Infection and Drug Resistance

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ORIGINAL RESEARCH

Emerging Prevalence and Clinical Features of *Elizabethkingia meningoseptica* Infection in Southwest China: A 9-Year Retrospective Study and Systematic Review

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Background: *Elizabethkingia meningoseptica* infections have gradually emerged as life-threatening nosocomial infections worldwide, accompanied by increasing incidence, multidrug resistance and poor outcomes. However, the epidemiology and clinical features of *E. meningoseptica* infection are still limited in mainland China.

Methods: Patients with *E. meningoseptica* infections from 2011 to 2019 in southwestern China were retrospectively analyzed. The clinical features, infection patterns and outcomes were extracted from medical records and analyzed. A comprehensive systematic review was performed in accordance with PRISMA guidelines from conception to August 23, 2021.

Results: Ninety-two patients were ultimately included, with the prevalence rapidly rising from 0 in 2011 to 0.19 per 1000 inpatients in 2019. A total of 93.48% of *E. meningoseptica* isolates were multidrug resistant, including 100% resistance to carbapenem. Furthermore, 75% of *E. meningoseptica* infections were concomitant with other pathogens. The mortality of our cohort was 36.96%, with risk factors for mechanical ventilation (OR=9.51, P=0.004), male sex (OR=0.27, P=0.031) and more concomitant pathogens. After propensity score matching, central venous catheters, exposure to carbapenem and antifungal drugs, and underlying tumors were associated with *E. meningoseptica* infection. Sixteen articles were also summarized, with reported mortality rates ranging from 11.0% to 66.6%. Blood and respiratory tract were the common sources. Piperacillin/tazobactam, trimethoprim/sulfamethoxazole, fluoroquinolone and minocycline were the most sensitive antibiotics. Inappropriate antibiotic treatment was the most commonly reported risk factor for mortality.

Conclusion: Nosocomial infection with *E. meningoseptica* has become an emerging problem with high mortality in southwestern China. Inappropriate antibiotic treatment and central venous catheters are risk factors for infection and death and should receive adequate attention.

Keywords: meningoseptica, nosocomial infection, epidemiology, risk factor, multidrug resistance, infection control

Introduction

Elizabethkingia meningoseptica (*E. meningoseptica*), also known as *Chryseobacterium meningosepticum and Flavobacterium meningosepticum*, is a nonfermentative, nonmotile, oxidase- and catalase-positive, aerobic, gram-negative bacterium.[1] Although *E. meningoseptica* is ubiquitously distributed in water, soil and medical devices, *E. meningoseptica infection* in humans is relatively rare and was first reported in 1959.[2] *E. meningoseptica* is an opportunistic pathogen and

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primarily infects immunocompromised patients such as elders and neonates as well as those with sepsis, diabetes, malignant tumors, hypertension and critical conditions. In particular, meningitis in premature infants and low-weight neonates caused by *E. meningoseptica* has been reported to occur more frequently.[3,4] Therefore, *E. meningoseptica* infection is gradually becoming a life-threatening nosocomial infection worldwide.

Unfortunately, *E. meningoseptica* infection is difficult to treat and can lead to high mortality. The drug-resistant spectrum of *E. meningoseptica* is obviously different from that of other gram-negative bacteria. *E. meningoseptica* possesses two different main types of β-lactamases: class A extended-spectrum β-lactamases (ESBLs) and class B metallo-β-lactamases (MBLs).[5,6] ESBLs confer resistance to cephalosporin, while MBLs produce resistance to carbapenems. *E. meningoseptica* infection can manifest as pneumonia, meningitis, skin infections and even bacteremia.[7] The mortality of *E. meningoseptica* infection has been documented as high as 65.6% in adult patients with bacteremia[8] and 66.7% in pediatric patients.[9]

However, the epidemiology, risk factors, clinical treatment and outcomes of *E. meningoseptica* infection remain largely undefined owing to the low rate of *E. meningoseptica* infection. Most published articles are case reports, case series, and retrospective studies with relatively small sample sizes. To our knowledge, no related data in mainland China have been published. Therefore, a nine-year retrospective study of all patients with *E. meningoseptica* infection and a systematic review of published articles were conducted in this study to evaluate the epidemiology, clinical features, treatment, outcomes and risk factors for *E. meningoseptica* infection and death.

Methods

Study Design and Ethical Approval

This study comprised a retrospective study and a systematic review. This nine-year retrospective study was conducted between 1/1/2011 and 31/12/2019 in the Southwest Hospital of the Army Medical University. The Southwest Hospital is located in southwestern China and receives approximately 130,000 inpatients annually. Ethics approval was granted by the Ethics Committee of Southwest Hospital (No. KY201991). Because this study did not refer to the privacy of any individual, written informed consent was not needed. Furthermore, a systematic review of studies on *E. meningoseptica* infection in all populations was also conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10]

Patient Screening, Propensity Score Matching and Data Extraction

A thorough search was conducted in the LIS system, WHOnet database and electronic medical records to identify patients with *E. meningoseptica* infection in our hospital. Patients meeting the following criteria were included: patients with a definite diagnosis of *E. meningoseptica* infection admitted between January 1, 2011, and December 31, 2019. Exclusion criteria included patients who had *E. meningoseptica* infection at admission, patients who had a positive culture but no clinical symptoms or signs, and patients with incomplete clinical data. To screen risk factors for infection, patients with similar age, sex, diagnosis, department and years were randomly matched at a 1:1.2 ratio through the propensity score matching method. The extracted data included mainly demographic data (gender, age, height, weight), clinical factors (diagnosis, department, central venous catheterizations [CVCs], mechanical ventilation, operations, underlying diseases), infection information (pathogen sources, antimicrobial spectrum, coinfections, treatment, white blood cell count, platelet count, neutrophil percentage and others), and outcomes (death, survival).

Definition

E. meningoseptica infection was diagnosed according to the Centers for Disease Control and Prevention criteria. *E. meningoseptica* infection was suspected when clinicians decided to change the antibiotic strategy and was diagnosed based on the following criteria:[11] 1) body temperature newly elevated to higher than 38°C; 2) leukocyte count decreased to $<4 \times 10^9$ cells/L or increased to more than 12×10^9 cells/L; 3) new pulmonary infiltrations appeared on chest radiography; 4) positive bacterial culture of blood, sputum, urine or wounds. According to proposals by international experts,[12] multidrug resistance (MDR) indicates acquired resistance to at least one agent in three or more antimicrobial

categories. Extensive drug resistance (XDR) is defined as the resistance of a pathogen to at least one agent in all except two or fewer antimicrobial categories.

Bacterial Isolate Identification and Antimicrobial Susceptibility Test

In accordance with standards from the Clinical and Laboratory Standards Institute (CLSI), identifications were routinely accomplished through VITEK-2 compact system analysis (bioMérieux, France), and positive samples were further confirmed by MALDI-TOF-MS methods to discriminate between *Elizabethkingia anopheles* and *E. meningoseptica*. In detail, MALDI-TOF-MS was performed on a MALDI instrument (Bruker, Germany) with the in-house expanded spectrum database (DB-10694-3813 database) and expanded spectral library provided by the CDC (https://microbenet.cdc.gov/). Antimicrobial susceptibility tests were conducted according to the CLSI document M100.

Systematic Review

The PubMed/MEDLINE, Web of Science and Embase databases were thoroughly searched from conception to August 23, 2021, using the following strategy: "Elizabethkingia meningoseptica" or "meningoseptica" in the title/abstract field. The search was limited to publications published in English from conception to August 23, 2021. Basic studies focusing only on molecular and genetic mechanisms and not including patients were excluded. Papers describing *E. anopheles* were also excluded. Moreover, case reports and series (sample size less than 5), surveys, and hospital infection control policies were excluded. The quality of the included articles was evaluated with the Joanna Briggs Institute (JBI) checklist for prevalence systematic reviews.[13] The article information, including author, year, country, study type, study period, sample size, sex, age, treatment, mortality, identification methods, length of stay prior to infection, risk factors for death, risk factors for infection, pathogen sources, and drug resistance, was extracted. The clinical outcome was all-cause in-hospital death.

Statistical Analysis

The data were analyzed with SPSS 25.0 statistical software. Categorical data are expressed as frequencies and percentages. Chi-square tests or Fisher's exact tests were used to compare categorical variables (gender, hypertension, diabetes, operation, mechanical ventilation, CVCs, intensive care unit [ICU] admission, principal disease, fungal infection, exposure to different antibiotics, mortality). Continuously quantitative data (age, diagnosis days, white blood cell [WBC] count, neutrophil percentage, platelet count, lymphocyte count, lymphocyte percentage, proealcitonin) were expressed as the mean ± standard deviation and compared by *t* test. Discontinuously quantitative data (numbers of coinfected pathogens) were expressed as the median ± interquartile range (IQR) (difference between 75th to 25th percentiles) and were subjected to the Mann–Whitney *U*-test. Multiple logistic regression analyses were used to identify risk factors for infection and death. Variable assignments are detailed in Tables S1 and S2. The significance level was set as 0.05.

Results

Incidence and Baseline

From January 2011 to December 2019, a total of 92 patients were diagnosed with *E. meningoseptica* infection and were included in this study. A total of 1,136,248 inpatients were admitted to this hospital during the same period. The total incidence of *E. meningoseptica* infection was 0.08 per 1000 inpatients in our population. The prevalence of *E. meningoseptica* infection obviously increased from 0 in 2011 to 0.19 per 1000 inpatients in 2019 (Figure 1A). The baseline data are illustrated in Table 1 and Figure 1. Most patients were males (69.6%), with a mean age of 55.41 years. Adults aged 18~65 years were the most common (67.39%), followed by elders (29.35%) and 1- to 18-year-old juveniles (3.26%) (Figure 1B). As the primary disease, nervous system disease accounted for the largest proportion (34.78%), followed by tumor (22.83%) and trauma (13.04%) (Figure 1C). Furthermore, 47 patients (51.09%) were treated in the ICU, 52 patients (56.52%) underwent operations, and 64 patients (69.57%) received mechanical ventilation. CVCs were placed in 73 patients (79.35%).

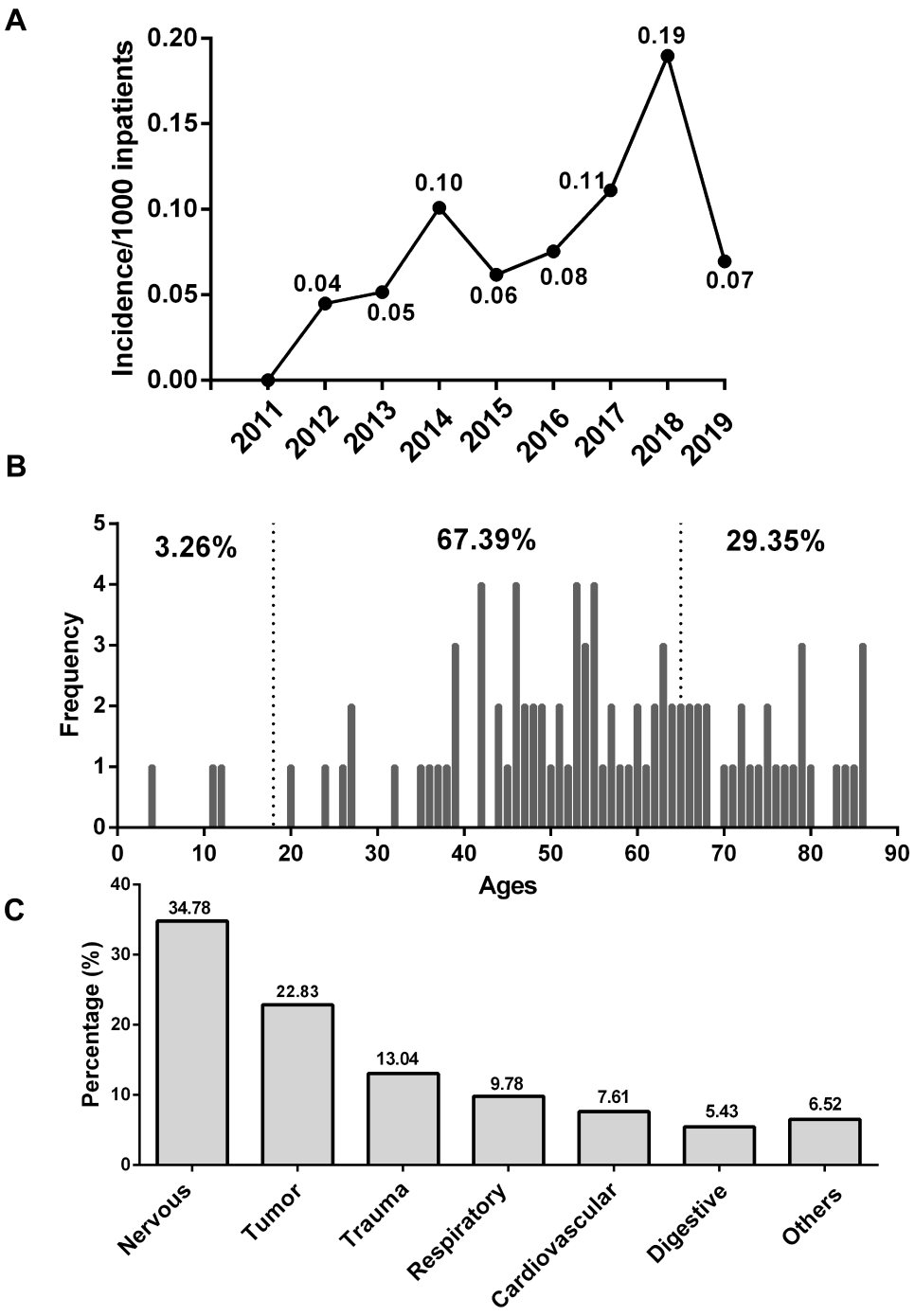

Figure 1 The incidence and baseline data of *E. meningoseptica* infections. (**A**) The annual incidence of *E. meningoseptica* infections 2011–2019. (**B**) Age distribution of patients with *E. meningoseptica* infections. (**C**) Distribution of principal diseases.

Pathogen Sources and Antimicrobial Resistance

The mean day of first detection of *E. meningoseptica* was 21.10 days (SD: 20.40), ranging from 4 to 160 days. In addition, 50% of patients were diagnosed at 2–3 weeks after admission (Figure 2A). Sputum was the most common source of pathogens, accounting for 77.17%. The percentages of blood and cerebrospinal fluid were 4.35% and 2.17%, respectively (Figure 2B). As shown in Figure 2C, 93.48% of *E. meningoseptica* were MDR bacteria, and 5.43% were XDR bacteria. Only one strain was not MDR. The antimicrobial resistance of *E. meningoseptica* is shown in Table 2. Overall, the rates of *E. meningoseptica* resistance to carbapenem, cephalosporin and aminoglycoside were obviously

Table 1 Clinical Features of *E. Meningoseptica* Infection

	Total (n=92)	Survivors (n=58)	Deaths (n=34)	*P*
Age (Years)(mean±SD)	55.41±17.78	52.21±17.97	60.88±16.27	0.023
Male, n(%)	64(69.57)	44(75.86)	20(58.82)	0.104
Underlying diseases, n(%)				
Hypertension, n(%)	27(29.35)	16(27.59)	11(32.35)	0.643
Diabetes, n(%)	7(7.61)	4(6.90)	3(8.82)	0.707
Operation, n(%)	52(56.52)	30(51.72)	22(64.71)	0.278
Mechanical ventilation, n(%)	64(69.57)	33(56.90)	31(91.18)	0.0004
CVCs, n(%)	73(79.35)	42(72.41)	31(91.18)	0.036
Numbers of coinfected pathogen(median, IQR)	1.0,2.50	2.0,4.75	2.0,2.0	0.93
Diagnosis days(mean±SD)	21.10±20.40	21.31±24.41	20.74±10.87	0.897
ICU admission, n(%)	44(47.83)	23(39.66)	21(61.76)	
Principle disease				0.032
Nervous system, n(%)	32(34.78)	15(25.86)	17(50.00)	0.024
Tumor, n(%)	21(22.83)	12(20.69)	9(26.47)	0.609
Trauma, n(%)	12(13.04)	10(17.24)	2(5.88)	0.199
Respiratory, n(%)	9(9.78)	8(13.79)	1(2.94)	0.147
Cardiovascular, n(%)	7(7.61)	3(5.17)	4(11.76)	0.417
Digestive, n(%)	5(5.43)	5(8.62)	0(0)	0.154
Others, n(%)	6(6.52)	5(8.62)	1(2.94)	0.407
Fungal infection, n(%)	20(21.74)	16(27.59)	4(11.76)	0.115
#WBC count(*10^9/L) (mean±SD)	10.50±5.51	10.37±4.69	10.71±6.67	0.780
#Neutrophil percentage(%)(mean±SD)	77.97±13.97	79.61±9.98	75.37±18.53	0.168
#Platelet(×10^9/L) (mean±SD)	217.77±133.74	222.34±124.73	210.50±148.60	0.688
#Lymphocyte count(×10^9/L) (mean±SD)	1.09±0.67	1.11±0.62	1.05±0.74	0.677
#Lymphocyte percentage(%)(mean±SD)	13.33±12.93	12.19±8.03	15.13±18.22	0.301
&Proealcitonin (ng/mL) (mean±SD)	1.80±4.82	1.40±3.14	2.23±6.17	0.518

Notes: #Survivors, n=54, deaths, n=34; &Survivors, n=30, deaths, n=28.
Abbreviations: SD, standard deviation; IQR, interquartile range; CVCs, central venous catheterizations; ICU, intensive care unit; WBC, white blood cell.

higher than those to fluoroquinolone, sulfanilamide, β-lactamase inhibitors and tetracycline. All 92 strains were resistant to imipenem and meropenem but were sensitive to minocycline. The resistance rate of *E. meningoseptica* was 80.0%-94.5% to aminoglycoside and cephalosporin, compared with 29.3%-46.0% to fluoroquinolone, sulfanilamide and piperacillin. Piperacillin/tazobactam had the second highest sensitivity rate (74.3%), followed by levofloxacin (54.0%) and ciprofloxacin (40.3%).

Concomitant Pathogens

E. meningoseptica is an opportunistic pathogen, and patients may show simultaneous infection with other pathogens. Indeed, approximately 75% of *E. meningoseptica* infections showed simultaneous coinfection with at least one type of pathogen. The coinfections of *E. meningoseptica* are shown in Figure 3 and Table S3. In detail, 31.52%, 17.39% and 10.87% of patients were coinfected with one, two and three types of microorganism, respectively (Figure 3A). Moreover, 15.22% were coinfected with four or more types of pathogens. Sputum was the most common source of concomitant pathogens, accounting for 80.00%. Among the 150 coinfected strains, gram-negative bacteria were predominant (73.65%), followed by gram-positive bacteria (19.59%) (Figure 3B). The top 11 coexisting pathogens were *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Stenotrophomonas maltophilia, Enterobacter cloacae, Escherichia coli, Staphylococcus epidermidis, Candida albicans, Haemophilus influenzae* and *Acinetobacter loffei*, accounting for 75.33% of the total pathogens (Figure 3C). The detailed pathogen distribution is shown in Table S3.

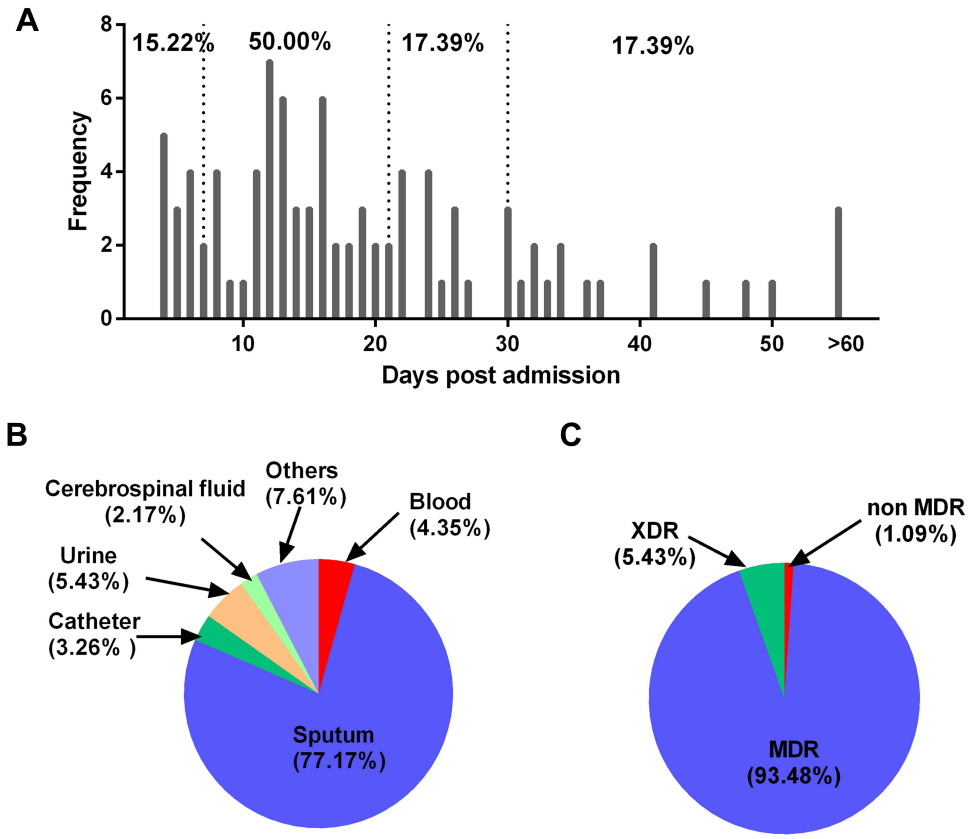

Figure 2 Pathogen sources and antimicrobial resistance of *E. meningoseptica* isolates. (**A**) The distribution of *E. meningoseptica* infection days after admission. (**B**) Sample sources. (**C**) Overall drug resistance of *E. meningoseptica* isolates.
Abbreviations: MDR, multidrug resistance; XDR, extensive drug resistance.

Mortality and Risk Factors for Death

A total of 34 deaths occurred, with a mortality of 36.96%. As shown in Table 1, compared with survivors, the 34 patients who died were significantly older (60.88±16.27 vs 52.21±17.97 years, P<0.05) and had significantly more mechanical

Table 2 Antimicrobial Susceptibilities of 92 *E. Meningoseptica* Strains

Antimicrobial Agent	Resistant Rate (%)	Intermediate Rate (%)	Sensitive Rate (%)
Piperacillin	35.87	35.87	28.26
Piperacillin/tazobactam	5.43	20.65	73.91
Ceftazidime	94.57	0.00	5.43
Cefotaxime	94.57	0.00	5.43
Cefepime	94.57	5.43	0.00
Imipenem	100.00	0.00	0.00
Meropenem	100.00	0.00	0.00
Amikacin	80.43	9.78	9.78
Gentamicin	90.22	4.35	5.43
Netilmicin	89.13	4.35	6.52
Tobramycin	89.13	5.43	5.43
Ciprofloxacin	45.65	14.13	40.22
Levofloxacin	45.65	0.00	54.35
Aztreonam	89.13	5.43	5.43
Trimethoprim/Sulfamethoxazole	29.35	32.61	38.04
Minocycline	0.00	0.00	100.00

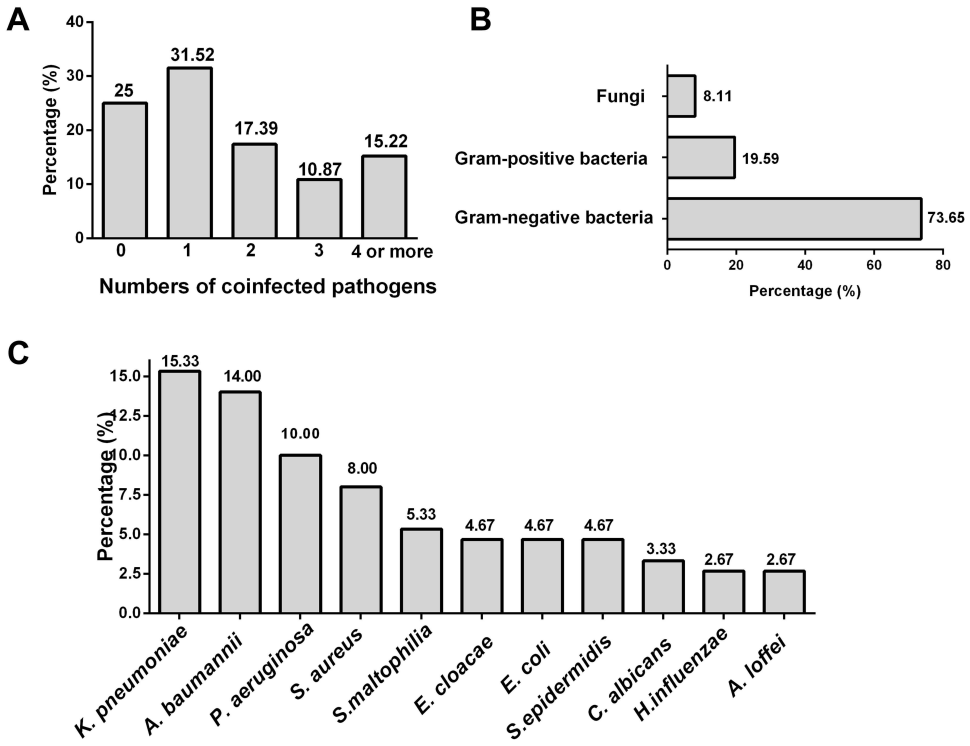

Figure 3 Concomitant pathogens with *E. meningoseptica* infections. (**A**) Distribution of the numbers of coinfected pathogens. (**B**) The composition of different types of concomitant pathogens. (**C**) Top 11 most common pathogens.

ventilations (91.18% vs 56.90%, P<0.001) and more CVCs (91.18% vs 72.41%, P<0.05). Furthermore, the distribution of primary diseases showed a significant difference, with a higher percentage of nervous diseases in patients who died than in survivors (50.00% vs 25.86%, P=0.024). However, WBC count, neutrophil percentage, lymphocyte count and proealcitonin showed no significant differences. Logistic regression analysis showed that mechanical ventilation was most associated with mortality (OR=9.51, P=0.004), followed by coinfected pathogens (OR=1.85, P=0.014) and older age (OR=1.04, P=0.019) (Table 3). Male sex was a protective factor against death (OR=0.27, P=0.031).

Risk Factors for *E. meningoseptica* Infection

A total of 92 patients in the infection group and 110 patients in the non infection group were analyzed. The baseline data, including sex, age and primary disease, showed no obvious difference between patients with and without *E. meningoseptica* infection (Table 4). However, the proportion of mechanical ventilation, CVCs, fungal infection and the numbers of coinfected pathogens in patients with infection were significantly higher than in patients without infection (Table 4). Patients with infection had more frequent use of β-lactamase inhibitors, carbapenem, tigecycline and antifungal drugs than patients without infection (Table 4). Further logistic regression analysis found that CVCs, exposure to carbapenem, exposure to antifungal drugs, and underlying tumors were significant risk factors for *E. meningoseptica* infection (Table 5).

Table 3 Multivariate Logistic Regression Analysis of Risk Factors Related to Mortality

Variables	B	SE	OR	95% CI	*Wald*	*P*
Male	−1.32	0.61	0.27	0.08–0.89	4.66	0.031
Older age	0.04	0.02	1.04	1.01–1.08	5.53	0.019
Mechanical ventilation	2.25	0.77	9.51	2.09–43.21	8.50	0.004
More coinfected pathogens	0.61	0.25	1.85	1.13–3.01	6.07	0.014

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval.

Table 4 Comparison Between Patients with and without *E. Meningoseptica* Infection

	Infection (n=92)	Non-Infection (n=110)	*P*
Age (Years)(mean±SD)	55.41±17.78	50.91±18.67	0.083
Male, n(%)	64(69.57)	76(69.09)	1.000
Operation, n(%)	52(56.52)	53(48.18)	0.260
Mechanical ventilation, n(%)	64(69.57)	42 (38.18)	<0.0001
CVCs, n(%)	73(79.35)	47(42.73)	<0.0001
Numbers of coinfected pathogen(median, IQR)	1.0,2.50	0,1	<0.0001
Primary disease			0.747
Nervous, n(%)	32(34.78)	52(47.27)	
Tumor, n(%)	21(22.83)	11(10.00)	
Trauma, n(%)	12(13.04)	13(11.82)	
Respiratory, n(%)	9(9.78)	12(10.91)	
Digestive, n(%)	5(5.43)	9(8.18)	
Others, n(%)	13(14.13)	(11.82)	
Fungal infection, n(%)	20(21.74)	10(9.09)	0.016
Exposure to β-lactamase inhibitors, n(%)	55(59.78)	43(39.09)	0.005
Exposure to Carbapenem, n(%)	62(67.39)	24(21.82)	<0.0001
Exposure to Tigecycline, n(%)	17(18.48)	5(4.55)	0.003
Exposure to Fluoroquinolone, n(%)	16(17.39)	17(44.55)	0.849
Exposure to antifungal drugs, n(%)	15(16.30)	49(9.09)	<0.0001

Abbreviations: SD, standard deviation; IQR, interquartile range; CVCs, central venous catheterizations.

Table 5 Multivariate Logistic Regression Analysis of Risk Factors for *E.meningoseptica* Infection

Variables	B	SE	OR	95% CI	*Wald*	*P*
CVCs	1.38	0.37	3.99	1.92–8.28	13.75	0.000
Underlying Tumor	1.00	0.47	2.73	1.09–6.80	4.64	0.031
Exposure to Carbapenem	1.26	0.37	3.54	1.72–7.27	11.87	0.001
Exposure to antifungal drugs	1.45	0.40	4.26	1.94–9.35	13.11	0.000

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; CVCs, central venous catheterizations.

Systematic Review

The flow chart of study selection is shown in Figure 4. Sixteen of 520 articles involving 477 patients were ultimately included in this study.

Study Details

As shown in Table 6, the sample size of the included studies varied from 6 to 118 patients. Overall, a total of 569 patients, including 477 patients in 16 studies and 92 patients in this study, were ultimately analyzed. Males accounted for 63.80% of these 569 patients. Except for one prospective study in India, all the others were retrospective observational studies, ranging from 0.4 to 13 years. Studies were from Taiwan (n=5),[8,14–17] India (n=3),[8,18–20] Korea (n=1),[11] Turkey (n=2),[9,21] Mauritius (n=1),[22] Brazil (n=1),[23] United Kingdom (n=1),[24] Singapore (n=1),[25] and Pakistan (n=1).[26] All the included studies had a JBI score above 7 (Table S4), revealing a high level of quality.

Infection Features and Clinical Treatment

As shown in Table 6, eight studies reported the mean/median intervals from admission to infection diagnosis, ranging from 16 days to 50 days. The infection features and treatment are shown in Table S5. Blood and respiratory tract were the most common sources, followed by cerebrospinal fluid and catheters. The VITEK2 system was the most common method of identification, followed by mass spectrometry. Fourteen studies reported antimicrobial resistance and found that most *E. meningoseptica* isolates were highly susceptible to piperacillin/tazobactam, trimethoprim/sulfamethoxazole, fluoroquinolone

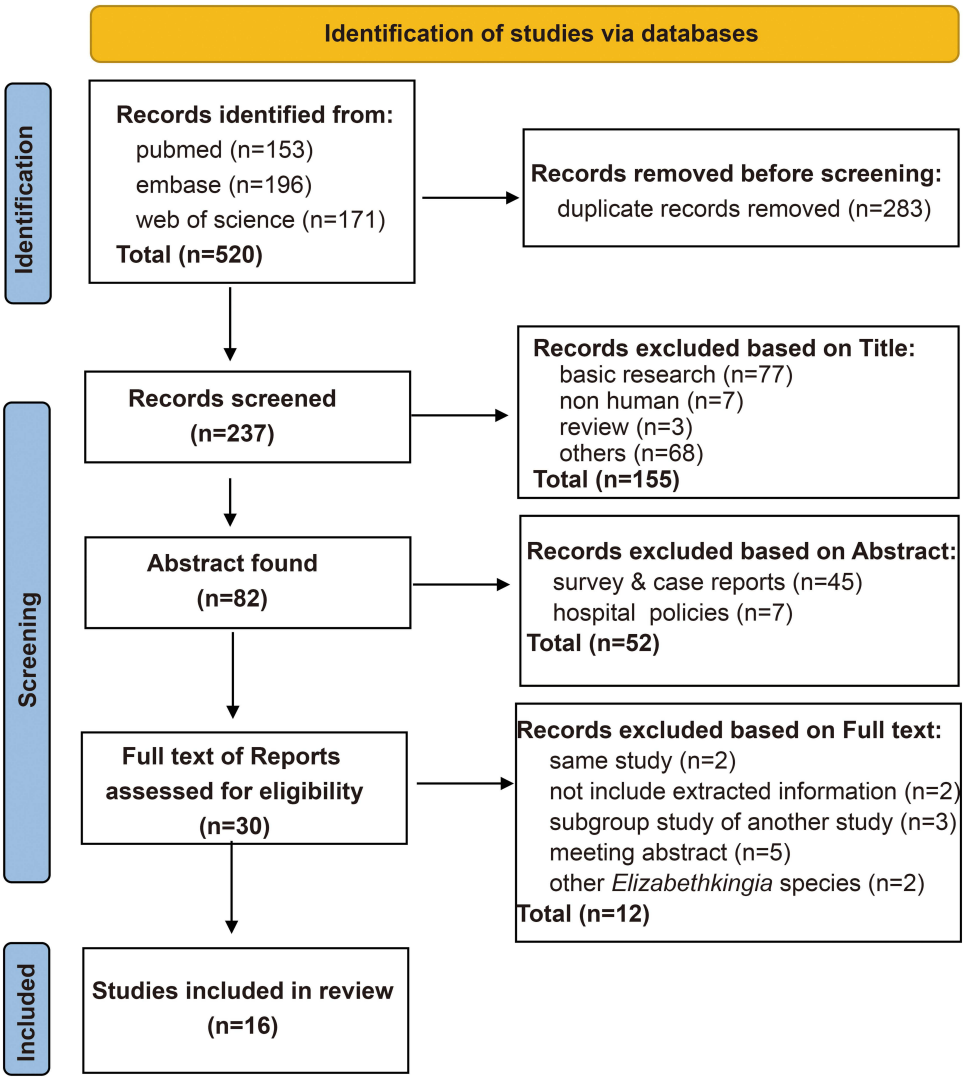

Figure 4 Flow diagram of the identification of studies for systematic review.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.[10]

and minocycline. Nine studies presented antibiotic therapy, and piperacillin/tazobactam, fluoroquinolone, trimethoprim/sulfamethoxazole and minocycline were the most commonly used antibiotics. Five studies performed combined antibiotic therapy, and the other four studies used a single antibiotic strategy.

Mortality

Among the 438 patients in 15 studies and the 92 patients in this study, 198 patients died, for an overall mortality of 37.36%. The reported mortality ranged from 16.7% to 66.7% (Table 6). The mortality of patients with bacteremia was reported as 44%[14] and 65.6%.[8] The mortality of neonate and pediatric patients varied greatly, with reports of 12.5%,[22] 15.4%,[25] and 66.7%.[9] The mortality of ICU patients was reported as 16.7%,[24] 25%,[18] and 47.6%.[19] In studies covering all populations, the reported mortalities were 23.4%,[15] 29.4%,[21] 30%,[11,17] 33.3%,[23] 38.5%,[26] and 45%.[20] Mortality was reported to be from 23.4% to 65.6% in six studies with more than 30 patients.[8,11,14,15,24] Four studies investigated risk factors for death.[8,14,15,17] Inappropriate antibiotic treatment was the most commonly reported risk factor for mortality. Others included shock, acquisition of bacteremia in the ICU, abnormal WBC count (neutropenia) and previous exposure to tigecycline.

Table 6 Study Details of Included Studies Reporting *E.meningoseptica* Infection

Author(Year)	Study Period	Country/ Region	Study Center	Study Design	Study Population	Study Period(Years)	Sample Size, n	Male, n(%)	Age(Years)	Mean/Median Days From Admission to Infection	Mortality, n(%)
Lin, Y.T. et al (2009)[14]	2004.1–2007.02	Taiwan	Taipei Veterans General Hospital	Retrospective study	Bacteremia in adult patients	3	32	26	72.0 (22–89)	29	13(41%)
Hsu, M.S. et al (2011)[15]	1999–2006	Taiwan	National Taiwan University Hospital	Retrospective study	All	7	118	71	64.8(5–100)	25	28(23.4%)
Issack, M.I. et al (2011)[23]	2002.08–2003.12	Mauritius	Jawarhlal Nehru hospital	Retrospective study	Neonate	1.7	8	2	10(6–20) days	Not reported	2(12.5%)
Pereira, G. H. et al (2013)[24]	2010.08–2012.04	Brazil	Dante Pazzanese Institute and the Hospital Brigadeiro	Retrospective study	All	2	9	4	39.1(0.4–81)	33.8	3(33.3%)
Ratnamani, M. et al (2013)[19]	2011.12–2012.06	India	Apollo Hospitals	Retrospective study	ICU bedside hemodialysis patients	0.5	8	4	52.3(3–76)	Not reported	2(25%)
Chang, Y. C. et al (2014)[16]	2007–2011	Taiwan	Central Laboratory of Central Region Hospital Alliance	Retrospective study	All	5	39	31	72.2(2–98)	Not reported	Not reported
Ann, S.Y. et al (2015)[11]	2006.3–2013.2	Korea	Dankook University Hospital	Retrospective study	Adult	8	30	17	68.5(19–90)	33	9(30%)
Moore, L.S. P. et al (2016)[25]	2012.01–2013.10	United Kingdom	A West London teaching hospital	Retrospective study	ICU patients	1.8	30	22	45(17–83)	17	5(16.7%)
Rastogi, N. et al (2016)[20]	2007.06–2014.06	India	JPNA Trauma Centre	Retrospective study	Critically injured trauma patients	7	21	20	31.9 ± 1	Not reported	10(47.6%)
Huang, Y. C. et al (2017)[8]	2011.01–2015.07	Taiwan	Taipei Veterans General Hospital	Retrospective study	Bacteremia in adult patients	5	93	48	76.7	Not reported	61(65.6%)
Lin, J.N. et al (2018)[17]	2005.01–2018.06	Taiwan	E-Da Hospital	Retrospective study	All	13	20	15	56.6(18–80)	Not reported	6(30%)
Chan, J.C. et al (2019)[18]	2010.01–2017.12	Singapore	KK Women's and Children's Hospital	Retrospective study	Pediatrics (0–18 years)	8	13	6	2(12 days-9.5 year)	45	2(15.4%)
Pindi, G. et al (2019)[21]	2017.1–2018.12	India	A tertiary Liver care hospital in New Delhi	Prospective study	All	2	20	15	43.05(2–71)	16	9(45%)
Umair, A. et al (2021)[26]	2013.01–2018.12	Pakistan	Aga Khan University	Retrospective study	All	6	13	6	29(3–83)	Not reported	5(38.5%)
Erinmez, M., A. et al (2021)[9]	2019–2020	Turkey	Gaziantep University	Retrospective study	Pediatric in ICU	0.4	6	4	9(4–11) months	Not reported	4(66.7%)
Saygılı, N. et al (2021)[22]	2008.4–2019.7	Turkey	Tepecik Education and Research Hospital	Retrospective study	All	11	17	8	16.7(0.25–71)	50	5(29.4%)

Abbreviation: ICU, intensive care unit.

Discussion

Recently, *E. meningoseptica* infection has become an emerging infectious disease worldwide, accompanied by poor outcomes. However, to our knowledge, no epidemiological or clinical studies in mainland China have been reported. Owing to the relatively rare incidence of *E. meningoseptica* infection, the number and sample size of published studies are relatively small, leading to difficulties in comprehensively understanding the prevalence and clinical features of this disease. Therefore, the present study also conducted a systematic review of published articles on *E. meningoseptica* infection.

The prevalence of *E. meningoseptica* infection has obviously increased recently, although the detailed incidence is not entirely clear. Our data showed that the *E. meningoseptica* infection rate was 0.08 per 1000 inpatients, rising from 0 in 2011 to 0.19 per 1000 inpatients in 2019. In Taiwan, the incidence of *E. meningoseptica* bacteremia increased from 0.075 in 1996 to 0.356 in 2006 (per 1000 admissions).[15] In Korea, the incidence of *Elizabethkingia* species acquisition increased from 0.02 per 1000 admissions in 2009 to 0.88 per 1000 admissions in 2017.[27] Furthermore, outbreaks of *E. meningoseptica* infection occasionally occur in many other countries.[3,4,28] Such findings supported that *E. meningoseptica* infection has gradually become an emerging threat to public health and should not be overlooked.

E. meningoseptica is perceived as an opportunistic and antibiotic-selective pathogen.[29] Our study showed that male sex, age older than 50 years, age younger than one year, nervous system disease and tumors made patients more susceptible to *E. meningoseptica* infection. Furthermore, approximately 75% of patients in our cohort who were infected with *E. meningoseptica* were simultaneously coinfected with at least one type of pathogen. Therefore, *E. meningoseptica* infection may be caused by the reduced immune response in susceptible patients and subsequent bacterial infection. Our systematic review showed that inappropriate empirical antimicrobial therapy, the ICU environment, invasive procedures, and exposure to broad-spectrum antibiotics were the most common factors for nosocomial *E. meningoseptica* infections. Specifically, mechanical ventilation has been reported as an invasive procedure that causes *E. meningoseptica* infection.[27] Data from our population also supported that CVCs, exposure to carbapenem, exposure to antifungal drugs, and underlying tumors were also significant risk factors for *E. meningoseptica* infection. Previous studies have found that *E. meningoseptica* could be identified in hospital environments, including in saline solutions, water supplies, disinfectants, equipment surfaces and medical devices with fluids (respirators, intubation tubes, humidifiers).[3,4,30,31] Therefore, risk factors for *E. meningoseptica* infection are complex and need special attention in clinical settings.

The mortality of *E. meningoseptica* infection was high and was related to several risk factors. Our systematic review found that the mortality of *E. meningoseptica* infection ranged from 11.0% to 66.6%. Excluding the effect of small sample size, mortality was reported to be 23.4% to 65.6% in five studies with more than 30 patients. Consistent with these results, the mortality of our cohort was 36.96%. However, the risk factors for death varied greatly among different studies. Inappropriate use of antibiotics was the most reported factor in most studies. Other risk factors primarily included abnormal WBC count, neutropenia, significant comorbidities and shock.[8,14,15,17] Our data showed that mechanical ventilation, more coinfected pathogens and older age were risk factors, while male sex was a protective factor against death. Similar to other infectious diseases, early diagnosis and effective treatments, including eliminating possible risk factors and performing targeted antibiotic application, together contribute to a better outcome.

Most clinical isolates of *E. meningoseptica* were multidrug resistant, and antibacterial resistance showed minor differences among various studies. Owing to the ESBLs and MBLs, *E. meningoseptica* is inherently resistant to carbapenems and aminoglycosides. Our systematic and cohort analyses showed that the rates of susceptibility to β-lactamase inhibitors (cefoperazone/sulbactam and piperacillin/tazobactam), trimethoprim/sulfamethoxazole and fluoroquinolone (ciprofloxacin, moxifloxacin, levofloxacin) were relatively low. Minocycline was 100% sensitive in our study and varied from 60% to 100% in other studies. One retrospective study in Taiwan showed that patients treated with fluoroquinolone had lower mortality than those treated with nonfluoroquinolone (piperacillin/tazobactam, trimethoprim/sulfamethoxazole, minocycline).[32] However, another study in Taiwan found that the rate of gene mutation targeting fluoroquinolone was high in *E. meningoseptica*.[17] The combination of piperacillin/tazobactam and trimethoprim/sulfamethoxazole was recommended in one study in Taiwan.[25] Therefore, fluoroquinolone treatment should be chosen carefully. As described above, inappropriate antibacterial therapy is an independent risk factor for mortality and infection,

and antibacterial treatment would be more reliable under the guidance of antimicrobial susceptibility testing. Together, carbapenems and aminoglycosides were not recommended for *E. meningoseptica* infection. Single or combined piperacillin/tazobactam, trimethoprim/sulfamethoxazole and fluoroquinolone were recommended for empirical treatment.

There are two limitations to this study. In the first part, concerning epidemiological studies, only a single center was retrospectively analyzed, and the sample size was relatively small. Therefore, a systematic review was performed to supplement the results. Nevertheless, multicenter, large-scale clinical analyses are needed for further confirmation. In the second part of the systematic review, case reports and case series with sample sizes <5 were excluded to minimize publication bias. A final total of 45 case reports or series was ultimately excluded. But, most of the included articles were retrospective studies.

In conclusion, the present study conducted the first epidemiological investigation of *E. meningoseptica* infection in mainland China and performed a comprehensive systematic review of published articles. This study offers the following implications for clinicians. First, the prevalence of *E. meningoseptica* infection has rapidly increased in recent years and causes lethally opportunistic infections in patients. Second, CVCs, exposure to carbapenem and antifungal drugs, and underlying tumors were risk factors for *E. meningoseptica* infection. Third, mechanical ventilation, more coinfected pathogens and male sex were associated with *E. meningoseptica* death. Finally, most *E. meningoseptica* isolates showed good susceptibility to β-lactamase inhibitors (piperacillin/tazobactam), trimethoprim/sulfamethoxazole, fluoroquinolone (ciprofloxacin, moxifloxacin, levofloxacin) and minocycline. However, inappropriate antibacterial therapy is an independent risk factor for mortality and infection. Therefore, antibacterial treatment would be more reliable under the guidance of antimicrobial susceptibility tests. Special attention should be given to the risk factors and treatment of *E. meningoseptica* infection in the future.

Data Sharing Statement

All materials needed to replicate the findings of the article are available as Supplementary Materials. Readers can contact the corresponding author if they want access to additional materials.

Ethic Statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Disclosure

The authors have no conflict of interest to disclose.

References

1. Rahi M, Amoah K, Gunasekaran K, Kapil R, Kwon JS. Elizabethkingia meningoseptica sepsis associated with COVID-19 infection: an emerging nosocomial pathogen. *Am J Respir Crit Care Med*. 2021;203.
2. Kim KK, Kim MK, Lim JH, Park HY, Lee ST. Transfer of Chryseobacterium meningosepticum and Chryseobacterium miricola to Elizabethkingia gen. nov. as Elizabethkingia meningoseptica comb. nov. and Elizabethkingia miricola comb. nov. *Int J Syst Evol Microbiol*. 2005;55:1287–1293. doi:10.1099/ijs.0.63541-0
3. Balm MND, Salmon S, Jureen R, et al. Bad design, bad practices, bad bugs: frustrations in controlling an outbreak of Elizabethkingia meningoseptica in intensive care units. *J Hospital Infection*. 2013;85:134–140. doi:10.1016/j.jhin.2013.05.012
4. Chawla K, Gopinathan A, Varma M, Mukhopadhyay C. Elizabethkingia meningoseptica outbreak in intensive care unit. *J Glob Infect Dis*. 2015;7:43–44. doi:10.4103/0974-777X.150890
5. Agrawal A, Ravikumar R, Varun CN, et al. Global Proteome Profiling Reveals Drug-Resistant Traits in Elizabethkingia meningoseptica: an Opportunistic Nosocomial Pathogen. *j Integrative Biol*. 2019;23:318–326. doi:10.1089/omi.2019.0039
6. Wadhwa T, Sengupta S, Sarma S, Kaur A, Kumar N, Baveja U. Emergence of Elizabethkingia meningoseptica as a nosocomial pathogen causing outbreaks and lessons learnt in containing the spread in the hospital. *Antimicrob Resist Infect Control*. 2017;6. doi:10.1186/s13756-016-0149-9

7. Jung SH, Lee B, Mirrakhimov AE, Hussain N. Septic shock caused by Elizabethkingia meningoseptica: a case report and review of literature. *BMJ Case Rep*. 2013. doi:10.1136/bcr-2013-009066
8. Huang YC, Huang YW, Lin YT, Wang FD, Chan YJ, Yang TC. Risk factors and outcome of levofloxacin-resistant Elizabethkingia meningoseptica bacteraemia in adult patients in Taiwan. *Eur J Clin Microbiol Infect Dis*. 2017;36:1373–1380. doi:10.1007/s10096-017-2942-7
9. Erinmez M, Buyuktas Manay A, Zer Y. Investigation of an outbreak of Elizabethkingia meningoseptica on a pediatric intensive care unit. *GMS Hygiene Infection Control*. 2021;16:1548.
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
11. Ann SY, Sung Hyeok Ryou MD, Kim JW. Experience with Elizabethkingia meningoseptica Infection in Adult Patients at a Tertiary Hospital. *Acute Critical Care*. 2015;30:241–248.
12. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18:268–281. doi:10.1111/j.1469-0691.2011.03570.x
13. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc*. 2015;13:147–153. doi:10.1097/XEB.0000000000000054
14. Lin YT, Chiu CH, Chan YJ, et al. Clinical and microbiological analysis of Elizabethkingia meningoseptica bacteremia in adult patients in Taiwan. *Scand J Infect Dis*. 2009;41:628–634. doi:10.1080/00365540903089476
15. Hsu MS, Liao CH, Huang YT, et al. Clinical features, antimicrobial susceptibilities, and outcomes of Elizabethkingia meningoseptica (Chryseobacterium meningosepticum) bacteremia at a medical center in Taiwan, 1999-2006. *Eur J Clin Microbiol Infect Dis*. 2011;30:1271–1278. doi:10.1007/s10096-011-1223-0
16. Chang YC, Lo HH, Hsieh HY, Chang SM. Identification and epidemiological relatedness of clinical Elizabethkingia meningoseptica isolates from central Taiwan. *J Microbiol Immunol Infection*. 2014;47:318–323. doi:10.1016/j.jmii.2013.03.007
17. 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;7:6489.
18. Ratnamani M, Rao R. Elizabethkingia meningoseptica: emerging nosocomial pathogen in bedside hemodialysis patients. *Indian J Critical Care Med*. 2013;17:304–307. doi:10.3205/dgkh000390
19. Rastogi N, Mathur P, Bindra A, et al. Infections due to Elizabethkingia meningoseptica in critically injured trauma patients: a seven-year study. *J Hospital Infection*. 2016;92:30–32. doi:10.1016/j.jhin.2015.07.008
20. Pindi G, Kale P, Khillan V, Khodhare A. Elizabethkingia meningoseptica: waiting to Strike. *J Clin Diagnostic Res*. 2019;13:DC16–DC20.
21. Saygılı N, Doğan G. A rare agent; growth of Elizabethkingia Meningoseptica, 11 years of evaluation. *Ann Clin Analytical Med*. 2021;12:855–859.
22. Issack MI, Neetoo Y. An outbreak of Elizabethkingia meningoseptica neonatal meningitis in Mauritius. *J Infect Dev Ctries*. 2011;5:834–839. doi:10.3855/jidc.1885
23. Pereira GH, Garcia DDO, Abboud CS, Barbosa VLDB, da Silva PSL. Nosocomial infections caused by Elizabethkingia meningoseptica: an emergent pathogen. *Br J Infect Dis*. 2013;17:606–609. doi:10.1016/j.bjid.2013.02.011
24. Moore LSP, Owens DS, Jepson A, et al. Waterborne Elizabethkingia meningoseptica in Adult Critical Care. *Emerg Infect Dis*. 2016;22:9–17. doi:10.3201/eid2201.150139
25. Chan JC, Chong CY, Thoon KC, et al. Invasive paediatric elizabethkingia meningoseptica infections are best treated with a combination of piperacillin/tazobactam and trimethoprim/sulfamethoxazole or fluoroquinolone. *J Med Microbiol*. 2019;68:1167–1172. doi:10.1099/jmm.0.001021
26. Umair A, Nasir N. Clinical features and outcomes of critically ill patients with Elizabethkingia meningoseptica: an emerging pathogen. *Acute Critical Care*. 2021;36(3):256–261. doi:10.4266/acc.2020.01158:5
27. Choi MH, Kim M, Jeong SJ, et al. Risk Factors for Elizabethkingia Acquisition and Clinical Characteristics of Patients, South Korea. *Emerg Infect Dis*. 2019;25:42–51. doi:10.3201/eid2501.171985
28. Balakrishnan S, Sankar P, Shareek PS, Nath J, Pisharody R. Elizabethkingia meningoseptica outbreak in adult hemodialysis unit-outbreak investigation and intervention analysis. *Nephrol Dialysis Transplantation*. 2017;32:iii672. doi:10.1093/ndt/gfx178.MP653
29. Patro P, Das P, Padhi P. Intrinsically Resistant Bacteria as Looming Disaster: a Rare Case Report of Elizabethkingia meningoseptica Meningitis in a Neonate. *J Lab Physicians*. 2021;13:70–73. doi:10.1055/s-0041-1724234
30. de-las-Casas-Cámara G, Martín-Ríos MD. Under-utilization of taps in intensive care unit as a cause of reservoirs of nonfermenting gram-negative bacilli. *Enferm Infecc Microbiol Clin*. 2018;36:214–217. doi:10.1016/j.eimc.2017.01.008
31. Erinmez M, Büyüktas Manay A, Zer Y. Investigation of an outbreak of Elizabethkingia meningoseptica on a pediatric intensive care unit. *GMS Hyg Infect Control*. 2021;16:358.
32. Huang Y-C, Lin Y-T, Wang F-D. Comparison of the therapeutic efficacy of fluoroquinolone and non-fluoroquinolone treatment in patients with Elizabethkingia meningoseptica bacteraemia. *Int J Antimicrob Agents*. 2018;51:47–51. doi:10.1016/j.ijantimicag.2017.05.018