Infection and Drug Resistance

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ORIGINAL RESEARCH

Clinical Characteristics and Risk Factors for Infection and Death in Critically Ill Patients with Pulmonary Infection with *Elizabethkingia* Spp.

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Purpose: *Elizabethkingia* spp. infections have recently increased, and they are difficult to treat because of intrinsic antimicrobial resistance. This study aimed to investigate the clinical characteristics of patients with pulmonary infection with *Elizabethkingia* spp. and reveal the risk factors for infection and death.

Patients and Methods: In this retrospective case–control study, patients were divided into infection and control groups based on the bacterial identification results. Patients in the infection group were further divided into survival and death groups according to their hospital outcomes. Clinical characteristics between different groups were compared. We further analyzed antimicrobial susceptibility testing results of the isolated strains.

Results: A total of the 316 patients were divided into infection (n = 79), 23 of whom died, and control (n = 237) groups. Multivariate logistic regression analysis showed that glucocorticoid consumption (OR: 2.35; 95% CI: 1.14–4.81; P = 0.02), endotracheal intubation (OR: 3.74; 95% CI: 1.62–8.64; P = 0.002), and colistin exposure (OR: 2.50; 95% CI: 1.01–6.29; P = 0.046) were significantly associated with pulmonary infection with *Elizabethkingia* spp. Advanced age (OR: 1.07, 95% CI: 1.00–1.15; P = 0.046), high acute physiology and chronic health evaluation (APACHE) II score (OR: 1.21; 95% CI: 1.01–1.45; P = 0.037), and low albumin level (OR: 0.73, 95% CI: 0.56–0.96; P = 0.025) were significantly associated with in-hospital mortality of infected patients. *Elizabethkingia* spp. was highly resistant to cephalosporins, carbapenems, macrolides, and aminoglycoside, and was sensitive to fluoroquinolones, minocycline, and co-trimoxazole in vitro.

Conclusion: Glucocorticoid consumption, tracheal intubation, and colistin exposure were associated with pulmonary infection with *Elizabethkingia* spp. for critically ill patients. Patients with advanced age, high APACHE II score, and low albumin level had higher risk of death from infection.

Keywords: *Elizabethkingia* spp, intensive care unit, infection, mortality, antimicrobial susceptibility testing

Introduction

Pulmonary infection is one of the most common infectious diseases, resulting in the fourth leading cause of death in the world in 2019 and the second cause of death in low-income countries.[1] Nosocomial pneumonia is defined as a pulmonary infection that occurs after 48 h of admission to the hospital and accounts for 22% of nosocomial infections.[2] It is also the most common intensive care unit (ICU)-acquired infection.[3] With the increase of drug-resistant bacteria in ICU,[4] treatment of nosocomial pneumonia in critically ill patients has become challenging.

Elizabethkingia spp., belonging to the Flavobacteriaceae family, were discovered in the 1950s and was once named *Flavobacterium meningosepticum*.[5] *Elizabethkingia* spp. are aerobic, non-motile, non-sugar-fermenting, oxidase-positive, and Gram-negative bacilli.[6] They widely present in natural environments, can survive in chloride-treated urban water systems, and can colonize in hospital environments, such as ventilator tubing, humidifiers, intravenous catheters, and

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refrigerators. Due to their intrinsic resistance to a variety of antibiotics,[7–16] *Elizabethkingia* spp. can cause serious opportunistic infections. *Elizabethkingia* spp. mainly infect the infants, older people, and immunocompromised patients, leading to pneumonia, meningitis, bacteremia, and skin infections.[17–20] The mortality rate of *Elizabethkingia* spp. infections were 13.5–70%.[7–10,19–23]

Elizabethkingia spp. infection are increasing in many countries,[10,20,24] and there are outbreaks of infection.[17,21] A study in South Korea showed that the infection rate of *Elizabethkingia* spp. in inpatients of the Severance Hospital in Seoul increased from 0.002% in 2009 to 0.088% in 2017.[19] Another study in Taiwan showed that the infection rate of *Elizabethkingia* spp. in carbapenem-resistant non-fermenting, Gram-negative bacilli was only second to that of *Acinetobacter baumannii*.[25]

Although there have been some studies on *Elizabethkingia* spp. infection in China, few of them focusing on the clinical characteristic, antibiotic resistance, and risk factors of pulmonary infection with *Elizabethkingia* spp. in critically ill patients. We aim to depict those aspects of *Elizabethkingia* spp. infection and provide scientific evidence for treatment.

Materials and Methods

Research Subjects

This retrospective case–control study was conducted at the First Affiliated Hospital of Nanjing Medical University. The clinical data of critically ill patients with pulmonary infection with *Elizabethkingia* spp. who admitted to ICU between 1 January 2019 and 30 November 2021 were collected. Only the first episode was considered for patients with more than one positive *Elizabethkingia* spp. culture. Pulmonary infection with *Elizabethkingia* spp. criteria: (1) positive *Elizabethkingia* spp. detection in sputum or alveolar lavage fluid samples; (2) body temperature >38°C, white blood cell counts $>12\times10^9$/L, and typical chest imaging features. Exclusion criteria: (1) hospital stay <48 h; (2) age <18 years old; (3) who had multiple bacterial species detected in their culture simultaneously; (4) clinical data incomplete.

Control group defined as selected patients with non-*Elizabethkingia* spp. infection who hospitalized in the same ward during the same time (at a 3:1 ratio to the infection group).

Clinical data, including age, gender, underlying diseases, Charlson comorbidity index (CCI), acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, vital signs, chest imaging results, laboratory results, antibiotic treatments, and invasive procedures, were collected from the electronic medical record system. The main outcome measure of this study was in-hospital mortality.

Recent surgery was defined as surgery performed within 14 days before the first diagnosis of *Elizabethkingia* spp. infection. The use of glucocorticoids was defined as at least 20 mg of prednisone per day or equivalent. Antibiotic exposure was defined as treatment with antibiotic intravenously or by nebulization for more than 24 h within 1 month before *Elizabethkingia* spp. infection. Susceptible antibiotic therapy was defined as the use of at least one antibiotic to which the *Elizabethkingia* spp. was susceptible according to the minimum inhibitory concentration (MIC) within 72 h of confirmed infection.

Bacterial Identification and Antimicrobial Susceptibility Tests

Specimens were cultured and isolated in accordance with the third edition of National Clinical Laboratory Procedures. Following incubation on 5% sheep blood agar and MacConkey agar plates (bioMerieux, Shanghai, China) and incubated at 35 °C for 18–24 h, all positive cultures were subjected to Gram staining and microscopic examinations. Microbial identification was performed using the VITEK-2 system (bioMerieux, Marcy L'Etoile, France).

Susceptibilities of the isolates to antimicrobials were determined using epsilometer test (E-test) strips (bioMerieux, Marcy L'Etoile, France). The results of antimicrobial susceptibility testing (AST) were determined according to the Clinical and Laboratory Standards Institute (CLSI) M100 (2020) for "other non-Enterobacteriaceae" as there are no standard guidelines for reporting AST for *Elizabethkingia* spp.

Statistical Analysis

As mentioned above, all patients were divided into infection and control groups. Patients in the infection group were subdivided into death and survival groups according to their prognosis. Continuous variables are presented as median and

interquartile ranges [M(P25, P75)] and were compared between groups using the Mann–Whitney *U*-test. Categorical variables are presented as frequency and percentile and were compared between groups using the chi-square test or Fisher's exact test. The variance inflation factor (VIF) was calculated to assess the multicollinearity problem. Univariate logistic regression analysis was used to analyze the factors related to infection and death in the patients. Variables with a statistical significance of $P < 0.1$ and $VIF < 2$ were included in the multivariate logistic regression analysis to determine the risk factors. The results were presented as an adjusted odds ratio (OR) and 95% confidence interval (CI). All statistical analyses were performed using R 4.2.2 software (The R Project for Statistical Computing, Vienna Austria). A $P < 0.05$ was considered statistically significant.

Ethics

This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2023-SR-412), which also exempted this trial from informed consent, considering that obtaining informed consent was impractical. Patient data was maintained with confidentiality. The study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards.

Results

General Conditions

A total of 114 critically ill patients had *Elizabethkingia* spp. isolated from the respiratory tract from 1 January 2019 to 30 November 2021, of which 79 patients were included in the infection group. A total of 237 were included in the control group. Patients in the infection group were divided into a death group, including 23 patients, and a survival group, including 56 patients, based on hospitalization outcomes. Details are shown in Figure 1. The median age of the infection group was 66 (52–72.5) years old, and 51 (64.6%) were males. Compared to the control group, more patients in the infection group use glucocorticoid (25.3% vs 13.5%), carbapenem antibiotics (63.3% vs 47.3%), and colistin (15.2% vs 5.49%) and have higher rates of invasive procedures such as indwelling central venous catheters (83.5% vs 67.5%), bronchoscopy (38% vs 20.7%), mechanical ventilation (81% vs 67.9%), and endotracheal intubation (88.6% vs 64.6%). Twenty-three (29.1%) infected patients died during hospitalization, a higher proportion than that of the control group, but the difference was not statistically significant. Compared to the surviving group, the mortality group had a higher proportion of patients with higher age (76 vs 64), disease severity score, coronary artery disease (34.8% vs 12.5%), kidney disease (47.8% vs 19.6%), and hemodialysis treatment (47.8% vs 14.3%), and lower recent surgery (30.4% vs 64.3%), hemoglobin (83 vs 95.5), platelets (106 vs 172), and serum albumin (31.3 vs 35.6). The demographic and clinical characteristics of the enrolled patients are detailed in Tables 1 and 2.

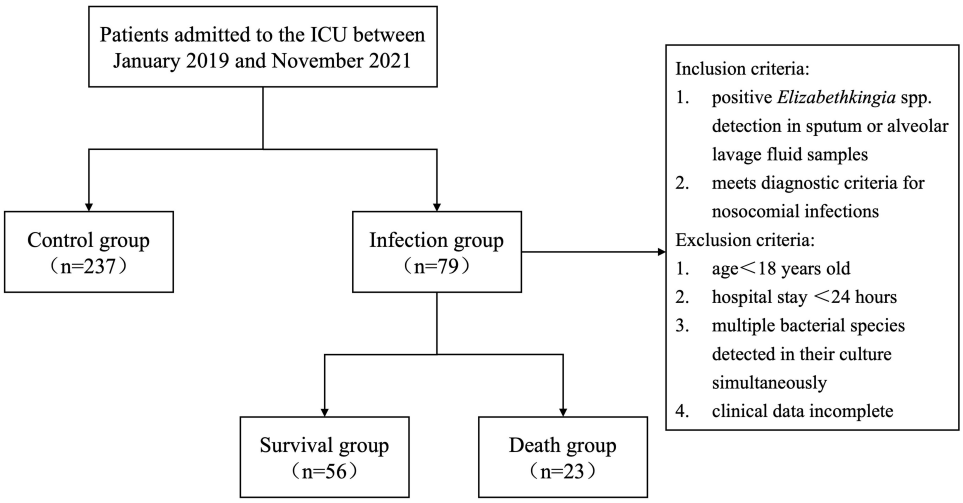

Figure 1 Flowchart of the study.

Table 1 Baseline Demographic and Clinical Characteristics Between Patients in Infection and Control Group

Characteristics		Infection Group	Control Group	P-value
		N = 79	N = 237	
Age (year), median (IQR)		66.0 (52.0, 72.5)	62.0 (52.0, 70.0)	0.178
Male, n (%)		51 (64.6)	158 (66.7)	0.837
CCI, median (IQR)		3.0 (2.0, 4.5)	3.0 (1.0, 5.0)	0.508
APACHE II score, median (IQR)		18 (13, 24)	17 (12, 21)	0.068
Comorbidity, n (%)				
	Hypertension	35 (44.3)	101 (42.6)	0.896
	Diabetes	17 (21.5)	54 (22.8)	0.938
	Coronary artery disease	15 (19)	38 (16)	0.664
	Central nervous system disorders	39 (49.4)	122 (51.5)	0.845
	COPD	6 (7.59)	13 (5.49)	0.584
	Liver diseases	12 (15.2)	29 (12.2)	0.629
	Kidney diseases	22 (27.8)	44 (18.6)	0.11
	Solid tumors	10 (12.7)	38 (16)	0.587
	Hematologic cancers	1 (1.27)	1 (0.42)	0.438
Surgical treatment, n (%)		43 (54.4)	121 (51.1)	0.697
Glucocorticoid consumption, n (%)		20 (25.3)	32 (13.5)	0.023
Invasive operation, n (%)				
	Central venous catheterization	66 (83.5)	160 (67.5)	0.01
	Gastrointestinal intubation	65 (82.3)	153 (64.6)	0.005
	Chest/abdominal tube insertion	27 (34.2)	87 (36.7)	0.787
	Intracranial drainage tube	12 (15.2)	31 (13.1)	0.776
	Bronchoscopy	30 (38)	49 (20.7)	0.003
Treatment measure, n (%)				
	Renal replacement therapy	19 (24.1)	37 (15.6)	0.126
	Mechanical ventilation	64 (81)	161 (67.9)	0.038
	Endotracheal intubation	70 (88.6)	153 (64.6)	<0.001
Antibiotic exposure, n (%)				
	Cephalosporin	52 (65.8)	138 (58.2)	0.289
	Enzyme-containing inhibitors	42 (53.2)	139 (58.6)	0.47
	Aminoglycosides	8 (10.1)	15 (6.33)	0.381
	Macrolides	0 (0)	1 (0.42)	1
	Fluoroquinolones	21 (26.6)	65 (27.4)	1
	Carbapenem	50 (63.3)	112 (47.3)	0.019
	Glycopeptide	27 (34.2)	70 (29.5)	0.526
	Colistin	12 (15.2)	13 (5.49)	0.012
	Others	40 (50.6)	85 (35.9)	0.028
In-hospital mortality, n (%)		23 (29.1)	51 (21.5)	0.22

Abbreviations: CCI, Charlson comorbidity index; APACHE II, acute physiology and chronic health evaluation II; COPD, chronic obstructive pulmonary disease.

Risk Factors for Pulmonary Infection with Elizabethkingia spp

Univariate logistic regression analysis showed that patients in the infection group had higher APACHE II score and higher proportions of kidney diseases, glucocorticoid consumption, central venous catheterization, gastrointestinal intubation, bronchoscopy, renal replacement therapy (RRT), mechanical ventilation, endotracheal intubation, carbapenem exposure, and colistin exposure than patients in the control group ($P < 0.1$). Multivariate logistic regression analysis of the above variables showed that glucocorticoid consumption (OR: 2.35; 95% CI: 1.14–4.81; $P = 0.02$), endotracheal intubation (OR: 3.74; 95% CI: 1.62–8.64; $P = 0.002$), and colistin exposure (OR: 2.50; 95% CI: 1.01–6.29; $P = 0.046$) were associated with pulmonary infection with *Elizabethkingia* spp. (Table 3).

Table 2 Baseline Demographic and Clinical Characteristics Between Patients in Survival and Death Group

Characteristics		Survival Group	Death Group	P-value
		N = 56	N = 23	
Age (year), median (IQR)		64 (50.8, 69)	76 (65, 82.5)	0.001
Male, n (%)		34 (60.7)	17 (73.9)	0.392
Hospital stays before bacterial isolation (day), median (IQR)		14.5 (10, 24)	16 (8, 22.5)	0.931
ICU stays before bacterial isolation (day), median (IQR)		11.5 (7, 20)	12 (7, 18.5)	0.961
Hospital stays (day), median (IQR)		28.5 (23, 42)	27 (20, 42.5)	0.876
ICU stays (day), median (IQR)		27 (13.8, 38.5)	23 (17, 32)	0.94
CCI, median (IQR)		2 (2, 4)	5 (2.5, 7)	0.001
APACHE II score, median (IQR)		16 (12.5, 23)	22 (21, 27)	0.002
SOFA score, median (IQR)		5 (3,7)	10 (7.5, 12.5)	<0.001
Comorbidities, n (%)				
	Hypertension	22 (39.3)	13 (56.5)	0.249
	Diabetes	9 (16.1)	8 (34.8)	0.078
	Coronary artery disease	7 (12.5)	8 (34.8)	0.03
	Central nervous system disorders	29 (51.8)	10 (43.5)	0.672
	COPD	3 (5.36)	3 (13)	0.35
	Liver diseases	8 (14.3)	4 (17.4)	0.738
	Kidney diseases	11 (19.6)	11 (47.8)	0.024
	Cancer	7 (12.5)	5 (21.7)	0.282
Surgical treatments, n (%)		36 (64.3)	7 (30.4)	0.013
Glucocorticoid consumption, n (%)		13 (23.2)	7 (30.4)	0.7
Invasive operation, n (%)				
	Central venous catheterization	45 (80.4)	21 (91.3)	0.326
	Gastrointestinal intubation	44 (78.6)	21 (91.3)	0.215
	Chest/abdominal tube insertion	20 (35.7)	7 (30.4)	0.851
	Intracranial drainage tube	11 (19.6)	1 (4.35)	0.164
	Bronchoscopy	18 (32.1)	12 (52.2)	0.158
Treatment measure, n (%)				
	Renal replacement therapy	8 (14.3)	11 (47.8)	0.004
	Mechanical ventilation	42 (75)	22 (95.7)	0.055
	Endotracheal intubation	48 (85.7)	22 (95.7)	0.271
Laboratory tests, median (IQR)				
	WBC	9.68 (7.14, 12.4)	8.26 (7.38, 11)	0.682
	Neu	7.23 (5.27, 10)	6.58 (5.85, 9.77)	0.734
	Hb	95.5 (84.8, 105)	83 (73, 90.5)	<0.001
	PLT	172 (113, 264)	106 (85.5, 154)	0.013
	TB	15.4 (10.3, 23.3)	21 (12.2, 33.3)	0.216
	Alb	35.6 (32.8, 38)	31.3 (29.8, 32.6)	<0.001
	Cr	67.7 (44.3, 94.8)	101 (56.2, 119)	0.039
	Pct	0.35 (0.11, 1.82)	0.61 (0.43, 2.06)	0.069
Antibiotic therapy, n (%)				
	Cephalosporin	14 (25)	4 (17.4)	0.662
	Enzyme-containing inhibitors	34 (60.7)	15 (65.2)	0.905
	Aminoglycosides	2 (3.57)	2 (8.7)	0.576
	Macrolides	56 (100)	23 (100)	1
	Fluoroquinolones	29 (51.8)	7 (30.4)	0.138
	Carbapenem	24 (42.9)	10 (43.5)	1
	Glycopeptide	18 (32.1)	6 (26.1)	0.793
	Colistin	5 (8.93)	5 (21.7)	0.145
	Others	15 (26.78)	7 (30.43)	0.872
Susceptible antibiotic therapy, n (%)		37 (66.1)	10 (43.5)	0.076

Abbreviations: CCI, Charlson comorbidity index; APACHE II, acute physiology and chronic health evaluation II score; SOFA: sequential organ failure assessment score; COPD, chronic obstructive pulmonary disease; WBC, White blood cell count; Neu, Neutrophil count; Hb, Hemoglobin; PLT, Platelets; TB: total bilirubin; Alb: Albumin; Cr: Creatinine; Pct: Procalcitonin.

Table 3 Risk Factors for Pulmonary Infection with Elizabethkingia Spp

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
APACHE II score	1.04 (1.00–1.07)	0.033		
Kidney diseases	1.69 (0.92–3.05)	0.087		
Glucocorticoid consumption	2.17 (1.14–4.06)	0.019	2.35 (1.14–4.81)	0.02
Central venous catheterization	2.42 (1.29–4.85)	0.005		
Gastrointestinal intubation	2.52 (1.37–4.95)	0.003		
Bronchoscopy	2.34 (1.34–3.08)	0.003		
Renal replacement therapy	1.71 (0.90–3.18)	0.099		
Mechanical ventilation	2.0 (1.09–3.86)	0.024		
Endotracheal intubation	4.2 (2.08–9.46)	<0.001	3.74 (1.62–8.64)	0.002
Carbapenem exposure	1.92 (1.14–3.27)	0.014		
Colistin exposure	3.08 (1.31–7.16)	0.01	2.50 (1.01–6.29)	0.046

Risk Factors for Death in Infected Patients

Patients with pulmonary infection with *Elizabethkingia* spp. in the death group had higher age, APACHE II score, SOFA score, creatinine, proportions of with diabetes, coronary artery diseases, kidney diseases, use of RRT and mechanical ventilation than that in the survival group. In contrast, survival patients more likely to have higher levels of hemoglobin, platelets, albumin, and fluoroquinolones and susceptible antibiotic therapy ($P < 0.1$). Multivariate logistic regression analysis showed that advanced age (OR: 1.07, 95% CI: 1.00–1.15; P = 0.046), high APACHE II score (OR: 1.21; 95% CI: 1.01–1.45; P = 0.037), and low albumin level (0.73, 95% CI: 0.56–0.96; P = 0.025) were risk factors for death in the infected patients (Table 4).

Drug Susceptibility Results

Elizabethkingia spp. isolated are resistant to commonly used antibiotics. The first antimicrobial susceptibility testing results for *Elizabethkingia* spp. isolated from infected patients are provided in Table 5.

Table 4 Risk Factors for Death in Patients with Pulmonary Infection with Elizabethkingia Spp

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.07 (1.02–1.12)	0.003	1.07 (1.00, 1.15)	0.046
APACHE II score	1.11 (1.04–1.19)	0.003	1.21 (1.01–1.45)	0.037
SOFA score	1.85 (1.39–2.46)	<0.001		
Diabetes	2.74 (0.87–8.63)	0.083		
Coronary artery diseases	3.65 (1.11–12.3)	0.033		
Kidney diseases	3.67 (1.27–10.9)	0.016		
Surgical treatment	0.33 (0.12–0.85)	0.021		
Renal replacement therapy	5.32 (1.76–17)	0.003		
Mechanical ventilation	6.42 (1.15–163)	0.031		
Hb	0.95 (0.92–0.99)	0.009		
Plt	0.99 (0.99–1)	0.035		
Alb	0.76 (0.65–0.91)	0.002	0.73 (0.56–0.96)	0.025
Cr	1.01 (1–1.01)	0.068		
Fluoroquinolone therapy	0.42 (0.14,1.15)	0.091		
Susceptible antibiotic therapy	0.4 (0.14–1.09)	0.072		

Table 5 Results of Antimicrobial Susceptibility Testing of Commonly Used Antibiotics for Elizabethkingia Spp

Antibiotics	Number of Detected Strains (n)	Susceptible		Intermediate		Drug-Resistant	
		Number of Strains (n)	Percentage (%)	Number of Strains (n)	Percentage (%)	Number of Strains (n)	Percentage (%)
Piperacillin	79	14	17.7	56	70.9	9	11.4
Ceftazidime	79	0	0	0	0	79	100
Ceftriaxone	79	0	0	0	0	79	100
Cefepime	79	0	0	0	0	79	100
Piperacillin–Tazobactam	79	57	72.2	5	6.33	17	21.5
Cefoperazone–Sulbactam	11	3	27.3	0	0	8	72.7
Aztreonam	79	0	0	0	0	79	100
Imipenem	79	0	0	0	0	79	100
Meropenem	79	0	0	0	0	79	100
Amikacin	79	1	1.27	1	1.27	77	97.5
Gentamicin	79	2	2.53	3	3.8	74	93.7
Tobramycin	79	0	0	0	0	79	100
Ciprofloxacin	79	46	58.2	2	2.53	31	39.2
Levofloxacin	79	53	67.1	1	1.27	25	31.6
Co-trimoxazole	79	56	70.9	0	0	23	29.1
Vancomycin	12	0	0	2	16.7	10	83.3
Tigecycline	6	2	33.3	1	16.7	3	50
Minocycline	4	3	75	0	0	1	25
Ceftazidime and avibactam	6	2	33.3	0	0	4	66.7

Discussion

Critically ill patients with impaired immune function and high rates of antimicrobial drug use are prone to nosocomial infections. In this study, we determined the risk factors for pulmonary infection with *Elizabethkingia* spp. in critically ill patients by logistic regression analysis. We further analyzed the risk factors for death in critically ill patients infected with *Elizabethkingia* spp. Because *Elizabethkingia* spp. is resistant to commonly used antibiotics, we also statistically analyzed the resistance of *Elizabethkingia* spp. in our region. It provides a reference for clinicians to diagnose and treat *Elizabethkingia* spp. infections.

Studies have shown that more than 85% of patients with *Elizabethkingia* spp. infection have at least one underlying disease.[18,26,27] In addition, diabetes, hypertension, end-stage kidney disease, malignancy, immunosuppressive therapy, invasive operation, and history of antibiotic exposure are risk factors for *Elizabethkingia* spp. infection.[9,10,17–19,23,28] In our study, the proportions of use glucocorticoid, carbapenem antibiotics, colistin, and invasive procedures such as indwelling central venous catheters, bronchoscopy, mechanical ventilation, and endotracheal intubation in patients with *Elizabethkingia* spp. infection were high. In addition, glucocorticoid consumption, endotracheal intubation, and colistin exposure were risk factors for *Elizabethkingia* spp. infection. *Elizabethkingia* spp. can form biofilms,[11] facilitating their colonization in hospital environments, such as sinks and ventilator tubing that are difficult to remove. Glucocorticoids have multiple functions,[29] patients with asthma, autoimmune diseases, organ transplantation, etc., need to use glucocorticoids, and the surviving sepsis campaign guideline suggests that patients with septic shock can be treated with glucocorticoids.[30] However, glucocorticoids have significant side effects along with their therapeutic effects, such as elevated blood glucose, metabolic disorders, and suppression of immune function. Studies have shown that the incidence of serious and opportunistic infections increases with glucocorticoid use.[31] When patients are undergoing invasive procedures such as endotracheal intubation, the *Elizabethkingia* spp. can enter the body and induce opportunistic infections.[19] Carbapenem-resistant Enterobacteriaceae infections pose a major threat to human health due to limited treatment options. Colistin-based regimens have become a major treatment option,[32,33] and long courses of colistin therapy have reduced 30-day mortality in critically ill patients.[34] However, Huang et al showed that patients who

received nebulized colistin had a relatively high proportion of *Elizabethkingia* spp. infection,[25] and although the method of colistin use was different from that of our study, the results all demonstrated that the use of colistin was associated with *Elizabethkingia* spp. infections. *Elizabethkingia* spp. may become dominant and cause infection when using colistin due to its natural resistance to colistin. Hus et al showed that *Elizabethkingia* spp. isolated from approximately one of two adults and one of three infants were colonized bacteria.[35] In this study, among the 114 critically ill patients with *Elizabethkingia* spp. isolated from the respiratory tract, 79 patients (69.3%) were diagnosed with *Elizabethkingia* spp. infection. This rate was higher than in previous studies and may be related to the poor conditions, more invasive procedures and the high percentage of colistin use in critically ill patients.

The mortality rates of patients infected with *Elizabethkingia* spp. range from 13.5% to 70%.[7–10,19–23] For example, 25 of 75 patients with *Elizabethkingia* spp. infection died during the outbreak of *Elizabethkingia* spp. in Wisconsin and Illinois in the United States in 2014–2016.[36] In 2019, four of six children with *Elizabethkingia* spp. infection in the pediatric ICU of a hospital in Turkey died.[21] In this study, the mortality of critically ill patients with pulmonary infection with *Elizabethkingia* spp. was 29.1% (23/79 cases). The results of the multifactor logistic regression showed that advanced age, high APACHE II score, and low albumin level were risk factors for death in patients with pulmonary infection with *Elizabethkingia* spp. Aging is associated with changes in physiological, biological, immunological, and behavioral. Increased age leads to a progressive loss of cellular function and tissue renewal and a decline in immune function, which increases susceptibility to infection.[37,38] Previous studies have confirmed that high simplified acute physiological score (SAPS) II, elevated C-reactive protein-to-albumin ratio, and reduced hemoglobin level were correlated with death in patients with *Elizabethkingia* spp. infection.[10,18,22] SAPS II score and APACHE II score are tools for assessing the severity of disease in critically ill patients, and several studies have shown that the APACHE II score has a good predictive efficacy for patient prognosis.[39] Serum albumin plays an important role in volume expansion, maintenance of vascular endothelial integrity, and anti-inflammation.[40] Reduced serum albumin levels are strongly associated with mortality in patients with cardiovascular disease, heart failure, and cirrhosis.[41,42]

Resistant to multiple antibiotics is one of the biological characteristics of *Elizabethkingia*.[9–13,18,26,43] In our study, the rates of resistance to cephalosporins, aztreonam, imipenem, and meropenem reached 100%. *Elizabethkingia* spp. carries two types of antimicrobial resistance genes. These include bla_{CME}, which encodes an extended spectrum β-lactamase that mainly mediates resistance to cephalosporins, and bla_{BlaB} and bla_{GOB}, which encode metallo-β-lactamase that mediates resistance to all β-lactam antibiotics, including carbapenems.[9,10,17] However, the susceptibility of *Elizabethkingia* spp. to antibiotics containing enzyme inhibitors varies considerably. The susceptibility of isolated strains to piperacillin–tazobactam was 72.2%, while their rates of resistance to cefoperazone–sulbactam and ceftazidime–avibactam were 72.7% and 66.7%, respectively. *Elizabethkingia spp*. also carries GCN5-related N-acetyltransferases (GNATs) and nucleoside transferase (ANT(6)), which mediate resistance to aminoglycoside antibiotics. Shirmast et al showed that the carrying rate of the *ant(6)* gene of this bacterial genus was 92.4–100%.[16] In this study, the isolate strains were 100% resistant to tobramycin and >90% resistant to amikacin and gentamicin. More than 83% isolated strains were resistance to vancomycin. *Elizabethkingia* spp. carry *vanW* and *vanB* genes, which encode metabolic enzymes to synthesize low-affinity precursors to eliminate vancomycin targets.[14,44] The susceptibilities of isolated strains to ciprofloxacin and levofloxacin were 58.2% and 67.1%. Studies have shown multiple amino acid mutations in the quinolone resistance determination region (QRDR) of the DNA gyrase subunits or topoisomerase IV subunits of *Elizabethkingia* spp., leading to a decrease in the affinity or inability of binding between target proteins and drugs.[9,17,18,26] In our study, *Elizabethkingia* spp. were susceptible to co-trimoxazole (70.9%) and minocycline (75%). In addition, *Elizabethkingia* spp. have multiple drug-resistance mechanisms via chloramphenicol acetyltransferase, ribosomal protection proteins, and multidrug efflux pumps, which are related to resistance to chloramphenicol, tetracycline, and erythromycin.[11,14,16]

Moreover, the drug resistance of *Elizabethkingia* spp. varies in different regions. For example, more than 88% of *Elizabethkingia* spp. in the United States, South Korea, Taiwan, and Shanghai are susceptible to piperacillin–tazobactam.[7,17,18,26,45] However, 68.7% of the isolated *Elizabethkingia* spp. strains in the Australia are resistant to piperacillin–tazobactam.[14] In Taiwan, *Elizabethkingia* spp. had a susceptibility to fluoroquinolones of 78.6% in Kaohsiung[13] and a resistance rate of 85% in Taipei.[26]

How to treat patients infected with *Elizabethkingia* spp. is a tricky question. Previous studies suggest that removal of indwelling intravenous catheters improves the curative rate in patients with *Elizabethkingia* spp. infection.[21,27] The early identification of these clinical factors in patients with *Elizabethkingia* spp. infection could be essential to improve prognosis. Lack of effective antibiotic treatment is an independent predictor of death.[35] Although *Elizabethkingia* spp. has been reported to be sensitive to minocycline, piperacillin–tazobactam, and fluoroquinolones, the benefits of using fluoroquinolones[46,47] and piperacillin-tazobactam[10,21] have been conflicting in different studies. This may be related to the complex drug-resistance mechanism of *Elizabethkingia* spp., and the drug resistance of *Elizabethkingia* spp. varies among different strains and in different regions. Patients with *Elizabethkingia* spp. infection should be treated promptly according to the results of drug-susceptibility testing. Literature reports that the MIC value of *Elizabethkingia* spp. to vancomycin is usually 8–256 mg/L, [7,18] and in this study, no vancomycin-sensitive *Elizabethkingia* spp. strains were isolated. However, other studies have shown that the combined use of vancomycin with other antibiotics achieved bacterial clearance and curative outcomes in clinical practice.[24] The mechanism may be that vancomycin controls Gram-positive bacterial infection while destroying the cell wall of *Elizabethkingia* spp., which facilitates the entry of other drugs into the bacteria for action.

Nevertheless, this study has certain limitations. First, there was no species classification or gene sequencing of the genus *Elizabethkingia* spp. Second, the results and conclusion of this single-center study may be affected by geographic location, hospital management strategies, and infection control policies. Furthermore, due to the retrospective research design, some key factors of *Elizabethkingia* spp. infection may have been overlooked, without intervention on the use of antibiotics. Finally, the relatively small sample size of this study may affect the reliability of the results.

Conclusion

Elizabethkingia spp. is a common pathogen in the ICU with multi-drug resistance and requires considerable attention in clinical practice. Patients with glucocorticoid, endotracheal intubation and colistin are prone to *Elizabethkingia* spp. infection. Patients with *Elizabethkingia* spp. infection, along with advanced age, high APACHE II score, and low albumin level, should be of particular concern. Minocycline, and co-trimoxazole can be used empirically.

Abbreviations

ICU, intensive care unit; CCI, Charlson comorbidity index; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment score; MIC, minimum inhibitory concentration; AST, antimicrobial susceptibility testing; VIF, variance inflation factor; OR, odds ratio; CI, confidence interval; RRT, renal replacement therapy; COPD, chronic obstructive pulmonary disease; WBC, White blood cell count; Neu, Neutrophil count; Hb, Hemoglobin; PLT, Platelets; TB, total bilirubin; Alb: Albumin; Cr: Creatinine; Pct: Procalcitonin; SAPS II, simplified acute physiological score II; QRDR, quinolone resistance determination region.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2023-SR-412), with a waiver of informed consent. The study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards.

Author Contributions

All authors made a significant contribution to the work reported, whether that is 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.

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Disclosure

The authors declare that they have no competing interests in this work.

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