

Neonatal Meningitis and Septicemia Caused by Multidrug-Resistant *Elizabethkingia anophelis* Identified by 16s Ribosomal RNA: An Emerging Threat

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Abstract

Elizabethkingia anophelis infections are emerging, especially among premature newborns, immunocompromised, and critically ill patients. The importance of correctly identifying this Gram-negative organism lies in the fact that it is associated with fatal complications such as meningitis, acute pulmonary edema, congestive cardiac failure, septic shock, and death. In addition, it is inherently resistant to multiple antibiotics which are used to treat Gram-negative bacilli. Here, we report a case of *E. anophelis* related meningitis and septicemia in a preterm neonate along with a brief review of literature.

Keywords: *Elizabethkingia anophelis*, meningitis, neonate, preterm, septicemia

INTRODUCTION

Elizabethkingia anophelis is an opportunistic pathogen that causes infection mainly in neonates, immunocompromised patients, and critically ill patients. Neonates, especially preterm, suffering from *E. anophelis* meningitis or septicemia, in the first two weeks of life have high chances of mortality.^[1] Following meningitis, the patients may develop various neurological complications such as hydrocephalus, deafness, and developmental delay.^[2] Prompt identification of the organism can help in early institution of the appropriate therapy.

CASE REPORT

One preterm male neonate (11 days old, 2.3 kg) born by cesarean section was referred to our hospital with fever and abnormal body movements (tonic posturing) since 3 days and up rolling of eyes for 2 days. The birth history was insignificant. On examination, the neonate had body temperature (T): 98.8°F, heart rate: 112/min, SpO₂ (percentage of oxygen saturation): 92% on oxygen supplementation, pupils bilaterally normal in size and reactive to light stimuli and bulging anterior fontanelle. Chest X-ray revealed patchy nonhomogeneous opacities in the right upper and mid zone suggesting bronchopneumonia. Due to progressive respiratory distress and hypoxia, the neonate

was intubated and mechanically ventilated. A probable diagnosis of septicemia with acute bacterial meningitis was made and antibiotics namely injection gentamicin 16 mg intravenous (IV) once daily and injection ampicillin 300 mg IV 8 h were started empirically.

Initial blood investigations revealed high C-reactive protein (164.9 mg/L) and procalcitonin (7.18 ng/ml). Cerebrospinal fluid (CSF) analysis from lumbar puncture revealed cell count of >1000/μL of which 74% were neutrophils, protein - 216 mg/dl, lactate - 73.7 mg/dl, and glucose level below the measuring range. Gram stain of CSF showed numerous polymorphonuclear leucocytes and Gram-negative bacilli. Blood culture was performed. Urine culture was also performed and was sterile. Both blood and CSF samples were inoculated in Paeds Plus/F bottles and incubated in BD BACTEC FX40 (Becton Dickinson Diagnostics, USA).

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Both the bottles flagged positive signal after 12 h. The organism was Gram-negative bacillus which was nonfermentative and oxidase positive. The antibiotics were changed to injection meropenem and injection amikacin. Identification and antibiotic sensitivity testing was done using the BD Phoenix automated identification and susceptibility testing system (Becton Dickinson Diagnostics, USA). Both blood and CSF cultures revealed the growth of *Elizabethkingia meningoseptica*. Based on the organism's identification and a brief literature review, the antibiotics were changed to injection vancomycin 50 mg IV 6 h and injection piperacillin (1.125 g) - tazobactam (330 mg) IV 6 h. The Clinical and Laboratory Standards Institute criteria for Gram-negative bacteria were used to interpret the antimicrobial susceptibility as no recommendations regarding break-points are available for this rare pathogen and showed that the isolate was only sensitive to ciprofloxacin, levofloxacin, and co-trimoxazole and resistant to piperacillin-tazobactam. Vancomycin minimum inhibitory concentration (MIC) testing could not be performed due to unavailability of E-strips. MICs of the organism with respect to various antibiotics are shown in Table 1. After the antibiotic sensitivity report, ciprofloxacin was also added to the treatment regimen and piperacillin-tazobactam was continued though it had a higher MIC > 64/4 µg/ml. Appropriate infection control measures were taken to prevent the spread of the organism in the neonatal intensive care unit. The neonate recovered and was discharged after 25 days.

Elizabethkingia isolates from both CSF and blood culture were subjected to 16S ribosomal RNA (rRNA) gene sequencing for species confirmation. The *Elizabethkingia* isolates which were identified as *E. meningoseptica* based on biochemical phenotyping in the BD Phoenix system were found to be *E. anophelis* based on 16S rRNA gene sequencing report. The 16S rRNA gene sequence of *E. anophelis* isolated from CSF and blood have been deposited in the GenBank sequence database under accession no. MK811253 and MK811254, respectively [Figure 1].

DISCUSSION

Elizabethkingia species are nonmotile, nonfastidious, and glucose nonfermentative Gram-negative bacilli under the family *Flavobacteriaceae*, with three species *E. meningoseptica*, *Elizabethkingia miricola*, and *E. anophelis*, known to cause human clinical infections.^[1] *E. anophelis* which was initially isolated from the mid-gut of the mosquito *Anopheles gambiae*, was soon reported to be a clinically significant pathogen causing septicemia.^[3-5] *E. anophelis* is the dominant species of the genus *Elizabethkingia* causing septicemia and is associated with fulminant complications such as acute pulmonary edema, congestive cardiac failure, septic shock, and death. Infection due to *E. anophelis* should always be considered as clinically significant unless proven otherwise.^[3] *E. anophelis* is ubiquitously found in hospital environments and has been found to be associated with severe nosocomial infections related to contaminated medical devices. In our case, since the neonate

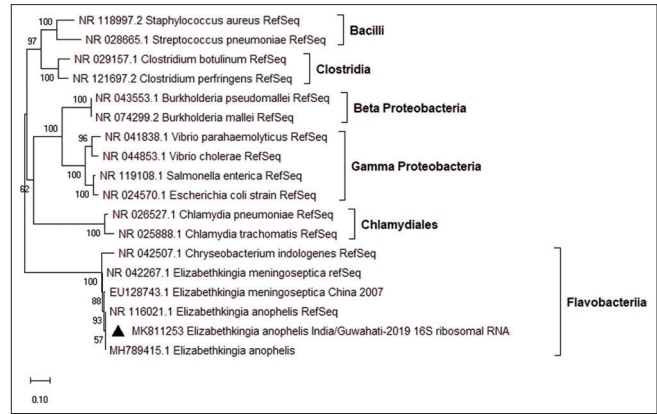


Figure 1: *Elizabethkingia anophelis* partial 16S ribosomal RNA (>872 bp) was analyzed for evolutionary history (phylogenetic tree) using the maximum likelihood method and Kimura 2-parameter model with gamma distribution for evolutionary rate, based on best-fit model testing. A 100 nos. of bootstrap replicate was performed to choose the best tree. This analysis involved 18 nucleotide sequences including representative reference sequences of different families of bacteria. Evolutionary analyses were conducted in MEGA X software

Table 1: Minimum inhibitory concentration of antibiotics determined by the BD phoenix automated system or broth Microdilution Method

Name of the antibiotic	MIC (µg/mL)
Amikacin	>32
Gentamicin	>8
Imipenem	>8
Meropenem	>8
Cefazolin	>16
Ceftazidime	>16
Cefotaxime	>32
Cefepime	>16
Cefoperazone-sulbactam	>16/8
Cefoxitin	8
Aztreonam	>16
Ampicillin	>16
Piperacillin	>64
Amoxicillin-Clavulanic acid	>16/8
Piperacillin-tazobactam	>64/4
Colistin	>2
Co-trimoxazole	2/38
Chloramphenicol	>16
Ciprofloxacin	1
Levofloxacin	≤1

MIC: Minimum inhibitory concentration

was referred to us from a different hospital, so the exact source of infection could not be ascertained.

There are several reports of mis-identification of *E. anophelis* as *E. meningoseptica* by Automated systems namely Vitek-2, API.^[5-7] Lau *et al.* in 2015 reported the failure of Matrix-Assisted Laser Desorption/Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) to correctly identify *E. anophelis*,^[8] while Chew *et al.* in 2018 reported that

78/79 (98.7%) of the isolates which were identified as either *E. meningosepticum* (96.2% isolates) or *E. miricola* (3.8%) by the Bruker MALDI Biotyper (bioMérieux), were actually identified as *E. anophelis* by 16S rRNA gene sequencing.^[9] In this case too, BD Phoenix could not correctly identify the species and may require a data base upgradation to include *E. anophelis* and other species as well.

A brief literature review showed the successful use of vancomycin, piperacillin-tazobactam, ciprofloxacin, etc., in *E. meningitis* and septicemia cases.^[10-12] In our case also, combination regimen of vancomycin, piperacillin-tazobactam, and ciprofloxacin administered to the patient yielded favorable outcome. Fluoroquinolones especially ciprofloxacin should be preferred due to their better penetration through the blood-brain barrier. Moreover, these drugs are not significantly affected by the variation of volume distribution during sepsis.^[13] In a previous study by Lau et al., all the 17 isolates of *E. anophelis* were sensitive to cefoperazone-sulbactam along with ciprofloxacin and vancomycin.^[3] However, in this case, the isolate was resistant to cefoperazone-sulbactam. As *E. meningoseptica* and *E. miricola* have similar antibiotic susceptibility profiles as *E. anophelis*, so for better clinical outcomes, a combination of two or three drugs namely vancomycin, ciprofloxacin, piperacillin-tazobactam, and cefoperazone-sulbactam can be administered empirically as soon as the identification of *Elizabethkingia* is known and can be modified later as per the sensitivity report. The importance of correctly identifying *Elizabethkingia spp.* isolates lies in the fact that it has a peculiar antibiotic sensitivity pattern. Hence, in this era of automated identification systems, the microbiologist should be alert and the organism's identification should be made known to the clinicians as soon as possible to facilitate the timely administration of the specific antibiotics.

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Conflicts of interest

There are no conflicts of interest.

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