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ORIGINAL ARTICLE

Clinical characteristics and risk factors for mortality in cefepime-resistant *Pseudomonas aeruginosa* bacteremia

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KEYWORDS
Bacteremia;
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Background: To identify the clinical characteristics and risk factors for mortality of patients with cefepime-resistant *Pseudomonas aeruginosa* (FRPa) bacteremia.
Methods: This retrospective study analyzed adult patients with FRPa bacteremia hospitalized between January 2006 and December 2011.
Results: Seventy eight patients (46 male, 32 female; mean age: 72.2 ± 14.1 years) were included. Of them, 46 (59.0%) had ventilator use and 45 (57.7%) had intensive care unit stay. All the bacteremia episodes were health-care associated or hospital acquired, and 55.1% of FRPa blood isolates were multidrug resistant. The sources of bacteremia were identified in 42 patients (53.8%), with pneumonia being the most common one (28/42; 66.7%). The mean interval between admission and the sample date of the first FRPa-positive blood culture was 45.8 ± 52.6 days. The mean Pittsburgh bacteremia score was 5.0 ± 3.4. The 15-day and 30-day mortality rates were 50.0% and 65.4%, respectively. Patients (41; 52.6%) on appropriate antibiotic therapy within 72 hours of the first FRPa-positive blood culture had a higher 30-day survival rate than those without (48.8% vs. 18.9%, $p = 0.011$ by log-rank test). Multivariate analyses revealed that a higher Pittsburgh bacteremia score was an independent risk factor for either 15-day ($p = 0.002$) or 30-day mortality ($p = 0.010$), and appropriate antibiotic therapy within 72 hours was an independent protecting factor for either 15-day ($p = 0.049$) or 30-day mortality ($p = 0.017$).

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Conclusion: FRPa bacteremia had a high mortality rate. The disease severity and appropriate antimicrobial therapy within 72 hours of positive blood culture were related to the patients' outcome.

Introduction

Pseudomonas aeruginosa has been a leading cause of nosocomial infections,[1,2] and infections caused by *P. aeruginosa* are often life threatening.[3] Emergence of antibiotic resistance in *P. aeruginosa* has been increasingly reported,[4,5] and its impact was the increased in-hospital mortality, cost, and hospital stay.[1,6,7] Identifying efficacious antimicrobial options for multidrug-resistant (MDR) *P. aeruginosa* is still a challenge for physicians.

Based on our computer-assisted microbiology laboratory database from January 2006 to December 2011, the disk diffusion antimicrobial susceptibility testing for the clinical nonduplicated *P. aeruginosa* blood isolates revealed that the drug-resistant rates to piperacillin, imipenem—cilastatin, ciprofloxacin, ceftazidime, cefepime, and amikacin were 14.1%, 12.7%, 10.7%, 10.3%, 7.8%, and 2.3%, respectively. Cefepime had the second lowest resistant rate (7.8%), which was only second to that of amikacin (2.3%). Therefore, cefepime has become an important empirical treatment option for patients with suspected *P. aeruginosa* infections in our clinical practice, particularly for those with high disease severity.

Croughs et al[8] had described a significant trend of increasing cefepime resistance in *P. aeruginosa* from 1998 to 2010 (4.8% to 6.4%; $p = 0.016$). Furthermore, Akhabue et al[9] had recognized that bacteremia caused by cefepime-resistant *P. aeruginosa* (FRPa) was an independent risk factor for in-hospital mortality. Thus, to investigate the clinical characteristics and risk factors for mortality of FRPa bacteremia, we conducted a retrospective study for patients with FRPa bacteremia.

Materials and methods

Setting

This retrospective study was conducted at the Chang Gung Memorial Hospital (CGMH, Linkou branch), a 3715-bed university-affiliated tertiary-care medical center with 308 intensive care unit (ICU) beds in northern Taiwan. This study was approved by the Institutional Review Board of CGMH-Linkou (number 101-0929B).

Study design and patients

Through the computer-assisted microbiology laboratory database, patients aged $\geq$ 18 years and at least one blood culture positive for FRPa admitted to our hospital between January 2006 and December 2011 were reviewed. Cases of FRPa bacteremia with symptoms and signs suggestive of systemic infection were included. The symptoms and signs of infection included at least one of the following clinical characteristics: (1) body temperature $<36^{\circ}C$ or $>38^{\circ}C$; (2) heart rate >90 beats per minute; (3) tachypnea $>$ 20breaths per minute; or an arterial partial pressure of carbon dioxide <32 mmHg; (4) white blood cell count <4000 cells/mm^3 or $>12{,}000$ cells/mm^3; or the presence of $>10\%$ immature neutrophils. For patients with multiple episodes of FRPa bacteremia, only the first episode was included for analysis.

Microbiology

Blood cultures were processed in the clinical microbiology laboratory, using the automated blood culture system (BACTEC 9240 system; Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). *P. aeruginosa* isolates were identified on the basis of the following properties: aerobic Gram-negative bacilli on a Gram's stain with glucose nonfermentation, positive oxidase test, production of blue—green or yellow—green fluorescent pigment, and growth at 42°C.[10] Antimicrobial susceptibilities testing was performed using the disk diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) M100-S22 criteria.[11] The antibiotic disks (BD Microbiology Systems, Cockeysville, MD, USA) for *P. aeruginosa* included amikacin, gentamicin, ceftazidime, cefepime, piperacillin, piperacillin—tazobactam, imipenem, meropenem, and ciprofloxacin. Based on the CLSI criteria,[11] nonsusceptible *P. aeruginosa* isolates were those with an inhibitory zone diameter for cefepime <18 mm, and these were classified as FRPa in this study. MDR *P. aeruginosa* was defined as *P. aeruginosa* with resistance to at least three of the following four antimicrobial classes: antipseudomonal penicillins (or cephalosporins), antipseudomonal carbapenems (including imipenem—cilastatin and meropenem), antipseudomonal fluoroquinolones (including ciprofloxacin and levofloxacin), and aminoglycosides. Resistance to each class was defined as intermediate or complete resistance to at least one agent of each class.[12]

Data collection and definition

Data on age, sex, comorbid diseases, image and laboratory findings, surgical findings, antimicrobial susceptibility testing, clinical characteristics, and outcomes of the patients with FRPa bacteremia were gathered by reviewing the inpatient medical records. The comorbid diseases identified were hypertension, end-stage renal disease,[13] diabetes mellitus, cerebral vascular accident, liver cirrhosis, chronic pulmonary disease, and malignancy. Ventilator use, ICU stay, Pittsburgh bacteremia score,

Charlson Comorbidity Index, and presence of central venous catheters (CVCs) on the sample date of the first blood culture positive for FRPa were recorded. CVCs were classified into short-term (*in situ* $<$ 14 days, such as central venous pressure or double lumen) and long-term ones (*in situ* $\geq$ 14 days, such as Port-a-Cath or Hickman).[14] The intervals between admission and the sample date of the first FRPa-positive blood culture were also recorded. Hospital-acquired infection was defined as an infection that occurred 48 hours after hospital admission. Severity of illness was calculated by the Pittsburgh bacteremia score.[15] A Pittsburgh bacteremia score $\geq$4 was defined as severely ill. The severity of comorbidities was evaluated using the Charlson Comorbidity Index for chronic diseases.[16]

The sources of bacteremia were determined according to the medical records, image studies, surgical findings, and microbiological evidence. The sources of bacteremia were categorized into lower respiratory tract, urinary tract, skin and soft tissue, catheter-related bloodstream infection (CRBSI), and intra-abdominal infection. According to the clinical practice guidelines updated by the Infectious Diseases Society of America in 2009, a definitive diagnosis of CRBSI requires that the same organism grows from at least one percutaneous blood culture and from a culture of the catheter tip.[14] The FRPa bacteremia with multiple sources was defined as FRPa bacteremia with at least two identified sources. If there was no identified source, it was categorized as primary FRPa bacteremia. Polymicrobial bacteremia was defined as one or more additional bacterial species isolated from blood simultaneously with FRPa.

Any one agent of the following four classes of antibiotics being used for at least 3 days within 3 months prior to the date of the first blood culture positive for FRPa was recorded: penicillins or cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides.

Treatment and outcome

Appropriate antibiotic therapy was defined as any one of antibiotic agents that was used for at least 3 days with correct dosage subsequently proved to be effective *in vitro* against the FRPa blood isolates. The time intervals between collection of index FRPa blood culture and appropriate antibiotic therapy were recorded. Empirical combination therapy was defined as therapy for Gram-negative infections with at least two classes of antimicrobial agents commenced prior to the identification of the causative microorganism and continued for at least 3 days regardless of the antimicrobial susceptibility for FRPa. The all-cause mortality rates of the cases at 15 days and 30 days were recorded.

Statistical analysis

All statistical analyses were performed using SPSS for Windows (version 18.0; SPSS Inc., Chicago, IL, USA). Categorical variables were compared using χ^2 test or Fisher exact test, as appropriate. Continuous variables were compared by Mann—Whitney *U* test. Variables with $p < 0.1$ in univariate analysis were included in a multiple logistic regression model using backward stepwise method to identify the risk factors for 15-day and 30-day mortalities. Adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated. The survival curve was plotted by the Kaplan—Meier method, and the log-rank test was used to compare univariate survival distribution. All tests were two-tailed, and $p < 0.05$ was considered significant.

Results

Patients and clinical characteristics

Between January 2006 and December 2011, 1323 non-duplicated *P. aeruginosa* blood isolates were identified, including 103 FRPa blood isolates. Finally, 78 adult patients with FRPa bacteremia were included in the study, and their demographic and clinical characteristics are shown in Table 1. All of them had at least one characteristic symptom and sign suggestive of systemic infection, and 74 patients (94.9%) had at least two characteristics. Of the 78 patients, 46 (59.0%) were men. The mean age was 72.2 $\pm$ 14.1 years (range: 33—94 years). The most common comorbid disease was hypertension (52.6%), followed by solid-organ malignancy (38.5%) and diabetes mellitus (33.3%). The mean interval between admission and the sample date of the first FRPa-positive blood culture was 45.8 $\pm$ 52.6 days (range: 0—227 days). Sixty-five patients (83.3%) had nosocomial infections, and the other 13 patients (16.7%) had hospitalization within 2 months prior to the FRPa bacteremia episode.

Sixty-five patients (83.3%) had CVC use, including 78.5% (51/65) short-term use and 21.5% (14/65) long-term use. Forty-six individuals (59%) had ventilator use, and 45 individuals (57.7%) stayed in the ICU when FRPa bacteremia occurred. The mean Pittsburgh bacteremia score was 5.0 $\pm$ 3.4, and the mean Charlson Comorbidity Index was 6.0 $\pm$ 10.0. Thirty-six patients (46.2%) had primary bacteremia, and the other 42 patients (53.8%) had the identified sources of FRPa bacteremia. The most common source of bacteremia was lower respiratory tract infection (28/42, 66.7%), followed by urinary tract infection (11/42, 26.2%). Ten patients (12.8%) had FRPa bacteremia with multiple sources, and 28 patients (35.9%) had polymicrobial bacteremia. Forty-three patients (55.1%) had MDR FRPa bacteremia.

As for prior antibiotics exposure within 3 months, 68 patients (87.2%) had the use of penicillins or cephalosporins, followed by 36 individuals (46.2%) with carbapenems use and 32 individuals (41.0%) with fluoroquinolones use.

Treatment and outcomes

A total of 18 patients (23.1%), 28 patients (35.9%), and 41 patients (52.6%) had appropriate antibiotic therapy within 24 hours, 48 hours, and 72 hours after the sample date of the first positive FRPa blood culture, respectively. Antipseudomonal carbapenems and antipseudomonal fluoroquinolones were the two most commonly used appropriate antibiotics (both 23.1%), followed by aminoglycosides (20.5%). Thirteen patients (16.7%) had the empirical combination therapy. The most common co-administered antimicrobial agent was aminoglycosides

Table 1 Clinical characteristics of 78 patients with cefepime-resistant *Pseudomonas aeruginosa* bacteremia

Variables	Value
Demographic parameters	
Age, y	72.2 ± 14.1
Male sex	46 (59.0)
Comorbid diseases	
Hypertension	41 (52.6)
Diabetes mellitus	26 (33.3)
End-stage renal disease	23 (29.5)
Liver cirrhosis	12 (15.4)
Chronic pulmonary disease	9 (11.5)
Cerebral vascular accident	18 (23.1)
Solid-organ malignancy	30 (38.5)
Hematology malignancy	6 (7.7)
Clinical conditions	
Interval between admission and the sample date of first positive blood culture for FRPa, day	45.8 ± 52.6
Central venous catheter use	65 (83.3)
Short term	51 (65.4)
Long term	17 (21.8)
Ventilator use	46 (59.0)
Intensive care unit stay	45 (57.7)
Pittsburgh bacteremia score	5.0 ± 3.4
Charlson Comorbidity Index	6.0 ± 10.0
Sources of FRPa bacteremia	
Primary	36 (46.2)
Lower respiratory tract	28 (35.9)
Urinary tract	11 (14.1)
Skin and soft tissues	7 (9.0)
Catheter-related bloodstream infection	5 (6.4)
Intra-abdominal infection	3 (3.8)
Multiple sources	10 (12.8)
Microbiology	
Polymicrobial bacteremia	28 (35.9)
Multidrug-resistant *P. aeruginosa*	43 (55.1)
Prior antibiotics exposure within 3 mo	
Penicillins or cephalosporins	68 (87.2)
Carbapenems	36 (46.2)
Fluoroquinolones	32 (41.0)
Aminoglycosides	14 (17.9)
Treatment	
Appropriate antibiotic therapy within 24 h	18 (23.1)
Appropriate antibiotic therapy within 48 h	28 (35.9)
Appropriate antibiotic therapy within 72 h	41 (52.6)
With antipseudomonal penicillins or cephalosporins	10 (12.8)
With antipseudomonal carbapenems	18 (23.1)
With antipseudomonal fluoroquinolones	18 (23.1)
With aminoglycosides	16 (20.5)
Combination therapy	13 (16.7)
With aminoglycosides	8 (10.3)
Other regimens	5 (6.4)
Outcome	
15-d mortality	39 (50.0)
30-d mortality	51 (65.4)

Data are presented as *n* (%) or mean ± standard deviation, unless indicated specifically.
d = day; FRPa = cefepime-resistant *P. aeruginosa*; h = hours; mo = months; y = years.

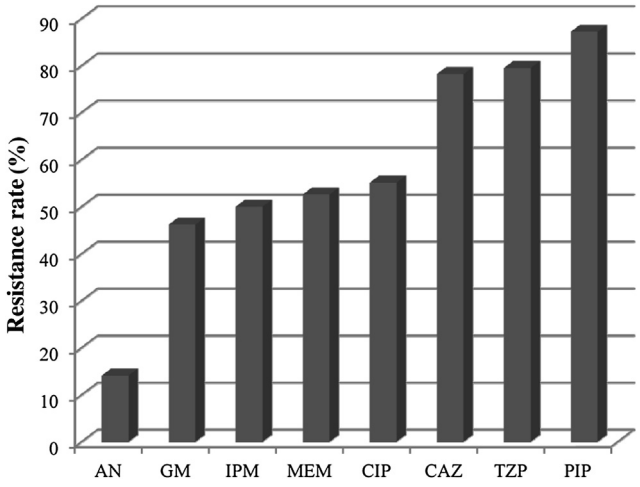

Figure 1. Coresistance of 78 cefepime-resistant *Pseudomonas aeruginosa* blood isolates to the antipseudomonal antimicrobial agents except cefepime. AN = amikacin; CAZ = ceftazidime; CIP = ciprofloxacin; GM = gentamicin; IPM = imipenem; MEM = meropenem; PIP = piperacillin; TZP = piperacillin–tazobactam.

(8/13, 61.5%). The 15-day mortality was 50.0% and 30-day mortality was 65.4% (Table 1).

Coresistance of FRPa blood isolates

The coresistance to antipseudomonal agents other than cefepime is shown in Fig. 1. The FRPa blood isolates in this

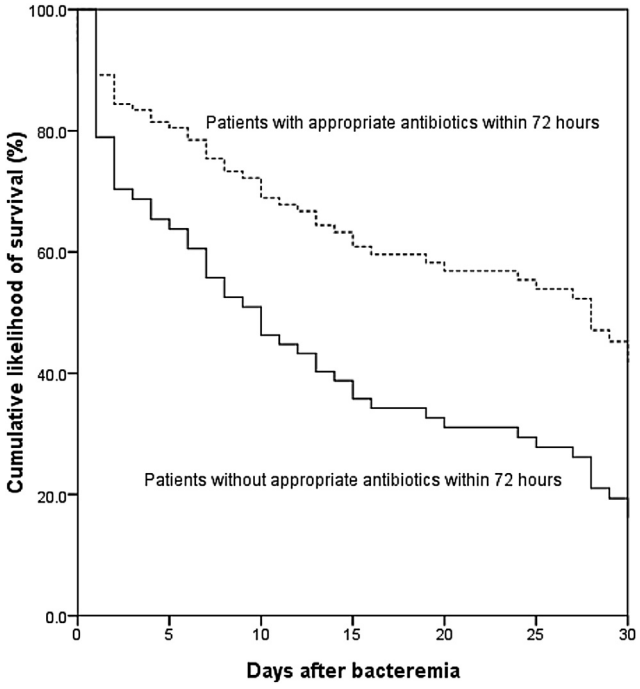

Figure 2. Kaplan–Meier survival curve in patients with and without appropriate antibiotic therapy within 72 hours after diagnosis of cefepime-resistant *Pseudomonas aeruginosa* bacteremia, with $p = 0.011$ (by log-rank test).

study had the lowest coresistance rate to amikacin (14.1%), and the coresistance rates were high for ceftazidime (78.2%) and piperacillin (87.2%). About half of the isolates were simultaneously resistant to ciprofloxacin (55.1%) and imipenem–cilastatin (50%).

Analyses of risk factors for 15- and 30-day mortality of FRPa bacteremia

The cumulative survival rate at 30 days revealed that patients with appropriate antibiotic therapy within 72 hours had a significantly higher survival rate than those without, and the survival curves showed significant difference (48.8% vs. 18.9%, $p = 0.011$ by log-rank test; Fig. 2).

In univariate analysis for 15-day mortality (Table 2), the deceased patients had a higher rate of ICU stay (71.8% vs. 43.6%, $p = 0.012$), a higher Pittsburgh bacteremia score (6.3 ± 3.6 vs. 3.7 ± 2.8, $p = 0.001$), and a lower rate of appropriate antibiotic therapy within 72 hours (41.0% vs. 64.1%, $p = 0.041$) when compared with those who survived. In multivariate analysis, a higher Pittsburgh bacteremia score was an independent risk factor for 15-day mortality (adjusted OR: 1.293; 95% CI: 1.098–1.522; $p = 0.002$), and appropriate antibiotic therapy within 72 hours was an independent protecting factor (adjusted OR: 0.2367; 95% CI: 0.135–0.998; $p = 0.049$).

In univariate analysis for 30-day mortality (Table 3), the deceased patients also had a higher rate of ICU stay (68.6% vs. 37.0%, $p = 0.007$), a higher Pittsburgh bacteremia score (5.7 ± 3.5 vs. 3.6 ± 2.9, $p = 0.007$), and a lower rate of appropriate antibiotic therapy within 72 hours (41.2% vs. 74.1%, $p = 0.006$) when compared with those who survived. In multivariate analysis, a higher Pittsburgh bacteremia score was an independent risk factor for 30-day mortality (adjusted OR: 1.261; 95% CI: 1.507–1.504; $p = 0.010$), and

Table 2 Univariate and multivariate analyses of risk factors for 15-day mortality of cefepime-resistant *Pseudomonas aeruginosa* bacteremia

Variables	Deceased	Survived	Univariate	Multivariate[a]		
	$n = 39$	$n = 39$	p	Adjusted OR	95% CI	p
Demographic parameters						
Age, y	71.64 ± 15.48	72.79 ± 12.65	0.901			
Male sex	24 (61.5)	22 (56.4)	0.818			
Comorbid diseases						
Hypertension	22 (56.4)	19 (48.7)	0.496			
Diabetes mellitus	14 (35.9)	12 (30.8)	0.631			
End-stage renal disease	15 (38.5)	8 (20.5)	0.082			
Liver cirrhosis	8 (20.5)	4 (10.3)	0.347			
Chronic pulmonary disease	5 (12.8)	4 (10.3)	> 0.99			
Cerebral vascular accident	8 (20.5)	10 (25.6)	0.591			
Solid-organ malignancy	12 (30.8)	18 (46.2)	0.163			
Hematologic malignancy	2 (5.1)	4 (10.3)	0.675			
Clinical conditions						
Intensive care unit stay	28 (71.8)	17 (43.6)	0.012			
Pittsburgh bacteremia score	6.26 ± 3.55	3.69 ± 2.83	0.001	1.293	1.098–1.522	0.002
Charlson Comorbidity Index	6.08 ± 2.8	5.9 ± 3.52	0.608			
Source of FRPa bacteremia						
Primary	15 (38.5)	21 (53.8)	0.173			
Lower respiratory tract	18 (46.2)	10 (25.6)	0.059			
Urinary tract	5 (12.8)	6 (15.4)	0.745			
Skin and soft tissues	6 (15.4)	1 (2.6)	0.108			
CRBSI	3 (7.7)	2 (5.1)	> 0.99			
Intra-abdominal site	0	3(7.7)	0.240			
Multiple sources	6 (15.4)	4 (10.3)	0.737			
Microbiology						
Polymicrobial bacteremia	17 (43.6)	11 (28.2)	0.157			
MDR *P. aeruginosa*	19 (48.7)	24 (61.5)	0.255			
Treatment						
Appropriate antibiotic therapy within 72 h	16 (41.0)	25 (64.1)	0.041	0.367	0.135–0.998	0.049
Combination therapy	4 (10.3)	9 (23.1)	0.224			
With aminoglycosides	1 (2.6)	7 (17.9)	0.056			
Other regimens	3 (7.7)	2 (5.1)	> 0.99			

[a] All variables with $p < 0.1$ in univariate analysis were included in a multivariate regression model using backward stepwise method.
Data are presented as n (%) or mean ± standard deviation, unless indicated specifically.
CI = confidence interval; CRBSI = catheter-related bloodstream infection; FRPa = cefepime-resistant *P. aeruginosa*; h = hours; MDR = multidrug resistant; OR = odds ratio; y = years.

Table 3 Univariate and multivariate analyses of risk factors for 30-day mortality of cefepime-resistant *Pseudomonas aeruginosa* bacteremia

Variables	Deceased	Survived	Univariate	Multivariate[a]		
	$n = 51$	$n = 27$	p	Adjusted OR	95% CI	p
Demographic parameters						
Age, y	72.5 ± 15.2	71.6 ± 11.8	0.610			
Male sex	30 (58.8)	16 (59.3)	0.970			
Comorbid diseases						
Hypertension	28 (54.9)	13 (48.1)	0.570			
Diabetes mellitus	18 (35.3)	8 (29.6)	0.614			
End-stage renal disease	18 (35.3)	5 (18.5)	0.122			
Liver cirrhosis	8 (15.7)	4 (14.8)	0.919			
Chronic pulmonary disease	7 (13.7)	2 (7.4)	0.485			
Cerebral vascular accident	11 (21.6)	7 (25.9)	0.664			
Solid-organ malignancy	17 (33.3)	13 (48.1)	0.201			
Hematologic malignancy	2 (3.9)	4 (14.8)	0.174			
Clinical conditions						
Intensive care unit stay	35 (68.6)	10 (37.0)	0.007			
Pittsburgh bacteremia score	5.7 ± 3.5	3.6 ± 2.9	0.007	1.261	1.057–1.504	0.010
Charlson Comorbidity Index	6.3 ± 3.4	5.4 ± 2.7	0.401			
Source of FRPa bacteremia						
Primary	22 (43.1)	14 (51.9)	0.463			
Lower respiratory tract	21 (41.2)	7 (25.9)	0.182			
Urinary tract	6 (11.8)	5 (18.5)	0.415			
Skin and soft tissues	7 (13.7)	0 (0.0)	0.089			
CRBSI	3 (5.9)	2 (7.4)	> 0.99			
Intra-abdominal site	1 (2.0)	2 (7.4)	0.274			
Multiple sources	7 (13.7)	3 (11.1)	> 0.99			
Microbiology						
Polymicrobial bacteremia	21 (41.2)	7 (25.9)	0.182			
MDR *P. aeruginosa*	25 (49.0)	18 (66.7)	0.136			
Treatment						
Appropriate antibiotic therapy within 72 h	21 (41.2)	20 (74.1)	0.006	0.252	0.082–0.779	0.017
Combination therapy	6 (11.8)	7 (25.9)	0.110			
With aminoglycosides	3 (5.9)	5 (18.5)	0.117			
Other regimens	3 (5.9)	2 (7.4)	> 0.99			

[a] All variables with $p < 0.1$ in univariate analysis were included in a multivariate regression model using backward stepwise method.
Data are presented as *n* (%) or mean ± standard deviation, unless indicated specifically.
CI = confidence interval; CRBSI = catheter-related bloodstream infection; FRPa = cefepime-resistant *P. aeruginosa*; MDR = multidrug resistant; OR = odds ratio; y = years.

appropriate antibiotic therapy within 72 hours was an independent protecting factor (adjusted OR: 0.252; 95% CI: 0.082–0.779; $p = 0.017$).

Discussion

In this epidemiological survey, patients with FRPa bacteremia were aged with one or more comorbid illnesses. All the FRPa bacteremia episodes were healthcare associated or hospital acquired. The disease severity was high. Ventilator use and ICU stay were common. Without a comparison group of patients with bacteremia caused by cefepime-susceptible *P. aeruginosa*, it is hard to indicate these characteristics were particularly associated with FRPa in this study. However, these clinical characteristics had been identified to be associated with FRPa infection or colonization in previous comparison studies. Akhabue et al[9] had recognized that patients with FRPa were associated with prior antibiotic use, ICU stay, transfer from another facility, and multiple concurrent illnesses while comparing patients with FRPa to those without. More than half of our FRPa blood isolates were MDR *P. aeruginosa*. Previous studies also reported that MDR *P. aeruginosa* bacteremia usually had a nosocomial onset[17] and was associated with a longer hospital stay,[17,18] mechanical ventilator use, and ICU stay.[19,20]

Akhabue et al[9] also indicated that patients with FRPa had a higher mortality rate than those without (20.2% vs. 13.2%, $p = 0.007$), and FRPa bacteremia was an independent risk factor for death ($p = 0.001$). Our study focused on patients with FRPa bacteremia, and further investigated their risk factors for mortality. Our patients had a 30-day mortality rate of 65.4%, which was higher than that in previous studies on *P. aeruginosa* bacteremia (ranged from 18.4% to 29%).[21–24] In risk factor analyses for 15-day and 30-day mortalities, Pittsburgh bacteremia score, which was

reflecting the high disease severity in our patient group, stood out as an independent risk factor. This finding was similar to that in previous studies for *P. aeruginosa* bacteremia; critical illness and ICU admission were usually associated with increased mortality in patients with such a bacteremia.[19,20,24] Either for 15-day or 30-day mortality, appropriate antibiotic therapy within 72 hours was an independent protecting factor whereas the Pittsburgh bacteremia score was included in multivariate analyses. In other words, absence of appropriate antibiotic therapy within 72 hours was also an independent risk factor for mortality in patients with FRPa bacteremia.

Previous studies have shown the trends toward increased mortality after inappropriate empirical antimicrobial treatment for *P. aeruginosa* bloodstream infections.[25–27] In a retrospective cohort study of 305 patients with *P. aeruginosa* bloodstream infection, the hospital mortality rate was statistically higher for patients with inappropriate initial antimicrobial treatment compared with appropriate initial treatment (30.7% vs. 17.8%; $p = 0.018$).[25] Inappropriate initial antimicrobial treatment was defined as the absence of an agent given with *in vitro* activity as determined by susceptibility testing, and was identified as an independent determinant of hospital mortality (adjusted OR: 2.04; 95% CI: 1.42–2.92; $p = 0.048$).[25]

In another retrospective cohort of 100 patients with *P. aeruginosa* bacteremia, the most significant delay break point to define the risk of 30-day mortality was 52 hours.[27] Patients receiving appropriate therapy over 52 hours after the index *P. aeruginosa* blood culture collection had a greater than twofold increase in 30-day mortality compared with those receiving appropriate therapy within 52 hours of index culture collection (43.8% vs. 19.2%; $p = 0.008$). Besides, antibiotic resistance to three or more drug classes was the most important determinant of delayed appropriate therapy (adjusted OR: 4.6; 95% CI: 1.9–11.2; $p = 0.001$). MDR might decrease the likelihood of receiving appropriate empirical antibiotics timely. In our study, only about half the patients had appropriate antibiotic therapy in the first 3 days of FRPa bacteremia, and more than half of the FRPa blood isolates were MDR *P. aeruginosa*.

Combination antimicrobial therapy for *P. aeruginosa* infections is still a matter for debate. Empirical combination therapy had been suggested to minimize inappropriate initial antimicrobial treatment in patients with *P. aeruginosa* bacteremia.[25,28] In one study for *P. aeruginosa* bloodstream infection, appropriate initial antimicrobial treatment was administered statistically more often among patients receiving empirical combination antimicrobial treatment for Gram-negative bacteria compared with empirical monotherapy (79.4% vs. 65.5%; $p = 0.011$).[25] However, the statistic difference between mortality rate and empirical combination therapy was not shown in the same study.[25] In a recent prospective cohort study in Barcelona, both empirical and definite combination antimicrobial therapy did not reduce the mortality risk compared with single-drug therapy in *P. aeruginosa* bloodstream infections.[29] Similar results were obtained in the study by Bowers et al.[30] In our cases, empirical combination therapy was uncommon (only 16.7%), the small case numbers might limit a comprehensive analysis to recognize the relationship between combination therapy and mortality. Further expanded studies may help us to clarify the role of combination therapy in FRPa bacteremia.

This study had several limitations. For the nature of retrospective design, the diagnosis and management of sepsis and antibiotic choice were based on individual clinicians' opinions. Our data were collected from a single site, so institutional differences in prescribing patterns, antibiotic formularies, and patient populations may affect the applicability of our results to other institutions. Finally, molecular types of the FRPa isolates were not identified, and resistance mechanisms were not investigated. Different genotypes of FRPa might have differences in clinical characteristics and outcomes.

In conclusion, patients with FRPa bacteremia had high disease severity and complicated clinical conditions. High Pittsburgh bacteremia score and absence of appropriate antimicrobial therapy within 72 hours were two independent risk factors for mortality of FRPa bacteremia. Further study should aim on active surveillance with the change of *P. aeruginosa* susceptibility profile for adjustment of adequate empirical antimicrobial therapy regimens to improve patients' outcome.

Conflicts of interest

The authors declare that they have no financial or nonfinancial conflicts of interest related to the subject matter or materials discussed in the manuscript.

References

1. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis* 2003;**36**:1433–7.
2. Klevens RM, Edwards JR, Gaynes RP. National Nosocomial Infections Surveillance System. The impact of antimicrobial-resistant, health care-associated infections on mortality in the United States. *Clin Infect Dis* 2008;**47**:927–30.
3. Osmon S, Ward S, Fraser VJ, Kollef MH. Hospital mortality for patients with bacteremia due to *Staphylococcus aureus* or *Pseudomonas aeruginosa*. *Chest* 2004;**125**:607–16.
4. Harris A, Torres-Viera C, Venkataraman L, DeGirolami P, Samore M, Carmeli Y. Epidemiology and clinical outcomes of patients with multiresistant *Pseudomonas aeruginosa*. *Clin Infect Dis* 1999;**28**:1128–33.
5. Bonomo RA, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. *Clin Infect Dis* 2006;**43**:S49–56.
6. Carmeli Y, Troillet N, Karchmer AW, Samore MH. Health and economic outcomes of antibiotic resistance in *Pseudomonas aeruginosa*. *Arch Intern Med* 1999;**159**:1127–32.
7. Livermore DM. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare? *Clin Infect Dis* 2002;**34**:634–40.
8. Croughs PD, Li B, Hoogkamp-Korstanje JA, Stobberingh E. Antibiotic Resistance Surveillance Group. Thirteen years of antibiotic susceptibility surveillance of *Pseudomonas aeruginosa* from intensive care units and urology services in the Netherlands. *Eur J Clin Microbiol Infect Dis* 2013;**32**:283–8.
9. Akhabue E, Synnestvedt M, Weiner MG, Bilker WB, Lautenbach E. Cefepime-resistant *Pseudomonas aeruginosa*. *Emerg Infect Dis* 2011;**17**:1037–43.

10. Henry DA, Speert DP. Pseudomonas. In: Versalovic J, Carroll KC, Funke G, Jorgensen JH, Landry ML, Warnock DW, editors. *Manual of clinical microbiology*. 10th ed. Washington, DC: American Society of Microbiology; 2011. p. 677—91.
11. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing: Twenty-second informational supplement. (CLSI document M100-S22)*. Wayne, PA: CLSI; 2012.
12. Ohmagari N, Hanna H, Graviss L, Hackett B, Perego C, Gonzalez V, et al. Risk factors for infections with multidrug-resistant *Pseudomonas aeruginosa* in patients with cancer. *Cancer* 2005;**104**:205—12.
13. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**:S1—266.
14. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;**49**:1—45.
15. Chow JW, Fine MJ, Shlaes DM, Quinn JP, Hooper DC, Johnson MP, et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991;**115**:585—90.
16. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;**47**:1245—51.
17. Morata L, Cobos-Trigueros N, Martínez JA, Soriano A, Almela M, Marco F, et al. Influence of multidrug resistance and appropriate empirical therapy on the 30-day mortality rate of *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother* 2012;**56**:4833—7.
18. Tam VH, Rogers CA, Chang KT, Weston JS, Caeiro JP, Garey KW. Impact of multidrug-resistant *Pseudomonas aeruginosa* bacteremia on patient outcomes. *Antimicrob Agents Chemother* 2010;**54**:3717—22.
19. Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabili S, Carmeli Y. Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. *Antimicrob Agents Chemother* 2006;**50**:43—8.
20. Cao B, Wang H, Sun H, Zhu Y, Chen M. Risk factors and clinical outcomes of nosocomial multi-drug resistant *Pseudomonas aeruginosa* infections. *J Hosp Infect* 2004;**57**:112—8.
21. Joo EJ, Kang CI, Ha YE, Kang SJ, Park SY, Chung DR, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia: clinical impact of antimicrobial resistance on outcome. *Microb Drug Resist* 2011;**17**:305—12.
22. Hirsch EB, Cottreau JM, Chang KT, Caeiro JP, Johnson ML, Tam VH. A model to predict mortality following *Pseudomonas aeruginosa* bacteremia. *Diagn Microbiol Infect Dis* 2012;**72**:97—102.
23. Peña C, Suarez C, Gozalo M, Murillas J, Almirante B, Pomar V, et al. Prospective multicenter study of the impact of carbapenem resistance on mortality in *Pseudomonas aeruginosa* bloodstream infections. *Antimicrob Agents Chemother* 2012;**56**:1265—72.
24. Kang CI, Kim SH, Kim HB, Park SW, Choe YJ, Oh MD, et al. *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. *Clin Infect Dis* 2003;**37**:745—51.
25. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. *Antimicrob Agents Chemother* 2005;**49**:1306—11.
26. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, et al. Bloodstream infections caused by antibiotic-resistant Gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. *Antimicrob Agents Chemother* 2005;**49**:760—6.
27. Lodise Jr TP, Patel N, Kwa A, Graves J, Furuno JP, Graffunder E, et al. Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. *Antimicrob Agents Chemother* 2007;**51**:3510—5.
28. Martínez JA, Cobos-Trigueros N, Soriano A, Almela M, Ortega M, Marco F, et al. Influence of empiric therapy with a beta-lactam alone or combined with an aminoglycoside on prognosis of bacteremia due to Gram-negative microorganisms. *Antimicrob Agents Chemother* 2010;**54**:3590—6.
29. Peña C, Suarez C, Ocampo-Sosa A, Murillas J, Almirante B, Pomar V, et al. Effect of adequate single-drug vs combination antimicrobial therapy on mortality in *Pseudomonas aeruginosa* bloodstream infections: a *post hoc* analysis of a prospective cohort. *Clin Infect Dis* 2013;**57**:208—16.
30. Bowers DR, Liew YX, Lye DC, Kwa AL, Hsu LY, Tam VH. Outcomes of appropriate empiric combination versus monotherapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother* 2013;**57**:1270—4.