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Original Article

Comparison of clinical characteristics of bacteremia from *Elizabethkingia meningoseptica* and other carbapenem-resistant, non-fermenting Gram-negative bacilli at a tertiary medical center

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Abstract *Background:* Acquired carbapenem resistance among non-fermenting Gram-negative bacilli (NFGNB), such as *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex (ACB complex), is a serious problem in nosocomial infections. We previously reported that patients infected with the intrinsically carbapenem-resistant *Elizabethkingia meningoseptica* were associated with high mortality. However, little information is available regarding the clinical outcome of *E. meningoseptica* bacteremia when compared to that of other carbapenem-resistant NFGNB.
Methods: We conducted an observational study that included consecutive patients with *E. meningoseptica*, carbapenem-resistant ACB complex, carbapenem-resistant *P. aeruginosa*, and *Stenotrophomonas maltophilia* bacteremia at a Taiwanese medical center in 2015. We compared the clinical characteristics and outcomes between patients with *E. meningoseptica* bacteremia and those with other carbapenem-resistant NFGNB bacteremia.
Results: We identified 30 patients with *E. meningoseptica*, 71 with carbapenem-resistant ACB complex, 25 with *S. maltophilia*, and 17 with carbapenem-resistant *P. aeruginosa* bacteremia. The clinical characteristics, disease severity, and previous antibiotic exposures were similar between patients with bacteremia either due to *E. meningoseptica* or other carbapenem-resistant NFGNB. Patients with *E. meningoseptica* bacteremia had a higher rate of appropriate

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empirical antibiotics than those with other carbapenem-resistant NFGNB and was less associated with central venous catheterization. The 28-day mortality rates were similar between patients with *E. meningoseptica* and the other carbapenem-resistant NFGNB bacteremia (46.7% vs 46%, p = 0.949).

Conclusion: The mortality rate of *E. meningoseptica* bacteremia was as high as other carbapenem-resistant NFGNB infections. The emerging *E. meningoseptica* infection calls for active surveillance and continued awareness from clinical physicians for this serious carbapenem-resistant infection.

Introduction

Non-fermenting Gram-negative bacilli (NFGNB) are aerobic, non-spore forming bacteria that cannot utilize carbohydrates to generate energy. *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex (ACB complex) and *Pseudomonas aeruginosa* are the most well-known NFGNB infection causing agents.[1,2] Phenotypically, these pathogens often show multidrug resistance. They are involved in various nosocomial infections in critically ill patients, including ventilator associated pneumonia, catheter related bloodstream infections, urinary tract infections, surgical site infections, and bacteremia.[1–6]

Carbapenem, a broad-spectrum antibiotic, is considered as the last resort for treating multidrug resistant pathogens in seriously ill patients. However, the increasing rate of acquired carbapenem resistance among ACB complex and *P. aeruginosa* in recent years is alarming.[3–6] According to the National Healthcare Safety Network (NHSN), the carbapenem-resistant rate among *Acinetobacter* spp. (62.6%) and *P. aeruginosa* (26.1%) was higher than carbapenem-resistant *Klebsiella pneumoniae* (12.8%) from 2009 to 2010.[4] One recent study conducted from 2013 to 2014 in southern Taiwan showed the rate of carbapenem resistance among *Acinetobacter* spp. and *Pseudomonas* spp. was 15.8% and 13.7%, respectively.[6] Moreover, carbapenem-resistant ACB complex and *P. aeruginosa* infections are usually associated with high mortality.[7–10] Apart from ACB complex and *P. aeruginosa*, some NFGNB, such as *Stenotrophomonas maltophilia* and *Elizabethkingia meningoseptica*, are intrinsically resistant to carbapenem. Their clinical characteristics received less attention in the literature owing to their inherent carbapenem resistance.[11,12]

We previously reported that *E. meningoseptica* bacteremia was associated with high mortality (43–54.4%) at our hospital.[13–15] Notably, *E. meningoseptica* infections have been reported increasingly in the literature.[16–18] *E. meningoseptica* was the fourth common pathogen of carbapenem-resistant bacteremia in a medical center in southern Taiwan[6] and the third common respiratory pathogen, next to ACB complex and *P. aeruginosa*, isolated from patients in an intensive care unit (ICU) in India.[5] However, little information is available regarding the clinical impact and outcome of *E. meningoseptica* bacteremia compared to other pathogenic carbapenem-resistant NFGNB. The risk factors for *E. meningoseptica* bacteremia among the carbapenem-resistant NFGNB bacteremia have never been described. In this study, we compared the clinical characteristics and outcomes of patients with *E. meningoseptica* bacteremia to those with carbapenem-resistant ACB complex, carbapenem-resistant *P. aeruginosa* and *S. maltophilia* bacteremia at a medical center in Taiwan.

Methods

Study design and population

This retrospective study was conducted at Taipei Veterans General Hospital, a major medical center and teaching hospital in northern Taiwan with a capacity of 2900 beds. From January 2015 to December 2015, we enrolled consecutive patients at least 20 years of age who had at least one positive blood culture of *E. meningoseptica*, carbapenem-resistant ACB complex, carbapenem-resistant *P. aeruginosa*, or *S. maltophilia* bacteremia. Only the first episode of bacteremia was included and polymicrobial bacteremia was excluded. We did not include *Burkholderia cepacia* complex bacteremia in this study because carbapenem susceptibility tests were not routinely performed. This study protocol was approved by the Institutional Review Board at Taipei Veterans General Hospital.

Variables and definition

The clinical information acquired from the medical charts included age, sex, underlying disease, recent surgery, indwelling device, mechanical ventilation, immunosuppression status, source of bacteremia, APACHE II (Acute Physiology and Chronic Health Evaluation) score, microbiological data, previous antibiotics exposure, and clinical outcomes. The healthcare-associated bacteremia was defined as patients who were either receiving intravenous therapy or renal dialysis during the previous 30 days, those who had been hospitalized for two or more days during the previous 90 days, or residing in a nursing home or long-term care facility.[19,20] Previous antimicrobial agent exposure was defined as the administration of antibiotics for more than 48 h within 28 days prior to the onset of bacteremia. The source of infection was clinically determined based on the isolation of the same organism at the time of drawing positive blood culture. Appropriate empirical antimicrobial treatment was defined as administration of antibiotic that is active against isolates $\leq$48 h from the onset of infection.

Appropriate definitive treatment was defined as administration of active antibiotics lasting for 48 h after the antimicrobial sensitivity was available. We assessed the 14-day, 28-day, and in-hospital mortality as the major outcomes. Clinical success was defined as survival over 14 days with resolution of sepsis, and no recurrence at the end of the treatment. Persistent bacteremia was defined as duration of bacteremia $\geq$7 days without clearance of bacteremia. Patients were followed up three months from the time of index blood culture collection or until their death before.

Microbiology

For identification of *E. meningoseptica*, ACB complex, *P. aeruginosa*, and *S. maltophilia*, matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (bioMérieux) was used. We referred to ACB complex in this study as *Acinetobacter* genospecies 1 (*A. calcoaceticus*), genospecies 2 (*A. baumannii*), genospecies 3 (*A. pittii*), and genospecies 13TU (*A. nosocomialis*) for their phenotypic similarities.[21] Susceptibilities of *E. meningoseptica* isolates to antimicrobial agents were determined by E-test strip (bioMérieux). Vitek2 system (bioMérieux) was used for other pathogens. The antimicrobial susceptibilities were interpreted according to the Clinical and Laboratory Standards Institutes (CLSI) breakpoint.[22] For ACB complex and *P. aeruginosa*, the criterion that defines susceptibility is a minimum inhibitory concentration (MIC) $\leq$ 2 μg/mL for imipenem, meropenem, and doripenem.[22] For agents without published CLSI criteria, the relevant criterion for non-*Enterobacteriaceae* was applied. Interpretation of tigecycline MIC results was determined according to the recommendations of the US Food and Drug Administration (FDA) given in the package insert for treating *Enterobacteriaceae*: susceptible $\leq$ 2 μg/mL; resistant $\geq$ 8 μg/ml.

Statistical analysis

The chi-square test or Fisher's exact test was used to compare categorical variables, and the Student *t* test or Wilcoxon rank sum test was used to compare continuous variables. For the analysis of risk factors for *E. meningoseptica* bacteremia and 28-day mortality among all carbapenem-resistant NFGNB bacteremia, all plausible variables with a p value of $<$0.10 in the univariate analysis were included in the multivariate analysis. A logistic regression analysis with backward selection was performed for the multivariate analysis. The survival curves of 28-day for the patients with *E. meningoseptica* and non-*E. meningoseptica* bacteremia were prepared according to the Kaplan–Meier method. The log-rank test was used to compare the survival curves. A p value less than 0.05 was considered statistically significant. All analyses were performed using SPSS statistics 22 (IBM Corp., Armonk, NY, USA).

Results

During the study period, 143 patients fulfilling the enrollment criteria with carbapenem-resistant NFGNB bacteremia were identified, including 30 patients with *E. meningoseptica*, 71 patients with carbapenem-resistant ACB complex, 25 patients with *S. maltophilia*, and 17 patients with carbapenem-resistant *P. aeruginosa*. The mean age of patients with carbapenem-resistant NFGNB bacteremia was 67.1 years old and predominantly male (59.4%). Most patients (n = 136, 95.1%) had hospital acquired infection, and half the patients (n = 70, 49%) acquired the bacteremia in ICU. The remaining 7 patients had healthcare-associated bacteremia, and no patients were classified as community-acquired infection. The in-hospital mortality rate among these patients was 54.5%.

Table 1 lists the comparison between the clinical characteristics of the carbapenem-resistant NFGNB bacteremia. *E. meningoseptica* bacteremia had a lower rate of ICU-acquired bacteremia, central venous catheterization, mechanical ventilation, indwelling urinary catheter and a lower severity (APACHE II score) than carbapenem-resistant ACB complex bacteremia. Compared to patients with *S. maltophilia* bacteremia, patients with *E. meningoseptica* bacteremia were older, had a lower rate of hematological malignancy, neutropenia, and central venous catheterization; but, a higher rate of pneumonia as source of bacteremia, chronic obstructive pulmonary disease and steroid use. When compared with carbapenem-resistant *P. aeruginosa*, patients with *E. meningoseptica* bacteremia were older, had a higher rate of primary bacteremia, and a lower rate of central venous catheterization. We then compared the clinical features of patients with *E. meningoseptica* bacteremia to those with non-*E. meningoseptica* bacteremia, and found that *E. meningoseptica* bacteremia was associated with older age, a higher rate of primary bacteremia and chronic obstructive pulmonary disease, and a lower rate of ICU acquired bacteremia and central venous catheterization. Interestingly, we found empyema complications in 2 patients, with *E. meningoseptica* being cultured from the pleural effusion. Empyema was not found in patients with other non-*E. meningoseptica* bacteremia in this study. Considering previous antibiotic exposure before bacteremia onset, there was no significant difference between patients with *E. meningoseptica* and non-*E. meningoseptica* bacteremia (Table 2).

Regarding treatment, patients with *E. meningoseptica* bacteremia had a significantly higher rate of appropriate empiric antibiotics (58.3%) than patients with non-*E. meningoseptica* bacteremia (26.4–29.2%) (Table 3). *E. meningoseptica* isolates showed a high susceptibility to sulfamethoxazole/trimethoprim (100%), piperacillin/tazobactam (90.5%), and a low susceptibility to levofloxacin (33.3%). Nine patients received piperacillin/tazobactam and 5 patients received levofloxacin as appropriate empiric antibiotics for *E. meningoseptica* bacteremia. As for outcomes of patients with carbapenem-resistant NFGNB bacteremia, the *E. meningoseptica* group had a high 14-day mortality (33.3%), 28-day mortality (46.7%), and in-hospital mortality (53.3%), which were similar to other groups. The rates of clinical success were also similar between *E. meningoseptica* and other groups. The Kaplan–Meier survival curve (Fig. 1) showed a similar 28-day survival between the *E. meningoseptica* group and the non-*E. meningoseptica* group (Log-rank test, p = 0.815).

We further analyzed the prognostic factors of 28-day mortality in different carbapenem-resistant NFGNB.

Table 1 Clinical characteristics of patients with *E. meningoseptica* bacteremia and other carbapenem-resistant ACB complex, *S. maltophilia*, and carbapenem-resistant *P. aeruginosa* bacteremia.

Variables	*E. meningoseptica*	Carbapenem-resistant ACB complex	*S. maltophilia*	Carbapenem-resistant *P. aeruginosa*	Non-*E. meningoseptica*	*p* Value (*E. meningoseptica* vs non-*E. meningoseptica*)
	n = 30	n = 71	n = 25	n = 17	n = 113	
Age (years), mean ± SD	74.0 ± 18.2	67.6 ± 20.2	61.6 ± 14.8*	60.9 ± 20.3*	65.3 ± 19.3	0.030
Male, no. (%)	19 (63.3)	43 (60.6)	14 (56)	9 (52.9)	66 (58.4)	0.625
Source of bacteremia, no. (%)						
Primary bacteremia	19 (63.3)	30 (42.3)	14 (56)	6 (35.3)*	50 (44.2)	0.029
Pneumonia	7 (23.3)	24 (33.8)	1 (4)*	4 (23.5)	29 (25.7)	0.794
Urinary tract infection	1 (3.3)	0 (0)	2 (8)	2 (11.8)	4 (3.5)	0.956
Intraabdominal infection	0 (0)	2 (2.8)	3 (12)	0 (0)	5 (4.4)	0.241
Soft tissue infection	0	3 (4.2)	0	0	4 (3.5)	0.296
Catheter related blood stream infection	3 (10)	12 (16.9)	5 (20)	5 (29.4)	22 (19.5)	0.225
ICU acquired, no. (%)	9 (30)	48 (67.6)*	9 (36)	4 (23.5)	61 (54)	0.019
Days before isolation, mean ± SD	37.4 ± 36.6	36.1 ± 34.4	23.8 ± 15.3	39.6 ± 42.5	34.0 ± 33.0	0.617
Days after isolation, mean ± SD	39.1 ± 71.4	35.3 ± 47.5	43.8 ± 63.4	19.5 ± 12.1	34.7 ± 48.3	0.692
Recent admission within 3 months	18 (60)	28 (39.4)	13 (54.2)	9 (52.9)	50 (44.2)	0.135
Underlying disease, no. (%)						
Malignancy	8 (26.7)	26 (36.6)	13 (52)	9 (52.9)	48 (42.5)	0.115
Hematologic malignancy	1 (3.3)	8 (11.3)	7 (28)*	2 (11.8)	17 (15)	0.086
Solid tumor	7 (23.3)	19 (26.8)	6 (24)	7 (41.2)	32 (28.3)	0.586
Cerebral vascular stroke	7 (23.3)	15 (21.1)	7 (28)	3 (17.6)	25 (22.1)	0.888
Liver cirrhosis	1 (3.3)	2 (2.8)	1 (4.0)	1 (5.9)	4 (3.5)	0.956
Diabetes mellitus	9 (30)	27 (38)	5 (20)	3 (17.6)	35 (31)	0.918
Congestive heart failure	7 (23.3)	13 (18.3)	3 (12)	3 (17.6)	19 (16.8)	0.411
Chronic obstructive pulmonary disease	8 (26.7)	8 (11.3)	0 (0)*	1 (5.9)	9 (8)	0.005
Chronic renal failure[a]	9 (30)	23 (32.4)	5 (20)	5 (29.4)	33 (29.2)	0.932
Hemodialysis	3 (10)	9 (12.7)	3 (12)	4 (23.5)	16 (14.2)	0.773
Rheumatology disease	2 (6.7)	7 (9.9)	0	0	7 (6.2)	0.925
Steroid[b]	8 (26.7)	20 (28.2)	1 (4)*	4 (23.5)	25 (22.1)	0.600
Transplantation	1 (3.3)	2 (2.8)	1 (4)	0	3 (2.7)	0.841
Chemotherapy within one month	5 (16.7)	13 (18.3)	7 (28)	3 (17.6)	23((20.4)	0.651
Neutropenia	1 (3.3)	5 (7)	5 (20)*	3 (17.6)	13 (11.5)	0.182
Alcoholism	1 (3.3)	1 (1.4)	2 (8)	0	3 (2.7)	0.841
Recent operation within one month	3 (10)	13 (18.3)	5 (20)	5 (29.4)	21 (18.6)	0.263
Indwelling device, no. (%)						
Abdominal drainage	2 (6.7)	6 (8.5)	6 (24)	4 (23.5)	16 (14.2)	0.271
Thoracic drainage	2 (6.7)	6 (8.5)	0	1 (5.9)	7 (6.2)	0.925
Surgical drain	4 (13.3)	11 (15.5)	3 (12)	3 (17.6)	17 (15)	0.814
Central venous catheterization	10 (33.3)	49 (69)*	18 (72)*	12 (70.6)*	79 (69.9)	<0.001
Total parenteral nutrition	1 (3.3)	0	1 (4)	1 (5.9)	2 (1.8)	0.595
Mechanical ventilation at isolation[c]	12 (40)	47 (66.2)*	7 (28)	3 (17.6)	57 (50.4)	0.309

(*continued on next page*)

Table 1 (*continued*)

Variables	*E. meningoseptica*	Carbapenem-resistant ACB complex	*S. maltophilia*	Carbapenem-resistant *P. aeruginosa*	Non-*E. meningoseptica*	*p* Value (*E. meningoseptica vs non-E. meningoseptica*)
	n = 30	n = 71	n = 25	n = 17	n = 113	
Nasogastric tube	24 (80)	64 (90.1)	14 (56)	10 (58.8)	88 (77.9)	0.802
Indwelling urinary catheter	19 (63.3)	58 (81.7)*	10 (40)	7 (41.2)	75 (66.4)	0.755
APACHE II score, median (IQR)	22.6 ± 8	27.1 ± 9.7*	22.1 ± 8.8	20.4 ± 10	25.0 ± 9.9	0.224

[a] Chronic kidney disease stage 4 and stage 5 for more than 3 months, including dialysis patients.
[b] Prednisolone use >10 mg/day or equivalent for over 7 days.
[c] Under mechanical ventilation support for more than 48 h prior to bacteremia onset.
Data are presented as mean ± standard deviation (SD) or frequency with percentage (%).
*p Value < 0.05 when compared with *E. meningoseptica* group.

Table 2 Previous antibiotics use of patients with *E. meningoseptica* bacteremia and other carbapenem-resistant ACB complex, *S. maltophilia* and carbapenem-resistant *P. aeruginosa* bacteremia.

Characteristics	*E. meningoseptica*	Carbapenem-resistant ACB complex	*S. maltophilia*	Carbapenem-resistant *P. aeruginosa*	Non-*E. meningoseptica*	*p* Value (*E. meningoseptica vs non-E. meningoseptica*)
	n = 30	n = 71	n = 25	n = 17	n = 113	
Previous antibiotics exposure, no. (%)						
Previous antifungal agent	6 (20)	18 (25.4)	11 (44)	6 (35.3)	35 (31)	0.237
Previous beta lactamase inhibitor[a]	16 (53.3)	40 (56.3)	12 (48)	7 (41.2)	59 (52.2)	0.913
Previous piperacillin/tazobactam	9 (30)	29 (40.8)	9 (36)	6 (35.3)	44 (38.9)	0.368
Previous glycopeptide[b]	8 (26.7)	29 (40.8)	13 (52)	8 (47.1)	50 (44.2)	0.081
Previous 1st and 2nd generation of cephalosporin[c]	6 (20)	16 (22.5)	7 (28)	7 (41.2)	30 (26.5)	0.463
Previous 3rd and 4th generation of cephalosporin[d]	6 (20)	28 (39.4)	7 (28)	5 (29.4)	40 (35.4)	0.108
Previous carbapenem[e]	13 (43.3)	34 (47.9)	14 (56)	6 (35.3)	54 (47.8)	0.664
Previous tigecycline	7 (23.3)	13 (18.3)	3 (12)	1 (5.9)	17 (15)	0.280
Previous metronidazole	3 (10)	8 (11.3)	3 (12)	3 (17.6)	14 (12.4)	0.719
Previous colistin iv	1 (3.3)	7 (9.9)	0	0	7 (6.2)	0.544
Previous colistin ih	4 (13.3)	5 (7)	1 (4)	0	6 (5.3)	0.126
Previous ciprofloxacin	1 (3.3)	0	1 (4)	2 (11.8)	3 (2.7)	0.841
Previous levofloxacin	7 (23.3)	15 (21.1)	2 (8)	2 (11.8)	19 (16.8)	0.411
Previous moxifloxacin	2 (6.7)	5 (7)	1 (4)	1 (5.9)	7 (6.2)	0.925
Previous fluoroquinolone[f]	10 (33.3)	20 (28.2)	3 (12)	4 (23.5)	27 (23.9)	0.294
Previous aminoglycosides	0	3 (4.2)	0	0	3 (2.7)	0.367
Previous any antibiotics	25 (83.3)	68 (95.8)	20 (80)	16 (94.1)	104 (92)	0.154

[a] Including amoxicillin/clavulanate, ampicillin/sulbactam, sulbactam, piperacillin/tazobactam.
[b] Including vancomycin, teicoplanin.
[c] Including cefazolin, cefuroxime, cefmetazole, flomoxef.
[d] Including cefoperazone, ceftazidime, ceftriaxone, cefepime.
[e] Including ertapenem, imipenem, meropenem, doripenem.
[f] Including ciprofloxacin, levofloxacin, moxifloxacin.
Data are presented as frequency with percentage (%).

Table 3 Treatment and outcomes of patients with *E. meningoseptica* bacteremia and other carbapenem-resistant ACB complex, *S. maltophilia* and carbapenem-resistant *P. aeruginosa* bacteremia.

Outcome	*E. meningoseptica*	Carbapenem-resistant ACB complex	*S. maltophilia*	Carbapenem-resistant *P. aeruginosa*	Non-*E. meningoseptica*	*p* Value (*E. meningoseptica vs* non-*E. meningoseptica*)
	n = 30	n = 71	n = 25	n = 17	n = 113	
Appropriate empirical antibiotics[a]	14 (58.3)	14 (26.4)*	7 (29.2)*	4 (26.7)	25 (27.2)	0.004
Appropriate definite antibiotics[a]	18 (75)	40 (75.5)	22 (91.7)	15 (100)*	77 (83.7)	0.324
14-d mortality	10 (33.3)	29 (40.8)	5 (20)	6 (35.3)	40 (35.4)	0.833
28-d mortality	14 (46.7)	37 (52.1)	8 (32)	7 (41.2)	52 (46)	0.949
In-hospital mortality	16 (53.3)	42 (59.2)	11 (44)	9 (52.9)	62 (54.9)	0.881
Clinical success	17 (56.7)	39 (54.9)	20 (80)	12 (70.6)	71 (62.8)	0.537
Persistent bacteremia	5 (16.7)	8 (11.3)	0*	0	8 (7.1)	0.272

[a] N = 24 in *E. meningoseptica* group, N = 53 in carbapenem-resistant ACB complex group, N = 24 in *S. maltophilia* group, N = 15 in carbapenem-resistant *P. aeruginosa* group, and N = 21 in non-*E. meningoseptica* group after elimination of cases with mortality within 48 h.
Data are presented as frequency with percentage (%).
*p Value < 0.05 when compared with *E. meningoseptica* group.

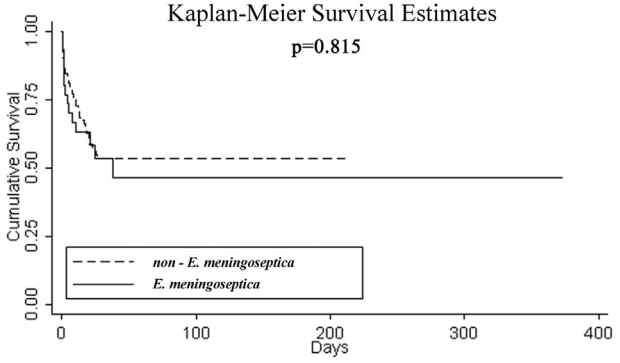

Figure 1. Survival after the onset of *E. meningoseptica* and non-*E. meningoseptica* (carbapenem-resistant ACB complex, *S. maltophilia* and carbapenem-resistant *P. aeruginosa*) bacteremia. The Kaplan–Meier survival curve showed a similar 28-day survival between the *E. meningoseptica* group and the non-*E. meningoseptica* group (Log-Rank test, p = 0.815).

Appropriate definite antibiotics was associated with 28-day survival in patients with *E. meningoseptica* (odds ratio [OR]:0.05, 95% confidence interval [CI]: 0.004–0.47, p = 0.01). Recent admission within 3 months (OR: 5.76, 95% CI: 1.32–25.04, p = 0.02) and hemodialysis (OR: 6.73, 95% CI: 1.09–41.50, p = 0.04) were associated with 28-day mortality in patients with carbapenem-resistant ACB complex bacteremia. Previous antifungal agent use was associated with 28-day mortality in patients with *S. maltophilia* bacteremia (OR: 19.89, 95% CI: 1.42–279.41, p = 0.027). In patients with carbapenem-resistant *P. aeruginosa* bacteremia, APACHE II score was the only risk factor (OR: 1.32, 95% CI: 1.04–1.69, p = 0.025) for 28-day mortality.

We further analyzed the risk factors of *E. meningoseptica* bacteremia among all carbapenem-resistant NFGNB bacteremia (Table 4). In this univariate analysis, older age, primary bacteremia, and chronic obstructive pulmonary disease were associated with *E. meningoseptica* bacteremia. ICU acquired bacteremia and central venous catheterization were associated with non-*E. meningoseptica* bacteremia. In the multivariate analysis, central venous catheterization was the protective factor against acquiring *E. meningoseptica* bacteremia (OR: 0.25, 95% CI: 0.11–0.61, p = 0.002).

Discussion

We compared the clinical characteristics and outcomes of *E. meningoseptica* with other carbapenem-resistant NFGNB bacteremia. The mortality rate of *E. meningoseptica* bacteremia was as high as other notorious carbapenem-resistant NFGNB, including ACB complex, *S. maltophilia* and *P. aeruginosa*. These findings suggest that *E. meningoseptica* has become a noteworthy carbapenem-resistant pathogen in Taiwan. We emphasize its role in nosocomial infection and advise that physicians should pay close attention to the emergence of *E. meningoseptica* bacteremia in Taiwan.

The increasing infections caused by carbapenem-resistant NFGNB have raised awareness in recent years.[3–6] Carbapenem-resistant ACB complex and *P. aeruginosa* infections are widely reported in the literature.[7–10] The intrinsic resistance natural of *S. maltophilia* has made it an emerging nosocomial pathogen among critically ill patients.[11,12] As an intrinsic carbapenem-resistant NFGNB, most reports of *E. meningoseptica* infections are from Taiwan and India.[5,6,13–18] However, comparison of the prevalence of these carbapenem-resistant NFGNB infections is lacking. Ko et al. found that *E. meningoseptica* is the third common Gram-negative bacilli causing ICU-acquired bacteremia in mechanically ventilated patients, only next to *K. pneumoniae* and ACB complex.[23] In India, *E. meningoseptica* is the third common NFGNB isolated from patients with respiratory tract infections in ICU, and is more

Table 4 Risk factors of *E. meningoseptica* bacteremia among all carbapenem-resistant non-fermenting Gram negative bacilli bacteremia.

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	*p* value	Odds ratio (95% confidence interval)	*p* Value
Age	1.03 (1.00–1.05)	0.030	–	–
Primary bacteremia	2.52 (1.08–5.87)	0.032	–	–
ICU acquired	0.37 (0.15–0.87)	0.022	–	–
Chronic obstructive pulmonary disease	4.20 (1.46–12.10)	0.008	2.81 (0.92–8.62)	0.071
Central venous catheterization	0.22 (0.09–0.51)	<0.001	0.25 (0.11–0.61)	0.002

prevalent than *S. maltophilia*.[5] In the current study, we first showed that the rate of *E. meningoseptica* bacteremia was second to ACB complex among these carbapenem-resistant NFGNB infections. Given the multidrug resistant nature of *E. meningoseptica*, the prevalent *E. meningoseptica* bacteremia in hospitals would be an important issue in the public health. The surveillance for *E. meningoseptica* among NFGNB, in addition to the well-known ACB complex, *P. aeruginosa*, and *S. maltophilia*, is necessary.

The clinical characteristics among patients with carbapenem-resistant NFGNB bacteremia were similar. We could not find specific risk factors for *E. meningoseptica* bacteremia among these patients. This suggests that *E. meningoseptica* infections should be considered when carbapenem-resistant NFGNB bacteremia are suspected clinically. We only found that patients with *E. meningoseptica* bacteremia received more colistin inhalation than those with other NFGNB infection, though this did not reach statistical significance. This may be due to the limited case number in the current study. Colistin is typically used for infections caused by carbapenem-resistant pathogens,[24] but it may facilitate *E. meningoseptica* acquisition by selection pressure. The dual resistance to colistin and carbapenem of *E. meningoseptica* make this infection a challenge clinically. Interestingly, we found that central venous catheterization predisposed to other non-*E. meningoseptica* NFGNB bacteremia in this study. In the literature, the rate of catheter related bloodstream infection was higher in carbapenem-resistant *A. baumannii* bacteremia (18.2%),[25] *S. maltophilia* bacteremia (12–24.6%)[12,26] and carbapenem-resistant *P. aeruginosa* bacteremia (24.3%)[10] than that in *E. meningoseptica* bacteremia (6–10%).[16,17] Our results may correspond to the lower rate of catheter related infection in *E. meningoseptica* in the literature and suggested the different portals of entry among these carbapenem-resistant NFGNB.

The 14-day or 28-day mortality of *E. meningoseptica* bacteremia is high in the literature (23–52%).[13–18] With regard to other NFGNB infections, carbapenem-resistant ACB complex bacteremia is also associated a high 14-day and 30-day mortality rate (35.5% and 43%, respectively).[7,8] *S. maltophilia* bacteremia is reported to be associated with a mortality around 23.9–34.5%.[11,12] Carbapenem-resistant *P. aeruginosa* bacteremia also leads to a high 30-day mortality (30–72%).[9,10] In this study, the high mortality rates of carbapenem-resistant ACB complex, *S. maltophilia*, and *P. aeruginosa* bacteremia were consistent with the literature. We demonstrated the similar poor outcome among patients with *E. meningoseptica* bacteremia in this study and established the pathogenic role of *E. meningoseptica* by comparison of the mortality among these carbapenem-resistant NFGNB bacteremia. Additionally, we observed the invasive presentation as empyema in two patients with *E. meningoseptica* bacteremia exclusively in this study. One study described that *E. meningoseptica* strains were capable of infecting and invading murine respiratory tract epithelial cells.[27] Central nervous infections caused by *E. meningoseptica* have also been reported in the literature[17,18] though were not found in the current 1-year study. All data suggests that *E. meningoseptica* has the capability to cause serious nosocomial infections, and is associated with invasive presentation. It appears that *E. meningoseptica* infection could be the next superbug in the future and more studies regarding its surveillance and prevention are necessary.

Patients with carbapenem-resistant NFGNB bacteremia usually receive inappropriate antibiotic treatment initially because of its multidrug resistant nature.[6] Interestingly, we found patients with *E. meningoseptica* bacteremia had a significantly higher rate of appropriate empiric antibiotics (58.3%) than patients with non-*E. meningoseptica* bacteremia (26.4–29.2%). In a previous study conducted in our hospital ICU, the rate of empiric appropriate antibiotics in *E. meningoseptica* bacteremia was as low as 16.7% from 2006 to 2009.[23] In the period from 2011 to 2015, the rate of appropriate empiric use in our recent study was 32.3%.[15] We studied *E. meningoseptica* bacteremia in our hospital and contributed to serial articles in the literature.[13–15] These retrospective studies may help alert our physicians about the emergence of this pathogen and early use of appropriate antibiotics.

Our study has several limitations. First, the patients included in this study were from a single medical center, which may make it difficult to apply our results to other general hospitals. Second, this is a retrospective study and possible selection bias could not be eliminated. Last, the limited patient number and the limited study period call for a longitudinal study to continuously investigate this important NFGNB pathogen.

In summary, we established the critical role of *E. meningoseptica* bacteremia in our hospital by comparing it with other carbapenem-resistant NFGNB bacteremia. The prevalent *E. meningoseptica* infection and its high mortality call for continued awareness from clinical physicians

and microbiologists towards understanding how to better manage *E. meningoseptica* infections.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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References

1. Memish ZA, Shibl AM, Kambal AM, Ohaly YA, Ishaq A, Livermore DM. Antimicrobial resistance among non-fermenting Gram-negative bacteria in Saudi Arabia. *J Antimicrob Chemother* 2012;**67**:1701—5.
2. Averbuch D, Avaky C, Harit M, Stepensky P, Fried I, Ben-Ami T, et al. Non-fermentative Gram-negative rods bacteremia in children with cancer: a 14-year single-center experience. *Infection* 2017;**45**:327—34.
3. Gniadek TJ, Carroll KC, Simner PJ. Carbapenem-resistant non-glucose-fermenting gram-negative bacilli: the missing piece to the puzzle. *J Clin Microbiol* 2016;**54**:1700—10.
4. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009—2010. *Infect Control Hosp Epidemiol* 2013;**34**:1—14.
5. Agarwal S, Kakati B, Khanduri S, Gupta S. Emergence of carbapenem resistant non-fermenting Gram-negative bacilli isolated in an ICU of a tertiary care hospital. *J Clin Diagn Res* 2017;**11**. Dc04-dc7.
6. Ting SW, Lee CH, Liu JW. Risk factors and outcomes for the acquisition of carbapenem-resistant Gram-negative bacillus bacteremia: a retrospective propensity-matched case control study. *J Microbiol Immunol Infect* 2017 Jun 23. https://doi.org/10.1016/j.jmii.2016.08.022.
7. Huang ST, Chiang MC, Kuo SC, Lee YT, Chiang TH, Yang SP, et al. Risk factors and clinical outcomes of patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia. *J Microbiol Immunol Infect* 2015;**45**:356—62.
8. Nutman A, Glick R, Temkin E, Hoshen M, Edgar R, Braun T, et al. A case-control study to identify predictors of 14-day mortality following carbapenem-resistant *Acinetobacter baumannii* bacteraemia. *Clin Microbiol Infect* 2014;**20**:O1028—34.
9. Lee CH, Su TY, Ye JJ, Hsu PC, Kuo AJ, Chia JH, et al. Risk factors and clinical significance of bacteremia caused by *Pseudomonas aeruginosa* resistant only to carbapenems. *J Microbiol Immunol Infect* 2017;**50**:677—83.
10. Buehrle DJ, Shields RK, Clarke LG, Potoski BA, Clancy CJ, Nguyen MH. Carbapenem-resistant *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and microbiologic treatment failure. *Antimicrob Agents Chemother* 2017;**61**(1). e01243—16.
11. Chang YT, Lin CY, Chen YH, Hsueh PR. Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options. *Front Microbiol* 2015;**6**:893.
12. Wang CH, Lin JC, Lin HA, Chang F-Y, Wang N-C, Chiu S-K, et al. Comparisons between patients with trimethoprim-sulfamethoxazole-susceptible and trimethoprim-sulfamethoxazole-resistant *Stenotrophomonas maltophilia* monomicrobial bacteremia: a 10-year retrospective study. *J Microbiol Immunol Infect* 2016;**49**:378—86.
13. Lin YT, Chiu CH, Chan YJ, Lin ML, Yu KW, Wang FD, et al. Clinical and microbiological analysis of *Elizabethkingia meningoseptica* bacteremia in adult patients in Taiwan. *Scand J Infect Dis* 2009;**41**:628—34.
14. 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—80.
15. Huang YC, Lin YT, Wang FD. 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.
16. Hsu MS, Liao CH, Huang YT, Liu CY, Yang CJ, Kao KL, 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—8.
17. Lin PY, Chen HL, Huang CT, Su LH, Chiu CH. Biofilm production, use of intravascular indwelling catheters and inappropriate antimicrobial therapy as predictors of fatality in *Chryseobacterium meningosepticum* bacteraemia. *Int J Antimicrob Agents* 2010;**36**:436—40.
18. Jean SS, Lee WS, Chen FL, Ou TY, Hsueh PR. *Elizabethkingia meningoseptica*: an important emerging pathogen causing healthcare-associated infections. *J Hosp Infect* 2014;**86**:244—9.
19. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;**137**:791—7.
20. Wu HS, Wang FD, Tseng CP, Wu TH, Lin YT, Fung CP. Characteristics of healthcare-associated and community-acquired *Klebsiella pneumoniae* bacteremia in Taiwan. *J Infect* 2012;**64**:162—8.
21. Chuang YC, Sheng WH, Lauderdale TL, Li SY, Wang JT, Chen YC, et al. Molecular epidemiology, antimicrobial susceptibility and carbapenemase resistance determinants among *Acinetobacter baumannii* clinical isolates in Taiwan. *J Microbiol Immunol Infect* 2014;**47**:324—32.
22. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing; 24th informational supplement*. CLSI document M100-S24. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
23. Ko HK, Yu WK, Lien TC, Wang JH, Slutsky AS, Zhang H, et al. Intensive care unit-acquired bacteremia in mechanically ventilated patients: clinical features and outcomes. *PLoS One* 2013;**8**:e83298.
24. Kaye KS, Gales AC, Dubourg G. Old antibiotics for multidrug-resistant pathogens: from in vitro activity to clinical outcomes. *Int J Antimicrob Agents* 2017;**49**:542—8.
25. Lee YT, Wang YC, Kuo SC, Chen CT, Liu CP, Liu YM, et al. Multicenter study of clinical features of breakthrough Acinetobacter bacteremia during carbapenem therapy. *Antimicrob Agents Chemother* 2017;**61**. e00931—17.
26. Jeon YD, Jeong WY, Kim MH, Jung IY, Ahn MY, Ann HW, et al. Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia. *Medicine (Baltimore)* 2016;**95**:e4375.
27. Lin PY, Chiu CH, Chu C, Tang P, Su LH. Invasion of murine respiratory tract epithelial cells by *Chryseobacterium meningosepticum* and identification of genes present specifically in an invasive strain. *New Microbiol* 2006;**29**:55—62.