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Investigation of Phylogeny and Drug Resistance Mechanisms of *Elizabethkingia anophelis* Isolated from Blood and Lower Respiratory Tract

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Elizabethkingia species are environmental bacteria associated with opportunistic infections in vulnerable populations. Traditionally, *Elizabethkingia meningoseptica* was considered the predominant pathogenic species. However, commercial identification systems have routinely misidentified *Elizabethkingia anophelis* as *E. meningoseptica*, leading to a mischaracterization of clinical strains and an underestimation of the role of *E. anophelis* in human disease. *Elizabethkingia* spp. harbor multidrug resistance (MDR) genes that pose challenges for treatment. Differentiation between *Elizabethkingia* spp. is particularly important due to differences in antimicrobial resistance (AMR) and epidemiological investigation. In this study, we describe a case of MDR *E. anophelis* isolated from the blood and lower respiratory tract of a patient who was successfully treated with minocycline. These isolates were initially misidentified by matrix assisted laser desorption ionization-time of flight as *E. meningoseptica*, whereas whole genome sequencing (WGS) confirmed the isolates as *E. anophelis* with the closest related strain being *E. anophelis* NUHP1, which was implicated in a 2012 outbreak in Singapore. Several AMR genes (blaBlaB, blaBlaGOB, blaCME, Sul2, erm(F), and catB) were identified by WGS, confirming the mechanisms for MDR. This case emphasizes the utility of WGS for correct speciation, elucidation of resistance genes, and relatedness to other outbreak strains. As *E. anophelis* is associated with a high mortality and has been found in hospital system sinks, WGS is critically important for determining strain relatedness and tracking outbreaks in the hospital setting.

Keywords: multidrug resistance, whole genome sequencing, *Elizabethkingia anophelis*

Introduction

ELIZABETHKINGIA spp., MEMBERS of the *Flavobacteriaceae* family, are nonmotile glucose nonfermenting oxidase positive gram-negative rod-shaped environmental bacteria.^{1–3} *Elizabethkingia* spp. are particularly resilient and can survive in chlorine-treated municipal water supplies.¹ The ability to colonize sink basins and taps in hospitals poses a concern for infection prevention,⁴ with patients colonized with the organism as a result of contaminated medical devices involving fluids.¹ *Elizabethkingia* spp. are considered opportunistic pathogens; patients >60 years of age, neonatal or immunocompromised individuals, and those with comorbidities at highest risk for infection.^{1–3,5,6} Moreover, multidrug resistance (MDR) is well documented in *Elizabethkingia* spp, which boasts a multitude of beta-lactamase genes,^{7–14} limiting effective treatment options.

Elizabethkingia meningoseptica was previously considered the most prominent pathogenic *Elizabethkingia* spp and is associated with meningitis, sepsis, bacteremia, pneumonia, skin and soft tissue infections, wound infections, ocular infections, sinusitis, bronchitis, abdominal abscesses, epididymitis, endocarditis, dialysis-associated peritonitis, and prosthetic joint infections.¹ However, mounting data support *Elizabethkingia anophelis* as the more prevalent *Elizabethkingia* species.^{8,9,15} *Elizabethkingia anophelis* was first isolated from the midgut of an *Anopheles gambiae* mosquito in 2011^{2,3} and has since been associated with hospital outbreaks,^{5,16} vertical transmission,¹⁷ bacteremia,^{8,10,15,18,19} and meningitis.^{17,20} Owing to misidentification of *E. anophelis* by commercial identification systems,^{3,4,9,16–22} the true prevalence and clinical significance of *E. anophelis* are greatly underestimated as sequencing^{14,16,19–21} or PCR^{19,23} is essential for accurate identification. *Elizabethkingia anophelis*

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is associated with a mortality rate of 23.5–30%^{3,14,15,24} and high rates of drug resistance,^{2,8–10,12–14,19,24} emphasizing the necessity of correct identification. In this study, we describe a case of highly resistant *E. anophelis* strains isolated from the blood and respiratory tract of a patient with a recent history of hospitalization in India. These isolates were originally misidentified by matrix assisted laser desorption ionization-time of flight (MALDI-TOF) as *E. meningoseptica*. Using whole genome sequencing (WGS), speciation was confirmed and the phylogeny and the resistance mechanisms were further elucidated.

Materials and Methods

Initial organism identification was acquired using MALDI-TOF (bioMérieux VITEK MS, Marcy-l'Étoile, France). Susceptibility was performed by broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) M100 29th Edition using panels prepared in house.

WGS was performed using MiSeq (Illumina, San Diego, CA) on the isolates from the tracheal aspirate (UCLAEA-1) and blood (UCLAEA-2) collectively referred to as the University of California, Los Angeles (UCLA) strains. BLAST (NCBI) analysis of their full-length 16S rRNA and *rpoB* genes were used for species identification. Center for Genomic Epidemiology (CGE) tools were used for identification of closely related strains, antimicrobial resistance (AMR) genes and mutations, and plasmids.^{25–29} CLC Genomics Workbench (Qiagen, Valencia, CA) and Geneious (Biomatters, New Zealand) were used to construct a Kmer tree and perform sequence alignment analysis to confirm genomic relatedness to closely related strains and genes, respectively. The sequences for UCLAEA-1 and UCLAEA-2 have been deposited in GenBank under accession nos. JADEZW000000000 and JADEZX000000000, respectively. Local IRB review waived.

Results

An 89-year-old male with no significant prior past medical history was air evacuated to Ronald Reagan-UCLA Medical Center (RR-UCLA) after a 4-week hospitalization in New Delhi, India. He was on vacation when he suffered a cardiac arrest complicated by a fall and cervical spine fracture requiring anterior decompression and fixation of the cervical spine. His hospital course was further complicated by chronic respiratory failure requiring intubation with subsequent tracheostomy placement, central venous catheter (CVC) line infections with *Staphylococcus haemolyticus* and *Enterococcus faecium*, and ventilator-associated pneumonias with MDR *Klebsiella pneumoniae* and *Acinetobacter baumannii*. He continued to be febrile with an ongoing vasopressor requirement and was transferred by air to RR-UCLA for continued care. At the time of transfer he was receiving cefepime/sulbactam (Supime), tigecycline, and inhaled colistin.

Upon arrival to RR-UCLA, he was afebrile, on mechanical ventilation (FiO₂ at 40%), and requiring norepinephrine 5 µg/kg/min to maintain mean arterial pressure >65 mmHg. Physical examination was notable for an elderly male in no acute distress, on mechanical ventilation with tracheostomy in place. Cardiopulmonary examination was unremarkable. He had an existing left upper extremity peripherally inserted central catheter (PICC) with normal appearance and func-

tion. His initial laboratory values were significant for a white blood cell count of 11.68 × 10³/µL and hemoglobin of 8.4 g/dL. The remainder of his complete blood count as well as his basic metabolic panel and hepatic function panel were unremarkable. Chest X-ray was obtained, which revealed diffuse pulmonary edema but no clear consolidations. Blood cultures from both the peripheral vein and PICC line were obtained and both resulted positive for Gram-negative rods at 12 hours.

His initial antibiotic regimen consisted of empiric broad-spectrum therapy along with therapy directed against the prior isolates of *K. pneumoniae* and *A. baumannii* based on their susceptibility profiles, and included aztreonam, ceftazidime-avibactam, polymyxin B, and inhaled colistin. On hospital day 2, the Gram-negative rods were identified as *Elizabethkingia meningosepticum* by MALDI-TOF. Susceptibility data for the organism indicated multidrug resistance to the antibiotics tested using standard broth microdilution according to CLSI guidelines (Table 1). His left upper extremity PICC line, the initial suspected source of infection, was removed. A new right femoral triple lumen CVC was immediately placed due to his continued need for vasopressors. Given the organism's known unusual susceptibility pattern, and its historical susceptibility to vancomycin despite being a Gram-negative organism,³⁰ this was added empirically. Intravenous minocycline was added to his regimen as the isolate was found to be susceptible. Blood cultures remained positive for 5 days, then cleared on hospital day 6.

Further studies performed during his early hospital course included computed tomography imaging of his cervical spinal hardware, as well as a transthoracic echocardiogram, which did not show any findings concerning for the source of bacteremia. His respiratory status remained stable on the ventilator and there was low clinical suspicion for a ventilator-associated pneumonia. He was weaned from vasopressors and his central line was removed on hospital day 7. His blood cultures remained negative and he completed a total 14-day course of minocycline with microbiological cure of his infection without relapse. He later died of unrelated complications.

Further genomic analysis of both the blood and tracheal aspirates revealed the organism's true identification as *E. anophelis*. There was 100% identity in both 16S and *rpoB* genes shared between the UCLA strains and the *E. anophelis* strain NUHP1 (CP007547), which was responsible for a 2012 outbreak among ICUs at the National University Hospital of Singapore.^{16,51} The alignment of the raw sequencing reads of the UCLA strains to the NUHP1 reference genome resulted in 93% genome coverage and 99.5% pairwise similarity. The close relatedness of the two strains is further demonstrated by the Kmer-based phylogenetic tree analysis, which showed that the UCLA strains clustered closely with the NUHP1 strain compared with other *E. anophelis* strains (Fig. 1).

The respiratory tract and blood isolates were genetically identical except for one single nucleotide polymorphism at genome position 3839450 (T>A), which is a silent mutation on an unknown gene encoding a hypothetical protein. Moreover, the strains had identical antimicrobial susceptibility patterns for the drugs tested (Table 1). Thus, the genetic determinants of AMR and the results of other genomic analysis of both isolates were described jointly as the

TABLE 1. ANTIMICROBIAL SUSCEPTIBILITY RESULTS OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES *ELIZABETHKINGIA ANOPHELIS* STRAINS

Antimicrobial agent	UCLAEA-1		UCLAEA-2	
	MIC ($\mu\text{g/mL}$)	CLSI susceptibility (SIR)	MIC ($\mu\text{g/mL}$)	CLSI susceptibility (SIR)
Piperacillin-tazobactam	>128	R	>128	R
Cefazolin	>32	R	Not tested	N/A
Ceftriaxone	>64	R	Not tested	N/A
Ceftazidime	>32	R	>32	R
Ceftolozane-tazobactam	>32	No interpretive criteria	Not tested	N/A
Ceftazidime-avibactam	>32	No interpretive criteria	Not tested	N/A
Aztreonam	>32	R	Not tested	N/A
Imipenem	>16	R	>16	R
Meropenem	>16	R	>16	R
Meropenem-vaborbactam	>32	No interpretive criteria	>32	No interpretive criteria
Gentamicin	>16	R	>16	R
Tobramycin	>16	R	>16	R
Amikacin	>64	R	>32	R
Ciprofloxacin	>4	R	>2	R
Levofloxacin	>8	R	>8	R
Moxifloxacin	>8	No interpretive criteria	>8	No interpretive criteria
Minocycline	≤ 0.5	S	≤ 0.5	S
Tigecycline	8	No Interpretive criteria	4	No Interpretive criteria
Colistin	>4	No interpretive criteria	>4	No interpretive criteria
Trimethoprim/sulfamethoxazole	4/80	R	4/80	R
Vancomycin	Not tested	N/A	16	No interpretive criteria
Rifampin	Not tested	N/A	4	No interpretive criteria

CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration; N/A, not applicable; R, resistant; SIR, susceptible/intermediate/resistant; UCLA, University of California, Los Angeles.

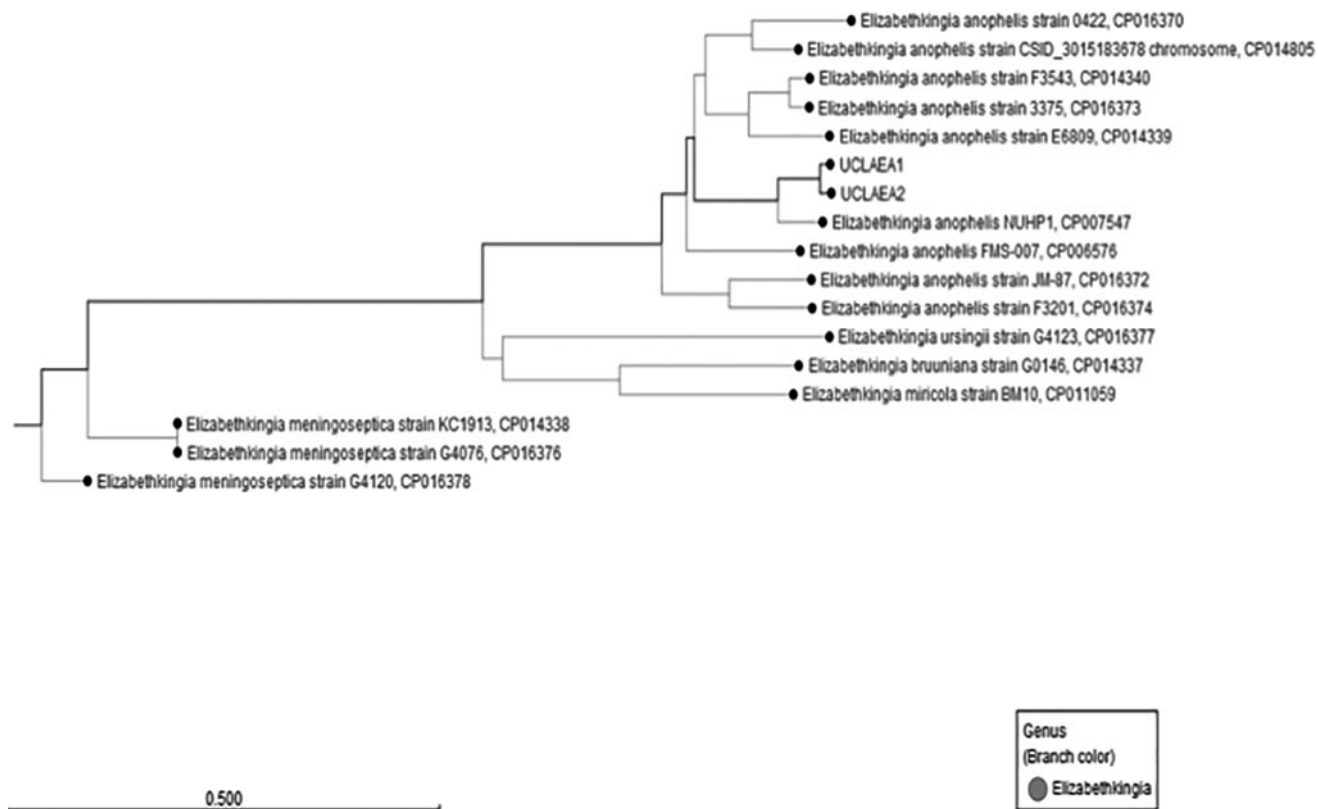


FIG. 1. Kmer tree of *Elizabethkingia* spp. A Kmer tree of UCLAEA1 and UCLAEA2 was constructed using CLCBio.

same UCLA strain. Survey of the UCLA strain's genome revealed multiple beta-lactamases commonly found in most *Elizabethkingia* spp.,^{2,7,8,11,12} including two metallo-beta-lactamases (MBL) genes (*blaB*-21 with 100% pairwise nucleotide identity to sequence ID NG_067210.1 and *blaGOB*-21-like gene with 99.9% pairwise nucleotide identity to sequence ID NG_067988.1 and a M138I mutation) and an extended spectrum beta-lactamase (ESBL) gene (*blaCME*-1, 99.5% pairwise nucleotide identity to sequence ID NG_048764.1 with all the three mutations silent), which explained the pan-resistance pattern to all beta-lactams tested (Table 1). Other resistance genes include *sul2*, *catB*, and *erm(F)* conferring resistance to sulfonamide, chloramphenicol, and macrolides, respectively. Interestingly, in the UCLA strain, *sul2* and *catB* are located on a 2,254 bp transposon that exhibited 100% pairwise sequence identity to *K. pneumoniae* (MK396843), *Salmonella enterica* (MK191844, MK191835, LR536427, CP037959), *Escherichia coli* (MH847633), *Citrobacter freundii* (CP036435), and *Acinetobacter baumannii* (CP033866), whereas *erm(F)* is located on a 2,347 bp genetic element and exhibited 100% pairwise identity to *Riemerella anatipestifer* (KP265718, CP007503, CP003787). In addition, we identified a point mutation at position 83 of *GyrA* gene (Ser83Ile; AGC to ATC) conferring resistance to fluoroquinolones. No plasmids were identified in the UCLA strain.

Discussion

Misidentification of *E. anophelis* has led to an underappreciation of this pathogenic MDR organism associated with high morbidity and mortality. Complementing the literature, commercial identification systems, specifically MALDI-TOF, misidentified *E. anophelis* in UCLA strain as *E. meningoseptica*. However, WGS confirmed the identity as *E. anophelis* and demonstrated close genomic relatedness to the NHUP1 strain, which was implicated in a Singapore hospital outbreak in 2012.¹⁶

Owing to differences in antibiotic resistance profiles, it is critical to differentiate between *E. anophelis* and other *Elizabethkingia* spp.^{9,24} Although broadly resistant to beta-lactams, *E. anophelis* strains have also shown resistance to aminoglycosides, polypeptide antibiotics, sulfonamides, quinolones, and tetracyclines.¹³ The UCLA strain was resistant to all antibiotics tested except for minocycline. Minocycline susceptibility has been demonstrated in isolates from China and Taiwan.^{8,14} WGS provided mechanisms for the observed MDR in UCLA strain. Beta-lactamase resistance was explained by the MBL (*blaBlaB*-21 and *blaGOB*-21-like gene) and an ESBL gene (*blaCME*-1). *blaBlaB* and *blaGOB* are found in all members of the *Elizabethkingia* genus, which supports acquisition from horizontal gene transfer in the genus.³² One study found that all *E. anophelis* isolates harbored *blaBlaB* and *blaGOB*, conferring carbapenem resistance.¹² *Sul1*, conferring resistance to sulfonamides, has also been identified in other *E. anophelis* isolates,¹⁰ whereas *catB*, conferring resistance to chloramphenicol, has been documented in *Elizabethkingia* spp.¹¹ The UCLA strain also had a point mutation at position 83 of *GyrA* (Ser83Ile; AGC to ATC), conferring resistance to fluoroquinolones. This particular mutation has been well documented in *Elizabethkingia* spp.^{8,12}

Our patient responded well to the administration of minocycline based on *in vitro* susceptibilities; however, the lack of reliably active agents for this organism makes empiric antibiotic selection very challenging and treatment should be guided by susceptibility testing. These isolates are routinely expected to harbor beta-lactamase genes conferring broad resistance to this class of antibiotics including, as seen in our case, to the newer beta-lactam/beta-lactamase inhibitor combinations ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam. Although fluoroquinolones and sulfonamides have shown activity in other series,⁵ that was not the case with our patient. U.S. susceptibility data are limited, but a recent report of 52 *Elizabethkingia* isolates from China demonstrated *in vitro* susceptibility most commonly for minocycline (100%), tigecycline (78.8%), rifampin (76.9%), and levofloxacin (71.2%), with minimum inhibitory concentrations to vancomycin of 16 or greater in 90% of isolates.⁸ Although historically vancomycin has been used for this gram-negative organism, particularly for *E. meningoseptica*, its true efficacy and current role is less clear and debatable.³³ We were unable to test the novel siderophore antibiotic cefiderocol, but limited *in vitro* testing demonstrates possible activity against *Elizabethkingia* spp.³⁴ At the time of testing we were unable to evaluate the tetracycline derivatives omadacycline and eravacycline; insufficient data exist to comment on their predicted activity at this time.

When compared with environmental isolates, clinical strains exhibit similar resistance profiles and genomic features. Hospital-isolated *E. anophelis* strains, but not hospital-isolated *E. meningoseptica* strains, had similar genomic content compared with *E. anophelis* strains isolated from the midgut of the *A. gambiae* mosquito.³¹ Interestingly, the carriage of resistance genes is not unique to strains isolated from humans as *E. anophelis* strains from mosquitoes carried multiple beta-lactamases, MBL, and penicillin binding proteins.³⁵ *blaBlaB* and *blaGOB* were found chromosomally encoded in an *E. miricola* strain isolated from a diseased frog in China.⁷ The UCLA strain also carried *erm(F)*, conferring resistance to macrolides, which is also found in *Riemerella anatipestifer*,³⁶ another member of the *Flavobacteriaceae* family that is a major pathogen of ducks and geese.³⁷ Thus, the antibiotic resistance genes are common in both clinical isolates and those from the environment.

Despite being found in mosquitoes originally, the main method of exposure is unknown and exposure to mosquitoes is not considered to be the primary route.³⁸ One case study found vertical transmission from mother to neonate,¹⁷ whereas another found tap water and sinks contaminated with *E. anophelis*.⁴ One risk factor for our patient was the use of mechanical ventilation, which has been strongly associated with *Elizabethkingia* spp. infection, with 79.6–97.3% of patients with *Elizabethkingia* spp. infections receiving mechanical ventilation.³⁸ The presence of *E. anophelis* in the respiratory tract supports this, although we suspect the bacteremia to be central line associated from our patient's PICC line.

Taken together, WGS provided an accurate identification of *E. anophelis* as well as valuable information regarding resistance mechanisms and strain relatedness. Although more recent MALDI-TOF database updates include *E. anophelis*, our case emphasizes that caution should be

exercised when using any commercial system as false identification can still occur. In the setting of infections by the extensively drug-resistant *E. anopheles*, minocycline appears to be an effective treatment option, as demonstrated by this case and the literature.

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Disclosure Statement

No competing financial interests exist.

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