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CASE REPORT

Combination Therapy of Trimethoprim-Sulfamethoxazole (TMP-SMZ) and Eravacycline for Treating Elizabethkingia anophelis-Induced Pulmonary Infections: A Case Report

Qimei Wei[1,*], Wenxia Zuo[2,*], Rong Cong[1], Kun Luo[1], Shanshan Dong[1]

[1]Department of Clinical Laboratory, Wuhan Asia Heart Hospital, Wuhan, 430022, People's Republic of China; [2]Department of Cardiac Critical Care Medicine, Wuhan Asia Heart Hospital, Wuhan, 430022, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shanshan Dong, Department of Clinical Laboratory, Wuhan Asia Heart Hospital, No. 753 Jinghan Avenue, Jianghan District, Wuhan, 430022, People's Republic of China, Tel +86 18162516279, Email 18162516279@163.com

Abstract: *Elizabethkingia anophelis* is an opportunistic pathogen that causes serious life-threatening infections. In this report, we describe a case of pulmonary infection caused by *E. anophelis* in a young female patient, following cardiac surgery, which was successfully treated with a combination of trimethoprim-sulfamethoxazole (TMP-SMZ) and eravacycline. Additionally, this report provides a summary of high-risk factors for *E. anophelis* infection, clinical manifestations, and therapeutic options. Given the high degree of antimicrobial drug resistance of the organism and the fact that inappropriate empirical antimicrobial therapy constitutes a risk factor for mortality, our case serves as a valuable reference for similar cases, highlighting potential strategies for effective management.

Keywords: *Elizabethkingia anophelis*, pulmonary infections, trimethoprim-sulfamethoxazole, eravacycline

Introduction

In recent years, *Elizabethkingia anophelis* has gained global attention, as it has been recognized as an opportunistic pathogen that causes life-threatening nosocomial infections, particularly in immunosuppressed patients and those who are critically ill. Studies have indicated that the mortality rate of infections caused by *E. anophelis* is alarmingly high, ranging from 24% to 60%.[1,2] *E. anophelis* is a gram-negative bacillus known for its aerobic, non-fermentative metabolism of glucose. Its colonies typically appear smooth, light-yellow, and translucent.[3] Initially isolated from the midgut of Anopheles gambiae mosquitoes, *E. anophelis* has since been associated with nosocomial infections.[4] The spectrum of clinical manifestations of *E. anophelis* infection is broad, encompassing bacteremia, pneumonia, catheter-related bloodstream infection, meningitis, and skin and soft tissue infection, to name a few.[1,5] Interestingly, a significant majority of infections (80–87.5%) occur in hospital settings, specifically affecting patients with compromised immunity.[3,6] *E. anophelis* is a multidrug-resistant bacterium; however, its mechanism of resistance remains unclear. Studies have demonstrated that *E. anophelis* isolates are highly resistant to most β-lactams (including those with enzyme inhibitors), carbapenems, fluoroquinolones, and aminoglycosides.[6,7] The treatment of *E. anophelis* infections is challenging due to its intrinsic resistance to multiple antibiotics. Current therapeutic options are limited, and there is a lack of comprehensive clinical trials to guide effective treatment protocols. Reports have suggested successful treatment of *E. anophelis* infections with piperacillin-tazobactam.[8] Furthermore, vancomycin is considered a potential therapeutic

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option for meningitis caused by *Elizabethkingia* infections.[9] Some studies propose that minocycline may serve as a viable treatment for *E. anophelis* infections.[3] However, the efficacy of these antibiotics can vary depending on the site of infection and the susceptibility profile of the bacterial strain. In this report, we describe a case of pulmonary infection caused by *E. anophelis* in a post-cardiac surgery patient that was successfully managed with TMP-SMZ and eravacycline.

Case Presentation

A 29-year-old woman presented to Wuhan Asia Heart Hospital with severe shortness of breath and palpitations. The patient has a history of tetralogy of Fallot, for which she underwent corrective surgery 19 years ago. She achieved full recovery post-surgery, with normal growth and development, and no recurrence of cyanotic symptoms. However, five years ago, after contracting COVID-19, she began experiencing recurring chest tightness and palpitations, which went untreated. More recently, she experienced severe shortness of breath and palpitations, prompting her to seek medical attention. Upon admission, a transcardiac ultrasound revealed severe pulmonary and tricuspid regurgitations. Given the severity of her condition, surgical intervention was deemed necessary, and she underwent pulmonary valve replacement and tricuspid valvuloplasty. Postoperatively, she experienced complications, including ventricular fibrillation and stress cardiomyopathy, necessitating coronary angiography and ECMO placement. During ECMO treatment, the patient underwent repeated thoracotomy and debridement. These procedures were necessary due to poor hemostasis of the trauma in the chest cavity and circulatory instability caused by cardiac compression. However, this intervention may have potentially exacerbated the infection. Despite this concern, all blood, urine, and pleural drainage fluid cultures submitted for testing were negative, except for a single alveolar lavage fluid culture that showed *Aspergillus* growth. The previous antibiotic regimen included piperacillin-tazobactam, vancomycin, and voriconazole. Moreover, the blood cortisol and adrenocorticotropic hormone levels were significantly reduced, suggesting adrenocortical hypofunction. Following hormone replacement therapy, there was noticeable improvement in her cardiac function. On the 6th day of the ICU stay, she experienced large circulatory fluctuations at night. Because of these symptoms, cardiac tamponade was suspected, and thoracotomy and delayed chest closure were urgently performed. Through active treatment, successful chest closure was achieved and ECMO was successfully removed 1 week later.

However, the patient developed severe respiratory distress, manifesting as a persistent high fever exceeding 38.5°C and significant difficulty breathing. Upon evaluation, the peripheral blood white blood cell count was 32.5×10^9/L, procalcitonin was 0.61 ng/mL, and high-sensitivity C-reactive protein was 160.17 mg/L. These findings suggested a severe inflammatory response, likely due to an underlying infection. Additionally, CT imaging revealed multiple infections in both lungs, with multiple patchy increased density shadows visible in both lungs, a few areas without lung markings in the right lung, and approximately 5% compression in the right lung (Figure 1). These findings are consistent with a pulmonary infection (pneumonia). Due to her prolonged ventilator use and subsequent inability to wean her from

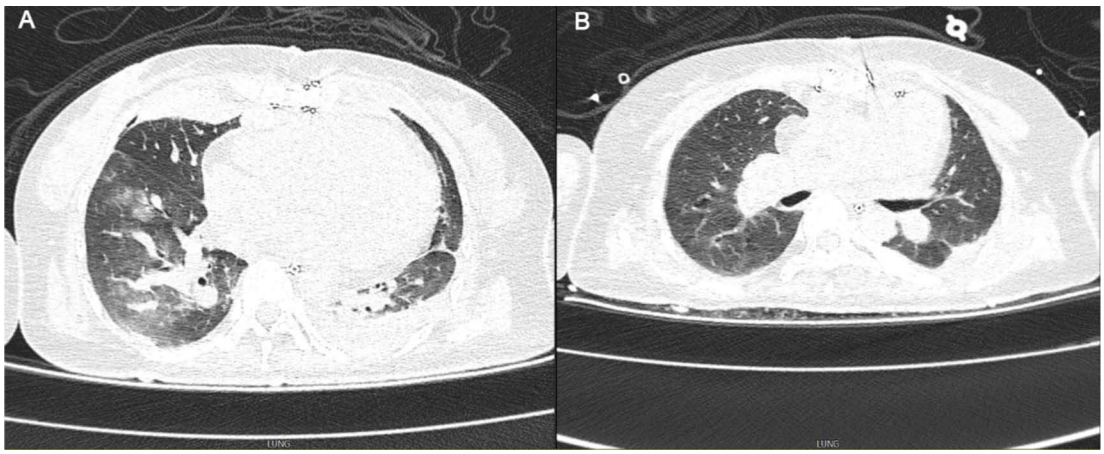

Figure 1 Chest CT image. **(A)** Initial CT showed widespread infections in both lungs; **(B)** CT shows significant lesion resorption 10 days post-treatment.

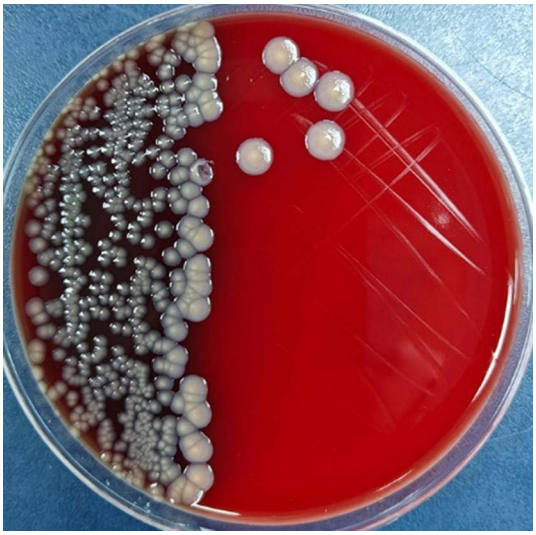

Figure 2 Colony morphology of *E. anophelis* after 48 h of growth on blood agar plates.

it in a short period of time, percutaneous tracheotomy was performed, and sputum was suctioned through the lower tube. The sputum was yellow and sticky. Subsequently, sputum samples were systematically sent for culture on three separate occasions, all of which yielded consistent results. Cultures cultivated on blood agar plates yielded colonies with a smooth surface and yellowish color (Figure 2). These were unequivocally identified as *E. anophelis* using a matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) system (Figure 3). Analysis of the drug susceptibility test results indicated resistance to cephalosporins, carbapenems, quinolones, and aminoglycosides and

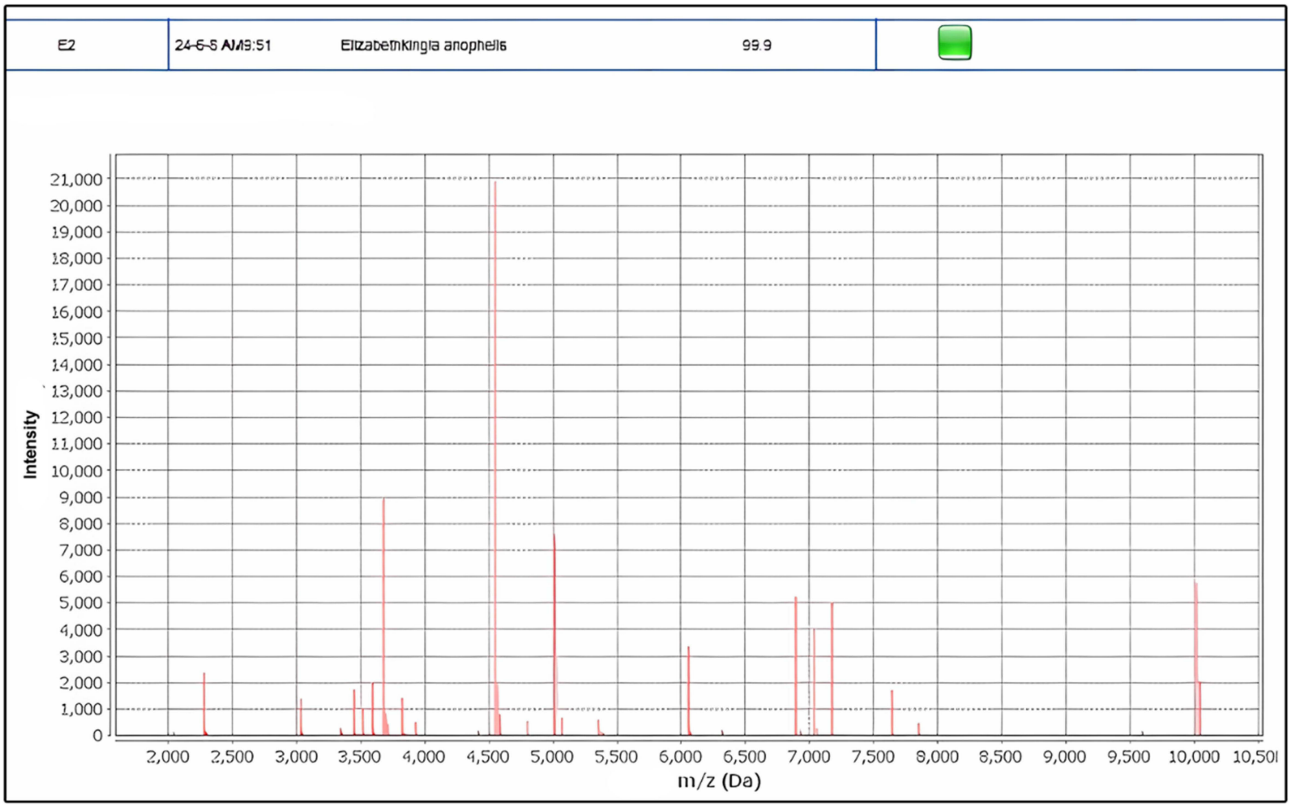

Figure 3 Identified as E.anophelis by MALDI-TOF MS.

Table 1 Results of Drug Resistance Phenotypes of E. Anophelis by MIC Drug Susceptibility Testing

Antibiotics	MIC (μg/mL)	Result
Piperacillin-Tazobactam	≥128	R
Ceftazidime	≥64	R
Cefoperazone/Sulbactam	≥64	R
Cefepime	≥32	R
Aztreonam	≥64	R
Imipenem	≥16	R
Meropenem	≥16	R
Amikacin	≥64	R
Tobramycin	≥16	R
Ciprofloxacin	≥4	R
Levofloxacin	≥8	R
Minocycline	≤1	S
Tigecycline	4	I
Trimethoprim-sulfamethoxazole	≤20	S

sensitivity to minocycline and TMP-SMZ (Table 1). Given the consistent identification across all lower respiratory tract samples, we conclude that *E. anophelis* is the causative organism of the infection rather than merely a colonizer. Based on this discovery, the attending physician immediately adapted the antibiotics to TMP-SMZ (po, 160/800 mg, q12h) combined with piperacillin-tazobactam. After 5 days of this combined treatment, there was some improvement in her inflammatory indicators. However, her body temperature remained elevated, and her infection symptoms did not show significant improvement. Consequently, the therapeutic antibiotics were further adjusted to TMP-SMZ (po, 160/800 mg, q12h) combined with eravacycline (ivgtt, 50 mg, q12h) to better target the *E. anophelis* infection. After another 5 days of treatment with this new combination, her body temperature normalized, procalcitonin dropped to 0.24 ng/mL, and the peripheral blood white blood cell count was reduced to 14.9×10^9/L, with a high-sensitivity C-reactive protein decreasing of 20.75 mg/L. A CT scan 10 days post-treatment showed significant absorption and improvement in the infectious lesions in both lungs compared with earlier scans. Although there was still slight exudation in the right lower lung and segmental under-expansion of both lower lungs, the overall texture of both lungs appeared clear, and the lung field transmittance was satisfactory. The most noticeable improvement in pulmonary infection symptoms included the normalization of body temperature, a significant reduction in procalcitonin levels, and a decrease in white blood cell count, which are indicative of resolving infection. Additionally, the patient's respiratory symptoms improved, with reduced cough and sputum production, and her oxygenation status stabilized, allowing for the removal of the tracheostomy tube. Notably, the sputum culture results were negative, indicating successful treatment of the pulmonary infection (Table 2). TMP-SMZ was prescribed for 2 weeks and then discontinued. Eravacycline was extended for 2 weeks without any recurrence of the pulmonary infection. After 2 weeks of this therapeutic regimen, her cardiac function significantly improved, her general condition markedly improved, and she was subsequently discharged from the hospital in a fully recovered state. One month after discharge, the patient returned to the hospital for follow-up examination. She reported no discomfort and demonstrated good recovery, with no recurrence of pulmonary infection.

Discussion

E. anophelis is predominantly associated with neonatal meningitis and bacteremia.[10] However, instances of pulmonary infection attributed to *E. anophelis* are infrequently documented. An examination of the literature revealed six cases of pulmonary infection linked to *E. anophelis* in recent years, all of which were fatal.[11–13] In these instances, the patients were also affected by other infections. Respiratory tract infections caused by *E. anophelis* are predominantly associated with mechanical ventilation and can include pneumonia, acute exacerbations of chronic obstructive pulmonary disease,

Table 2 The Summary Compares Clinical, Biochemical, and Microbiological Data Pre- and During TMP-SMZ and Eravacycline Treatment to Demonstrate Their Efficacy

Data	Day of Before PF	Day of PF	Day + 10	End of Treatment
Temperature (°C)	37.3	39.2	37.0	36.6
WBC (×10^9/L)	15.2	32.5	14.9	10.4
hsCRP (mg/L)	25.11	160.17	20.75	4.61
PCT (ng/mL)	0.24	0.61	0.24	0.16
Blood cultures	Negative	Negative	/	/
Sputum cultures	Aspergillus	*E. anophelis*	Negative	Negative
CT imaging	/	Widespread infections in both lungs	Significant absorption and improvement	/
Therapeutic drugs	Piperacillin-tazobactam, vancomycin, and voriconazole	TMP-SMZ and piperacillin-tazobactam	TMP-SMZ and eravacycline	/

Abbreviations: PF pulmonary infection, WBC white blood cells, hsCRP high-sensitivity C-reactive protein, PCT procalcitonin.

and secondary infections in patients with cystic fibrosis.[6] In the present case, *Aspergillus spp*. were detected in the initial sputum culture. However, when imaging confirmed a distinct pulmonary infection, only *E. anophelis* was identified in subsequent sputum cultures, with no evidence of other pathogens during the same timeframe. A treatment regimen of TMP-SMZ combined with eravacycline was selected to target *E. anophelis*, resulting in successful posttreatment outcomes. The patient had several predisposing factors that likely contributed to the development of *E. anophelis* pulmonary infection, including a history of prolonged glucocorticoid treatment, extended mechanical ventilation following cardiac surgery, and recent cardiac surgery. First, the patient had a history of prolonged glucocorticoid treatment, which is known to suppress the immune system and increase susceptibility to infections. Second, the patient underwent extended mechanical ventilation following cardiac surgery, a risk factor for respiratory infections due to the potential for biofilm formation, and colonization by opportunistic pathogens. Third, recent cardiac surgeries, particularly those involving the heart, can compromise the immune system and provide a portal of entry for pathogens. In addition to these primary risk factors, early *Aspergillus* infections may lead to a decrease in airway protection, making the patient more susceptible to other bacterial infections. Moreover, early broad-spectrum combination antibiotic administration disrupts the normal flora of the airways, increasing the likelihood that drug-resistant bacteria will colonize, leading to secondary pulmonary infections. The clinical presentation of *E. anophelis* pulmonary infection can be challenging to differentiate from other bacterial pneumonias. Common symptoms include fever, cough, dyspnea, and radiographic evidence of pneumonia. In our case, the patient initially presented with symptoms consistent with a respiratory infection. Pulmonary infections caused by *E. anophelis* lack distinctive imaging signatures, and CT imaging revealed multiple infection foci across both lungs. Primary inflammatory indicators in laboratory tests showed significant increases in peripheral blood white blood cell count (32.5 × 10^9/L) and high-sensitivity C-reactive protein (160.17 mg/L), while procalcitonin (0.61 ng/mL) was only slightly elevated. After controlling the infection, the levels of these indicators declined rapidly.

Hospital-acquired infections caused by *E. anophelis* should not be underestimated. Several factors make *E. anophelis* a challenging pathogen to manage. Firstly, *E. anophelis* often exhibits resistance to multiple antibiotics, making treatment options limited and complicating the management of infections. Secondly, accurate and timely identification of *E. anophelis* is crucial for effective treatment. Traditional microbial identification platforms often misidentify *E. anophelis* as *E. meningoseptica*, suggesting that the incidence of *E. anophelis* infection may be significantly underestimated.[3] Fortunately, recent improvements and updates to the matrix-assisted laser desorption/ionization (MALDI) database now enable accurate identification of *E. anophelis*.[14] The reference database of the MALDI-TOF MS system we utilized was updated accordingly to ensure accurate identification of the *E. anophelis* strain in this case. Thirdly, *E. anophelis* is widely present in water, soil, and medical environments, which complicates eradication efforts due to its resilience in chlorine-containing water.[15] Following the detection of *E. anophelis* in the respiratory tract of our

patient, the hospital's infectious disease department promptly initiated an investigation. This investigation involved sampling the water tank and the environment of the intensive care unit to identify potential sources of infection. However, no *E. anophelis* was detected in these samples, and no additional instances of *E. anophelis* infection were identified during the same period. Consequently, the source of infection remains unidentified. In response to such nosocomial infections, several infection control measures should be considered, including enhanced surveillance, environmental cleaning and disinfection, isolation precautions, and staff education and training. By implementing these measures, hospitals can better manage and mitigate the risks associated with nosocomial infections like *E. anophelis*.

E. anophelis exhibits resistance to a multitude of antibiotics. However, some studies have indicated that *E. anophelis* is susceptible to various antimicrobial drugs. A particular investigation into biofilm formation and antibiotic susceptibility showed that minocycline, doxycycline, and rifampin were efficacious against more than 90% of 197 *E. anophelis* isolates.[16] Furthermore, another study assessing the sensitivity of *E. anophelis* to various antibiotics revealed that minocycline had the highest sensitivity rate (>98%), followed by doxycycline (83–92%), piperacillin-tazobactam (27–-92%), levofloxacin (16–79%), and TMP-SMZ (4–92%).[10] In our patient, previous treatments included piperacillin-tazobactam, vancomycin, and voriconazole, with *E. anophelis* isolated from the patient's lower respiratory tract after 2 weeks of continuous treatment. Although previous reports indicated success with piperacillin-tazobactam and vancomycin in treating *E. anophelis* infections,[8,9] these antibiotics were ineffective in our case. This highlights the difficulty in treating pulmonary infections caused by *E. anophelis*, as confirmed by drug susceptibility testing results. Based on these results, we initially opted for TMP-SMZ as a treatment strategy against *E. anophelis* infection; however, this did not meet our expectations. It was not until we combined TMP-SMZ with eravacycline that significant therapeutic effects were noted. This suggests that eravacycline, with its broad-spectrum activity, may be effective against *E. anophelis*. Eravacycline, a groundbreaking, fully synthetic fluorocycline, has been approved for the treatment of infections caused by multidrug-resistant bacteria.[17] Studies advocate the efficacy of eravacycline in treating pulmonary infections,[18] highlighting its high concentrations in lung tissue, which are notably higher in the alveolar epithelial lining fluid and alveolar macrophages than plasma concentrations owing to its significant penetration rate.[19] Although there is limited specific clinical evidence for eravacycline's efficacy against *E. anophelis*, its successful use in treating other resistant Gram-negative infections supports its potential utility in this context.[20] Minocycline was disregarded because, despite susceptibility testing indicating sensitivity, it is limited to oral dosage forms in China. Given the patient's compromised gastrointestinal absorption and diminished effectiveness of orally administered drugs during pulmonary infection, eravacycline, which is available for intravenous use and is part of the tetracycline class, was selected. Following TMP-SMZ and eravacycline regimens, there was a noticeable improvement in the patient's pulmonary infection symptoms, laboratory indicators, and CT findings. Several factors, apart from the choice of antibiotics, likely contributed to this favorable outcome. Timely diagnosis and prompt initiation of treatment were crucial in effectively managing the infection. Supportive care measures, including nutritional support and respiratory therapy, also played significant roles in the patient's recovery. The absence of significant comorbidities allowed for a more favorable response to treatment. Furthermore, the prompt identification of the pathogen facilitated targeted therapy, enhancing the overall effectiveness of the treatment and ultimately leading to a successful conclusion.

Conclusion

In summary, the importance of early diagnosis and administration of appropriate antibiotic treatment cannot be overstated in patients with *E. anophelis* infections. Several factors contributed to the favorable outcomes observed in this case, including timely intervention, supportive care measures, and the absence of significant comorbidities. Additionally, the prompt identification of the pathogen played crucial roles in the successful management of the infection. In this context, the use of eravacycline in our case highlights its potential efficacy against multidrug-resistant organisms, supported by its mechanism of action and broad-spectrum activity. However, further clinical studies are warranted to establish its definitive role in treating *E. anophelis* infections.

Compliance with Ethics Guidelines

All identifying information has been removed or anonymized throughout the manuscript. Informed consent was obtained from the patient for publication of all related materials. All patient data was handled in accordance with applicable data protection regulations, ensuring that any information collected was stored securely and accessed only by authorized personnel. This study was approved by the Medical Ethics Committee of the Wuhan Asia Heart Hospital (approval no. 2024-B047).

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Qimei Wei and Wenxia Zuo contributed equally to this work and should be considered as co-first authors. The authors declare that they have no conflicts of interest.

References

1. Lau SK, Chow WN, Foo CH, et al. Elizabethkingia anophelis bacteremia is associated with clinically significant infections and high mortality. *Sci Rep*. 2016;6(1):26045. doi:10.1038/srep26045
2. Navon L, Clegg WJ, Morgan J, et al. Notes from the field: investigation of Elizabethkingia anophelis cluster - Illinois, 2014-2016. *MMWR Morb Mortal Wkly Rep*. 2016;65(48):1380–1381. doi:10.15585/mmwr.mm6548a6
3. Lin JN, Lai CH, Yang CH, Huang YH. Elizabethkingia infections in humans: from genomics to clinics. *Microorganisms*. 2019;7(9):295. doi:10.3390/microorganisms7090295
4. Kämpfer P, Matthews H, Glaeser SP, Martin K, Lodders N, Faye I. Elizabethkingia anophelis sp. nov. isolated from the midgut of the mosquito Anopheles gambiae. *International Journal of Systematic and Evolutionary Microbiology*. 2011;61(Pt 11):2670–2675. doi:10.1099/ijs.0.026393-0
5. Lee YL, Hsueh PR. Emerging infections in vulnerable hosts: stenotrophomonas maltophilia and Elizabethkingia anophelis. *Curr Opin Infect Dis*. 2023;36(6):481–494. doi:10.1097/qco.0000000000000953
6. Lin JN, Lai CH, Yang CH, Huang YH. Comparison of clinical manifestations, antimicrobial susceptibility patterns, and mutations of fluoroquinolone target genes between elizabethkingia meningoseptica and elizabethkingia anophelis isolated in Taiwan. *J Clin Med*. 2018;7(12):538. doi:10.3390/jcm7120538
7. Perrin A, Larsonneur E, Nicholson AC, et al. Evolutionary dynamics and genomic features of the Elizabethkingia anophelis 2015 to 2016 Wisconsin outbreak strain. *Nat Commun*. 2017;8(1):15483. doi:10.1038/ncomms15483
8. Mantoo MR, Ghimire JJ, Mahopatra S, Sankar J. Elizabethkingia anophelis infection in an infant: an unusual presentation. *BMJ Case Rep*. 2021;14(5):e243078. doi:10.1136/bcr-2021-243078
9. Seong H, Kim JH, Kim JH, et al. Risk factors for mortality in patients with elizabethkingia infection and the clinical impact of the antimicrobial susceptibility patterns of elizabethkingia species. *J Clin Med*. 2020;9(5):1431. doi:10.3390/jcm9051431
10. Mallinckrodt L, Huis in't Veld R, Rosema S, Voss A, Bathoorn E. Review on infection control strategies to minimize outbreaks of the emerging pathogen Elizabethkingia anophelis. *Antimicrob Resist Infect Control*. 2023;12(1). doi:10.1186/s13756-023-01304-1
11. Chaudhary S, Rijal A, Rajbhandari P, Acharya AB. The first reported case of elizabethkingia anophelis from Nepal. *Cureus*. 2023. doi:10.7759/cureus.45346
12. Singh N, Singh A, Gupta P, Agarwal A. Elizabethkingia anophelis infections: a case series from a tertiary care hospital in uttar Pradesh. *Cureus*. 2022. doi:10.7759/cureus.32057
13. Hu S, Jiang T, Zhang X, et al. Elizabethkingia anophelis isolated from patients with multiple organ dysfunction syndrome and lower respiratory tract infection: report of two cases and literature review. *Front Microbiol*. 2017;8. doi:10.3389/fmicb.2017.00382
14. Yung CF, Maiwald M, Loo LH, et al. Elizabethkingia anophelis and association with tap water and handwashing, Singapore. *Emerging Infectious Diseases*. 2018;24(9):1730–1733. doi:10.3201/eid2409.171843
15. Ratnamani MS, Rao R. Elizabethkingia meningoseptica: emerging nosocomial pathogen in bedside hemodialysis patients. *Indian J Critic Care Med*. 2013;17(5):304–307. doi:10.4103/0972-5229.120323
16. Hu S, Lv Y, Xu H, Zheng B, Xiao Y. Biofilm formation and antibiotic sensitivity in Elizabethkingia anophelis. *Front Cell Infect Microbiol*. 2022;12:953780. doi:10.3389/fcimb.2022.953780
17. Lee YR, Burton CE. Eravacycline, a newly approved fluorocycline. *Eur J Clin Microbiol Infect Dis*. 2019;38(10):1787–1794. doi:10.1007/s10096-019-03590-3
18. Van Hise N, Petrak RM, Skorodin NC, et al. A real-world assessment of clinical outcomes and safety of eravacycline: a novel fluorocycline. *Infect Dis Ther*. 2020;9(4):1017–1028. doi:10.1007/s40121-020-00351-0
19. Gotfried MH, Horn K, Garrity-Ryan L, et al. Comparison of omadacycline and tigecycline pharmacokinetics in the plasma, epithelial lining fluid, and alveolar cells of healthy adult subjects. *Antimicrob. Agents Chemother.* 2017;61(9). doi:10.1128/aac.01135-17
20. Zhanel GG, Cheung D, Adam H, et al. Review of eravacycline, a novel fluorocycline antibacterial agent. *Drugs*. 2016;76(5):567–588. doi:10.1007/s40265-016-0545-8