type 2 DM	63	Colistin	Cefepime-tazobactam	Death
4	16	M	Head Injury with sepsis	Nil	15	Cefepirazole-sulbactam, Netilmicin	Ciprofloxacin	Survived

fractures with hemopneumothorax, and one had head injury with acute Extra Dural Haematoma (EDH). Among the four, two of them underwent surgical procedures for long bone fracture and one underwent surgical evacuation of EDH. All four patients had history of a recent hospitalization. At the time of bacteremia, all four patients were in the ICU and required mechanical ventilation. All four patients had a central line at the time of bacteremia. All the patients received combination therapy with two or more antibiotics, which included ceftazidime-sulbactam, meropenem, tigecycline and colistin. Of the four patients, three died and one recovered. The clinical features and risk factors of all the patients are summarized in Table 2. Antimicrobial susceptibility of all the isolates was performed and the minimum inhibitory concentration (MICs) of the isolates are shown in Table 1. All four isolates were resistant to most of the antibiotics commonly use in the ICUs. Among the four only one isolate tested was susceptible to trimethoprim-sulfamethoxazole, ciprofloxacin, and levofloxacin.

E. meningoseptica is capable of survival in hospital environments. The source of the organism is most likely from contaminated water supply (since it survives chlorine treatment) or from hospital equipment and other sources such as saline solutions used for flushing procedures, disinfectants, hands of hospital staffs, infant formulas etc. (5). The risk factors for infection by this organism includes diabetes mellitus, steroid use, malignancies, organ transplantation, neutropenia, prolonged hospitalisation, prior exposure to multiple antibiotics, immunocompromised host and chronic haemodialysis (6). In our study, we observed that prolonged hospital stay especially in the ICUs, presence of central venous catheter (CVC), exposure to various broad spectrum antibiotics, presence of shock and recent surgery were the major risk factors. A similar study conducted in Taiwan showed that 60% of the infection were acquired in the ICUs (7). In our study too, all four patients were in the ICUs with CVC in place at the time of development of bacteraemia. One of the patients had diabetes mellitus as an underlying risk factor.

Elizabethkingia spp are known to be intrinsically resistant to tigecycline and polymyxins due to the production of both class A extended spectrum beta lactamases (ESBL) and class B metallo- β -lactamases (MBLs). The MBLs confer resistance to aztreonam and carbapenems, the latter being the mainstay drugs for the treatment of multidrug-resistant Gram negative bacteria (8). A study conducted by Khan *et al.* has shown that previous exposure to Gram negative antibiotic cover is known to predispose to hospital infections caused by *Elizabethkingia spp.* (9). Our study also showed similar findings where all four patients had received prolonged gram negative antimicrobial cover in the ICUs.

Infections caused by *Elizabethkingia spp.* are very difficult to treat and have a high mortality rate especially in immunocompromised patients. A study conducted by Boroda K *et al.* reported a 28 day mortality rate of 41% for nosocomial infections and 9.1% for community acquired infections (10).

We also observed a high mortality, where three out of four cases had a fatal outcome. Presence of shock and use of inappropriate antibiotics acted as independent risk factors for mortality as seen in the other studies (11). Delay in the identification of the organism may lead to treatment failure. Different AST methods gives varied susceptibility results, further complicating its management. The disc diffusion methods are considered to be unreliable and broth micro dilution is the preferred method. There are no standard guidelines for empiric treatment of *E. meningoseptica* infection and most authors suggest using antimicrobial agents based on the minimal inhibitory concentration results from properly performed susceptibility tests (12).

To conclude, *Elizabethkingia meningoseptica* is an emerging pathogen in trauma victims who undergo various surgical procedures. It is essential to keep a high index of suspicion for this infection since failure to start the appropriate antibiotic therapy may lead to a fatal outcome. In the hospital setting, strict contact isolation should be implemented to prevent colonisation of individuals and outbreak.

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