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Original Article

Clinical characteristics and treatment outcomes of vancomycin-resistant *Enterococcus faecium* bacteremia

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KEYWORDS
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Daptomycin;
Linezolid

Abstract *Background:* Vancomycin-resistant *Enterococcus faecium* (VRE-fm) bacteremia causes significant mortality in hospitalized patients. We sought to investigate clinical characteristics, treatment outcomes, and microbiological eradication associated with VRE-fm bacteremia.
Methods: A retrospective cohort study was conducted and included 210 adult patients admitted between January 1, 2011 and December 31, 2015.
Results: The mean Pitt bacteremia score was 4.7. ICU stay (48.6%) and mechanical ventilation (46.2%) were common. Diabetes mellitus was the most common concomitant disease (43.3%), followed by malignancies, including hematologic malignancies (14.3%) and solid cancers (28.1%). The 14-day and 28-day mortality rates were 37.1% and 50.5%, respectively. Linezolid or daptomycin treatment for at least 10 days and higher Pitt bacteremia scores were independently associated with 14-day and 28-day mortality. Longer treatment duration of linezolid or daptomycin predicted microbiological eradication independently. Daptomycin-treated patients tended to have higher 14-day and 28-day mortality, and lower microbial eradication rates (20.8% versus 8.7%; 40.6% versus 26.1%; 14.1% versus 26.1%; respectively) than

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; MIC, minimum inhibitory concentration; VRE, vancomycin-resistant *Enterococcus*; VRE-fm, Vancomycin-resistant *Enterococcus faecium*.

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linezolid-treated patients, and cumulative survival rates at 14 and 28 days tended to be lower in patients who received low-dose daptomycin (<10 mg/kg/day) than that in those who received linezolid and high-dose daptomycin (≥10 mg/kg/day); however, the differences were not statistically significant.
Conclusion: Higher disease severity and inappropriate treatment were associated with increased mortality and longer treatment duration of linezolid or daptomycin was associated with microbial eradication for the patient with VRE-fm bacteremia.
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Introduction

Vancomycin-resistant *Enterococcus faecium* (VRE-fm) was first reported in 1988, after which its prevalence significantly increased globally.[1–5] According to data from the Taiwan Surveillance of Antimicrobial Resistance program, *E. faecium* and *Enterococcus faecalis* together comprised nearly 95% of all enterococci; the proportion of *E. faecium* increased from 12.4% in 2002 to 27.3% in 2010.[6] Notably, susceptibility test revealed that vancomycin resistance in *E. faecium* increased from 0.3% in 2004 to 24.9% in 2010.[6] The inter- and intra-hospital spread of certain genotypes, and the horizontal transfer of vanA genes may contribute to the increase in VRE-fm.[7] Selective pressure after antimicrobial use was also found to be associated with the increase in VRE-fm infection cases.[8] The mortality rates of vancomycin-resistant *Enterococcus* (VRE) bacteremia ranged between 20% and 52%,[9–12] and were associated with inappropriate antimicrobial therapy and higher disease severity.[11,12]

The treatment options for VRE bloodstream infection are limited, and the clinical experience is available mainly for linezolid and daptomycin. Linezolid has been approved by the U.S. Food and Drug Administration for the treatment of VRE-fm infections, including cases with concurrent bacteremia. However, linezolid has only bacteriostatic activity (not bactericidal) against VRE-fm, and resistance of VRE-fm to linezolid has been reported.[13–15] On the other hand, daptomycin has rapid in vitro bactericidal activity against VRE-fm.[16,17] Although it is not FDA approved for the treatment of VRE-fm bacteremia, off-label use has been common in clinical practice.[18,19] Several systemic reviews with meta-analysis reported that the use of linezolid in treating VRE bacteremia was associated with a lower mortality, compared with daptomycin; however, the enrolled studies were retrospective with high heterogeneity.[20–22] A recent study reported that linezolid and higher-dose daptomycin (≥9 mg/kg/day) treatment were similar in terms of mortality, and had a survival benefit over lower-dose daptomycin (6–9 mg/kg/day).[23] On the other hand, another national cohort study among Veterans Affairs patients showed that linezolid treatment was associated with higher mortality and microbiologic failure, compared to daptomycin treatment with median dose of 5.93 mg/kg for VRE bacteremia.[24]

This study reviewed adult patients with VRE-fm bacteremia in our institution between January 1, 2011 and December 31, 2015. The purpose was to investigate the clinical characteristics, treatment, clinical and microbiological outcomes of VRE-fm bacteremia, factors associated with mortality as well as microbial eradication, and the impacts of different antimicrobial therapies.

Methods

Study designs, setting, and patients

This retrospective study was conducted at the Chang Gung Memorial Hospital (CGMH)-Linkou, 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 boards of CGMH-Linkou (Number: 201700315B0). The ethics committee granted a waiver for informed consent to be obtained.

Data of all the hospitalized patients above 18 years of age with at least one blood culture positive for VRE-fm occurring between January 1, 2011 and December 31, 2015 were reviewed. The study included the patients who had clinical significant VRE-fm bacteremia, which was defined as one of the following conditions: 1) the presence of two or more blood cultures positive for VRE-fm. 2) a single positive blood culture coupled with a clinical evident or culture-positive, other site of infection. For patients with multiple episodes of VRE-fm bacteremia, only the first episode was included.[25]

Demography and comorbidity

Data on age, sex, surgery including organ transplantation, and co-morbid illness were gathered by reviewing inpatient medical records. Co-morbid illnesses included hepatic dysfunction of a serum total bilirubin level over 2.5 mg/dL or liver cirrhosis, renal insufficiency of a serum creatinine level above 2.0 mg/dL or requirement of dialysis, chronic pulmonary disease, heart disease, diabetes mellitus, connective tissue diseases, and hematologic malignancies or solid cancers.

Clinical conditions, treatment and outcomes

Data regarding vital signs, mechanical ventilation, ICU stay, neutropenia with absolute neutrophil count less than 500 cells/mm,[3] receipt of chemotherapy, dates and

associated sites of VRE-fm growth, as well as concurrent infections not caused by VRE-fm were recorded. The Pitt bacteremia score was calculated based on temperature (35.1—36 °C or 39.0—39.9 °C: 1 point, ≤35 or ≥40 °C: 2 points), blood pressure (hypotension: 2 points), mental status (disorientation: 1 point, stupor: 2 points, coma: 4 points), respiratory status (mechanical ventilation: 2 points) and cardiac status (cardiac arrest: 4 points). All criteria were graded within 48 h before or on the day of first positive blood culture of VRE-fm. The highest point score during that time was recorded.[26,27] The dose and date of linezolid and daptomycin use were recorded and evaluated after the VRE-fm bacteremia occurrence. In the patients with impaired renal function or dialysis, daptomycin doses were evaluated according to their body weight and infusion intervals were adjusted with their estimated creatinine clearance. The 14-day and 28-day mortalities were defined as death occurring within 14 and 28 days after the onset of VRE-fm bacteremia respectively; in-hospital mortality was recorded. For patients who were discharged from the hospital earlier than 28 days, the outcomes were determined/followed until the date of discharge. When comparing the survival curves with log rank tests, these data were censored accordingly.

Microbiology

The VRE-fm isolates were identified as per the standard method at this hospital. Antibiotic susceptibility testing for ampicillin, penicillin, vancomycin, teicoplanin, linezolid and high-level gentamicin (Becton Dickinson, Franklin Lakes, NJ, USA) was performed and interpreted by a disc diffusion method according to the Clinical and Laboratory Standards Institute guideline. Interpretations of the diameters of the inhibitory zone of tigecycline were based on the criteria proposed by the U.S. FDA. *E. faecalis* ATCC29212 were used as control strains.[28—30]

The patients with VRE-fm infection or colonization underwent contact isolation, and follow-up cultures from infected sites, and anal swab or stool were obtained every week according to the hospital policy. Hand hygiene, isolation of all patients with VRE-fm infection in a single room, and use of aprons as well as gloves were implemented. Microbial eradication was defined as no growth of VRE-fm in all the follow-up cultures for 3 weeks sequentially. Relapse was defined as new isolation of VRE-fm after the initial eradication during hospitalization. Persistent bacteremia was defined as detection of VRE-fm bacteremia ≥5 days after onset of VRE-fm bacteremia in an episode. Polymicrobial bloodstream infection was defined as growth of bacteria other than VRE-fm or fungus in the blood cultures.

Statistical methods

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (Version 18.0; SPSS Inc., Chicago, IL, USA). Categorical variables were compared using χ^2 test or Fisher's exact test, as appropriate. Continuous variables were tested for normality of distributions by Kolmogorov—Smirnov test, and then compared by Student's *t*-test or the Mann—Whitney *U* test, as appropriate. Variables with a *P* value < 0.25 in univariate analysis were included in a logistic regression model for multivariate analysis. Adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated when appropriate. All tests were two-tailed, and a *P* value of <0.05 was considered significant. Kaplan—Meier survival curves were compared using the log-rank test.

Results

Patients, demography and concomitant diseases

Two hundred and ten patients with VRE-fm bacteremia were included. Males predominated (53.3%) with a mean age of 64.8 years. All the VRE-fm isolates from first blood cultures positive for VRE-fm were resistant to vancomycin, penicillin, and ampicillin, and susceptible to linezolid and tigecycline. Susceptibility testing was not conducted for daptomycin. Among the 210 initial VRE-fm blood isolates of each patient, 2 (1.0%) and 92 (43.8%) were susceptible to teicoplanin and high-dose gentamicin respectively, and none of the patients had received teicoplanin or gentamicin treatment for VRE-fm bacteremia. The most common concomitant diseases were diabetes mellitus (43.3%), followed by malignancies, including hematologic malignancies (14.3%) and solid cancers (28.1%) (Table 1).

Clinical conditions, treatment, and outcomes

Nearly half of the VRE-fm bacteremia cases were associated with ICU stay and mechanical ventilation. Polymicrobial bloodstream infection was common (42.9%). The mean Pitt bacteremia score was 4.7. The three major associated sites of VRE-fm growth were intra-abdominal organs or abscess and ascites (17.6%), central venous catheter (17.1%), and urinary tract (16.7%). Nearly half (46.2%) of the VRE-fm bacteremia cases were primary bacteremia cases. Concurrent infections not caused by VRE-fm were found in 114 patients (54.3%). Thirty-four patients (16.2%) had received linezolid treatment and 111 (52.9%) had received daptomycin treatment. Delayed treatment was common, and only 63 patients (30%) had received linezolid or daptomycin treatment within 72 h after the onset of VRE-fm bacteremia. Microbial eradication was investigated in 137 patients with follow-up cultures collected for at least one week after bacteremia, and microbial eradication occurred in 23 of 137 patients (16.8%). Among the 23 patients, none of them had a relapsing infection. The 14-day, 28-day, and in-hospital mortality rates were 37.1%, 50.5%, and 66.7%, respectively (Table 1).

Independent factors associated with 14-day mortality

In the univariate analysis, more patients with 14-day mortality had hepatic dysfunction, renal insufficiency, cardiac disease, hematologic malignancies, neutropenia, fungemia, and primary bacteremia, and the survivors were more likely

Table 1 Characteristics of 210 patients with VRE-fm bacteremia.

Characteristics	Value[a]
Demographic parameters	
Age, mean ± SD, years	64.8 (16.0)
Male/Female	112/98
Concomitant diseases	
Liver cirrhosis	42 (20.0)
Requirement for dialysis	69 (32.9)
Chronic pulmonary disease	21 (10.0)
Cardiac disease	37 (17.6)
Diabetes mellitus	91 (43.3)
Hematologic malignancies	30 (14.3)
Solid cancers	59 (28.1)
Clinical conditions	
Pitt bacteremia score	4.7 (3.5)
Chemotherapy or pulse therapy	42 (20.0)
Neutropenia	23 (11.0)
Surgery	29 (13.8)
Liver transplantation	10 (4.8)
ICU stay	102 (48.6)
Mechanical ventilation	97 (46.2)
Polymicrobial bloodstream infection	90 (42.9)
Fungemia	17 (8.1)
Persistent bacteremia	18 (8.6)
VRE-fm growth sites	
Primary bacteremia	97 (46.2)
Intra-abdominal organ, abscess, or ascites	37 (17.6)
Central venous catheter	36 (17.1)
Urinary tract	35 (16.7)
Skin, soft tissue, and wound	13 (6.2)
Multisite	13 (6.2)
Miscellaneous[b]	4 (1.9)
Concurrent infections not caused by VRE-fm	114 (54.3)
Treatment[c]	
Linezolid	34 (16.2)
Daptomycin	111 (52.9)
Tigecycline	25 (11.9)
Linezolid/daptomycin in 48 h	28 (13.3)
Linezolid/daptomycin in 72 h	63 (30.0)
Linezolid/daptomycin for at least 10 days	100 (47.6)
Clinical outcomes	
Microbiological eradication (N = 137)	23 (16.8)
14-day mortality	78 (37.1)
28-day mortality	106 (50.5)
In-hospital mortality	140 (66.7)

[a] Data are no (%) of subject and n = 210 unless otherwise indicated.
[b] Infectious spondylitis (n = 2); infective endocarditis (n = 1); pneumonia (n = 1).
[c] During the hospitalization, there were 66 patients who did not receive any antibiotic directed against VRE-fm. Twenty-two patients received more than one class of antibiotics. Ten patients had received linezolid and daptomycin.
Abbreviations: VRE-fm, vancomycin resistant *Enterococcus faecium*; SD, standard deviation; ICU, intensive care unit.

to have persistent bacteremia, VRE-fm growth on central venous catheter, linezolid use, daptomycin use, linezolid or daptomycin use in 72 h after bacteremia, and for at least 10 days. The patients with 14-day mortality had higher Pitt bacteremia scores (mean: 6.7 versus 3.5) than the survivors had ($P < 0.05$). In the multivariate analysis, Pitt bacteremia score (aOR, 1.443; 95% CI, 1.171 to 1.778; $P = 0.001$) and linezolid or daptomycin treatment for at least 10 days (aOR, 0.002; 95% CI, <0.001 to 0.020; $P < 0.001$) were associated with 14-day mortality (Table 2).

Independent factors associated with 28-day mortality

In the univariate analysis, more patients with 28-day mortality had hepatic dysfunction, renal insufficiency, hematologic malignancies, neutropenia, and primary bacteremia, and the survivors were more likely to have persistent bacteremia, VRE-fm growth on central venous catheter, multisite growth of VRE-fm, linezolid use, daptomycin use, linezolid or daptomycin use in 72 h after bacteremia, and for at least 10 days. The patients with 28-day mortality had higher Pitt bacteremia scores (mean: 6.2 versus 3.1) than the survivors had ($P < 0.05$). In the multivariate analysis, hepatic dysfunction (aOR, 4.142; 95% CI, 1.732 to 9.903; $P = 0.001$), Pitt bacteremia score (aOR, 1.314; 95% CI, 1.143 to 1.510; $P < 0.001$), and linezolid or daptomycin treatment for at least 10 days (aOR, 0.115; 95% CI, 0.037 to 0.352; $P < 0.001$) were associated with 28-day mortality (Table 3).

Linezolid versus daptomycin treatment for VRE-fm bacteremia

Of the 210 patients, 34 (16.2%) and 111 (52.9%) had linezolid and daptomycin treatment respectively. Six patients with treatment for less than 48 h and 10 with both drugs were excluded. Finally, a total of 119 patients who received linezolid or daptomycin monotherapy for more than 48 h were included in the comparison study of linezolid and daptomycin treatment for VRE-fm bacteremia. Twenty-three patients had linezolid treatment, with a mean duration of 13.1 days and 96 had daptomycin treatment with a mean duration of 15.0 days. Despite hepatic dysfunction occurring more frequently in the patient treated with daptomycin ($P < 0.05$), there were no significant differences in clinical characteristics, microbiological and clinical outcomes between the two groups. The patients with daptomycin treatment tended to have higher 14-day, 28-day, and in-hospital mortality rates (20.8% versus 8.7%; 40.6% versus 26.1%; 62.5% versus 52.5%, respectively), and a lower microbial eradication rate (14.1% versus 26.1%) compared to the patients with linezolid treatment, but the differences were not statistically significant (Table 4). The cumulative survival rates at 14 and 28 days were similar between the two groups by Kaplan–Meier method (Figs. 1 and 2). Data of body weight were available in 95 of the 96 patients with daptomycin therapy and daily doses of daptomycin were estimated. Among the 95 patients, 18 were in the high-dose daptomycin group (≥10 mg/kg/day) and 77 were in the low-dose daptomycin group (<10 mg/kg/day). The cumulative survival rates at 14 and 28 days tended to be lower with low-dose daptomycin treatment, compared to linezolid as well as high-dose daptomycin

Table 2 Univariate and multivariate analyses of the predictors for 14-day motality of VRE-fm bacteremia.

Variables	Survival[a]	Death[a]	Univariate	Multivariate[b]	
	N = 132	N = 78	*P*	*P*	aOR (95% CI)
Demographic parameters					
Age, mean ± SD, years	63.6 (16.1)	66.8 (15.7)	0.153	0.783	1.005 (0.967–1.045)
Male	71 (53.8)	41 (52.6)	0.864		
Concomitant diseases					
Liver cirrhosis	27 (20.5)	15 (19.2)	0.830		
Hepatic dysfunction	44 (33.3)	45 (57.7)	0.001	0.083	3.583 (0.848–15.130)
Requirement for dialysis	43 (32.6)	26 (33.3)	0.910		
Renal insufficiency	61 (46.2)	53 (67.9)	0.002	0.150	2.428 (0.725–8.126)
Chronic pulmonary disease	13 (9.8)	8 (10.3)	0.924		
Cardiac disease	18 (13.6)	19 (24.4)	0.049	0.072	4.455 (0.875–22.676)
Diabetes mellitus	58 (43.9)	33 (42.3)	0.818		
Hematologic malignancies	9 (6.8)	21 (26.9)	<0.001	0.072	7.102 (0.840–60.041)
Solid cancers	36 (27.3)	23 (29.5)	0.730		
Clinical conditions					
Pitt bacteremia score, mean ± SD	3.5 (2.8)	6.7 (3.7)	<0.001	0.001	1.443 (1.171–1.778)
Neutropenia	5 (3.8)	18 (23.1)	<0.001	0.051	21.368 (0.986–463.154)
Surgery	22 (16.7)	7 (0.9)	0.118	0.443	0.474 (0.070–3.192)
Liver transplantation	5 (3.8)	5 (6.4)	0.505		
Polymicrobial BSI[c]	51 (38.6)	39 (50.0)	0.108		
Fungemia	5 (3.8)	12 (15.4)	0.003	0.616	1.951 (0.143–26.521)
Persistent bacteremia	17 (12.9)	1 (1.3)	0.004	0.291	0.155 (0.005–4.927)
VRE-fm growth sites					
Central venous catheter	31 (23.5)	5 (6.4)	0.002	0.181	0.209 (0.021–2.071)
Primary bacteremia	50 (37.9)	47 (60.3)	0.002	0.429	0.564 (0.137–2.330)
Intra-abdominal organ, abscess, or ascites	28 (21.2)	9 (11.5)	0.075	0.078	0.185 (0.028–1.210)
Urinary tract	23 (17.4)	12 (15.4)	0.702		
Multisite	11 (8.3)	2 (2.6)	0.138	0.541	0.277 (0.004–17.077)
Concurrent infections	74 (56.1)	40 (51.3)	0.502		
Treatment					
Linezolid	30 (22.7)	4 (5.1)	0.001	0.895	0.859 (0.090–8.189)
Daptomycin	85 (64.4)	26 (33.3)	<0.001	0.206	2.750 (0.573–13.207)
Tigecycline	20 (15.2)	5 (6.4)	0.059	0.526	0.526 (0.072–3.830)
LIN/DAP in 48 h[c]	22 (16.7)	6 (7.7)	0.065		
LIN/DAP in 72 h	51 (38.6)	12 (15.4)	<0.001	0.852	1.199 (0.177–8.115)
LIN/DAP for at least 10 days	97 (73.5)	3 (3.8)	<0.001	<0.001	0.002 (<0.001–0.020)
Microbiology eradication[d]	22 (17.5)	1 (9.1)	0.690		

[a] Categorical data are no. (%) of subject, continuous data are expressed as mean (SD).
[b] All variables included in the final multivariable model are shown.
[c] Factors were not included in the final multivariate model.
[d] Data were available for 137 patients. 14-day mortality occurred in 11/137 (8.0%).
Abbreviations: VRE-fm, vancomycin resistant *Enterococcus faecium*; aOR, adjusted odds ratio; CI, confidence interval; SD, standard deviation; BSI, bloodstream infection; LIN, linezolid; DAP, daptomycin.

treatment; however, the differences were not statistically significant (Figs. 3 and 4).

Independent factors associated with microbiological eradication

Microbial eradication was investigated in 137 patients with follow-up cultures from infected sites, and anal swab or stool collected for at least one week after bacteremia, and microbial eradication occurred in 23 patients (16.8%) with no growth of VRE-fm in all the follow-up cultures for 3 weeks sequentially. Among the 73 patients without data for microbial eradication investigation, 55 (75.3%) died in one week after bacteremia. In the univariate analysis, more patients with microbiological failure had primary bacteremia, and the patients with microbial eradication had longer treatment duration of linezolid or daptomycin ($P < 0.05$). In the multivariate analysis, surgery (aOR, 6.211; 95% CI, 1.668 to 23.124; $P = 0.006$) and longer treatment duration of linezolid or daptomycin (aOR, 1.127; 95% CI, 1.050 to 1.210; $P = 0.001$) were independent predictors for microbial eradication (Table 5).

Discussion

In this study, the clinical characteristics of nosocomial infection, malignancy, immunosuppression, and high disease severity were in accordance with published studies of

Table 3 Univariate and multivariate analyses of the predictors for 28-day mortality of VRE-fm bacteremia.

Variables	Survival[a]	Death[a]	Univariate	Multivariate[b]	
	N = 104	N = 106	*P*	*P*	aOR (95% CI)
Demographic parameters					
Age, mean ± SD, years	65.2 (15.0)	64.4 (16.9)	0.735		
Male	56 (53.8)	56 (52.8)	0.883		
Concomitant diseases					
Liver cirrhosis	19 (18.3)	23 (21.7)	0.535		
Hepatic dysfunction	31 (29.8)	63 (59.4)	<0.001	0.001	4.142 (1.732–9.903)
Requirement for dialysis	33 (31.7)	36 (34.0)	0.731		
Renal insufficiency	48 (46.2)	71 (67.0)	0.002	0.398	1.414 (0.633–3.162)
Chronic pulmonary disease	11 (10.6)	10 (9.4)	0.783		
Cardiac disease	14 (13.5)	23 (21.7)	0.117	0.369	1.618 (0.566–4.625)
Diabetes mellitus	46 (44.2)	45 (42.5)	0.795		
Hematologic malignancies	7 (6.7)	23 (21.7)	0.002	0.277	2.369 (0.500–11.229)
Solid cancers	27 (26.0)	32 (30.2)	0.496		
Clinical conditions					
Pitt bacteremia score, mean ± SD	3.1 (2.6)	6.2 (3.6)	<0.001	<0.001	1.314 (1.143–1.510)
Neutropenia	3 (2.9)	21 (19.8)	<0.001	0.061	7.393 (0.911–60.025)
Surgery	19 (18.3)	10 (9.4)	0.064	0.121	0.388 (0.117–1.284)
Liver transplantation	3 (2.9)	7 (6.6)	0.332		
Polymicrobial BSI[c]	39 (37.5)	51 (48.1)	0.120		
Fungemia	5 (4.8)	12 (11.3)	0.084	0.998	0.998 (0.188–5.290)
Persistent bacteremia	14 (13.5)	4 (3.8)	0.012	0.168	0.363 (0.086–1.531)
VRE-fm growth sites					
Central venous catheter	26 (25.0)	10 (9.4)	0.003	0.561	0.702 (0.213–2.317)
Primary bacteremia	38 (36.5)	59 (55.7)	0.005	0.994	1.003 (0.422–2.387)
Intra-abdominal organ, abscess, or ascites	21 (20.2)	16 (15.1)	0.332		
Urinary tract	18 (17.3)	17 (16.0)	0.805		
Multisite	10 (9.6)	3 (2.8)	0.041	0.525	0.513 (0.065–4.026)
Concurrent infections	54 (51.9)	60 (56.6)	0.496		
Treatment					
Linezolid	25 (24.0)	9 (8.5)	0.002	0.881	0.907 (0.250–3.284)
Daptomycin	65 (62.5)	46 (43.4)	0.006	0.379	1.686 (0.527–5.393)
Tigecycline	16 (15.4)	9 (8.5)	0.123	0.954	1.037 (0.299–3.600)
LIN/DAP in 48 h[c]	17 (16.3)	11 (10.4)	0.203		
LIN/DAP in 72 h	42 (40.4)	21 (19.8)	0.001	0.194	0.516 (0.190–1.401)
LIN/DAP for at least 10 days	74 (71.2)	26 (24.5)	<0.001	<0.001	0.115 (0.037–0.352)
Microbiology eradication[d]	19 (19.2)	4 (10.5)	0.224		

[a] Categorical data are no.(%) of subject, continuous data are expressed as mean (SD).
[b] All variables included in the final multivariable model are shown.
[c] Factors were not included in the final multivariate model.
[d] Data were available for 137 patients. 28-day mortality occurred in 28/137 (20.4%).
Abbreviations: VRE-fm, vancomycin resistant *Enterococcus faecium*; aOR, adjusted odds ratio; CI, confidence interval; SD, standard deviation; BSI, bloodstream infection; LIN, linezolid; DAP, daptomycin.

VRE bacteremia.[10–12] The major associated sites of VRE-fm growth were intra-abdominal organ (including cultures from abscess and ascites), central venous catheter, and urinary tract, which were consistent with described colonization sites of VRE-fm, involving gastrointestinal tract, skin, and genitourinary tract.[31] In prior studies, the gastrointestinal colonization can persist for months to years.[32,33] In this study, the eradication rates of VRE-fm in the gastrointestinal tract were low, even in patients who had received adequate treatment and were recovering from VRE-fm infections, which increased the risk of spread of VRE-fm. For these patients, it is challenging to discontinue contact isolation during hospitalization and this may increase the complexity of clinical care and raise the medical cost.

The mortality rates were high, and delay in prescribing linezolid or daptomycin was common. Most patients received linezolid or daptomycin only after identification of VRE-fm in blood cultures, and consultation with infectious disease professionals. In a prior study of monomicrobial VRE bacteremia, the 7-day and 28-day mortalities were lower in the group with antibiotic treatment against VRE, and the

Table 4 Comparison of characteristics and outcomes among the patients who received linezolid or daptomycin monotherapy against VRE-fm for more than 48 h.

Variables	LIN group[a] N = 23	DAP group[a] N = 96	*P*
Demographic parameters			
Age, mean ± SD, years	64.1 (16.4)	63.0 (17.1)	0.775
Male	11 (47.8)	53 (55.2)	0.524
Concomitant diseases			
Liver cirrhosis	4 (17.4)	26 (27.1)	0.336
Liver dysfunction in 14 days	5 (21.7)	46 (47.9)	0.023
Liver dysfunction in 28 days	6 (26.1)	49 (51.0)	0.031
Requirement for dialysis	7 (30.4)	36 (37.5)	0.526
Renal insufficiency in 14 days	11 (47.8)	53 (55.2)	0.524
Renal insufficiency in 28 days	11 (47.8)	55 (57.2)	0.412
Chronic pulmonary disease	2 (8.7)	4 (4.2)	0.328
Cardiac disease	7 (30.4)	13 (13.5)	0.065
Diabetes mellitus	11 (47.8)	35 (36.5)	0.315
Hematologic malignancies	1 (4.3)	12 (12.5)	0.459
Solid cancers	3 (13.0)	39 (40.6)	0.095
Clinical conditions			
Pitt bacteremia score, mean ± SD	4.5 (2.7)	4.0 (3.1)	0.377
Chemotherapy or pulse therapy	1 (4.3)	17 (17.7)	0.191
Neutropenia in 14 days	0 (0)	8 (8.3)	0.351
Neutropenia in 28 days	0 (0)	8 (8.3)	0.351
Thrombocytopenia	11 (47.8)	61 (63.5)	0.166
Surgery	4 (17.4)	13 (13.5)	0.740
Liver transplantation	2 (8.7)	5 (5.2)	0.619
ICU stay in 14 days	12 (52.2)	46 (47.9)	0.714
ICU stay in 28 days	13 (56.5)	49 (51.0)	0.637
Mechanical ventilation in 14 days	11 (47.8)	43 (44.8)	0.524
Mechanical ventilation in 28 days	12 (52.2)	47 (49.0)	0.782
Polymicrobial BSI	9 (39.1)	42 (43.8)	0.688
Persistent bacteremia	4 (17.4)	17 (17.7)	1.000
VRE-fm growth sites			
Primary bacteremia	12 (52.2)	34 (35.4)	0.138
Intra-abdominal organ, abscess, or ascites	3 (13.0)	23 (24.0)	0.255
Central venous catheter	5 (21.7)	21 (21.9)	0.989
Urinary tract	3 (13.0)	17 (17.7)	0.761
Skin, soft tissue, and wound	2 (8.7)	5 (5.2)	0.619
Multisite	3 (13.0)	6 (6.3)	0.373
Concurrent infections	15 (65.2)	49 (51.0)	0.221
Treatment			
Treatment days	13.1 (4.6)	15.0 (9.0)	0.606
LIN/DAP in 48 h	4 (17.4)	17 (17.7)	1.000
LIN/DAP in 72 h	9 (39.1)	43 (44.8)	0.623
LIN/DAP for at least 10 days	19 (82.6)	72 (75.0)	0.440
Clinical outcomes			
Microbiology eradication (N = 101)[b]	6 (26.1)	11 (14.1)	0.208
14-day mortality	2 (8.7)	20 (20.8)	0.239
28-day mortality	6 (26.1)	39 (40.6)	0.197
In-hospital mortality	12 (52.2)	60 (62.5)	0.363

[a] Categorical data are no. (%) of subject, continuous data are expressed as mean (SD).
[b] Data were available for 101 patients. 78 of them were in daptomycin group.
Abbreviations: VRE-fm, vancomycin resistant *Enterococcus faecium*; LIN, linezolid; DAP, daptomycin; CI, confidence interval; SD, standard deviation; ICU, intensive care unit; BSI, bloodstream infection.

mortalities of patients receiving anti-VRE therapy within and later than 72 h after the onset of bacteremia did not differ significantly.[11] However, delay in initiating appropriate antibiotic treatment was usually associated with increased mortality in patients with severe infection.[34] For immunosuppressed patients with VRE-fm colonization, early empiric use of linezolid or daptomycin at the time of severe Gram-positive bacteremia might be considered.

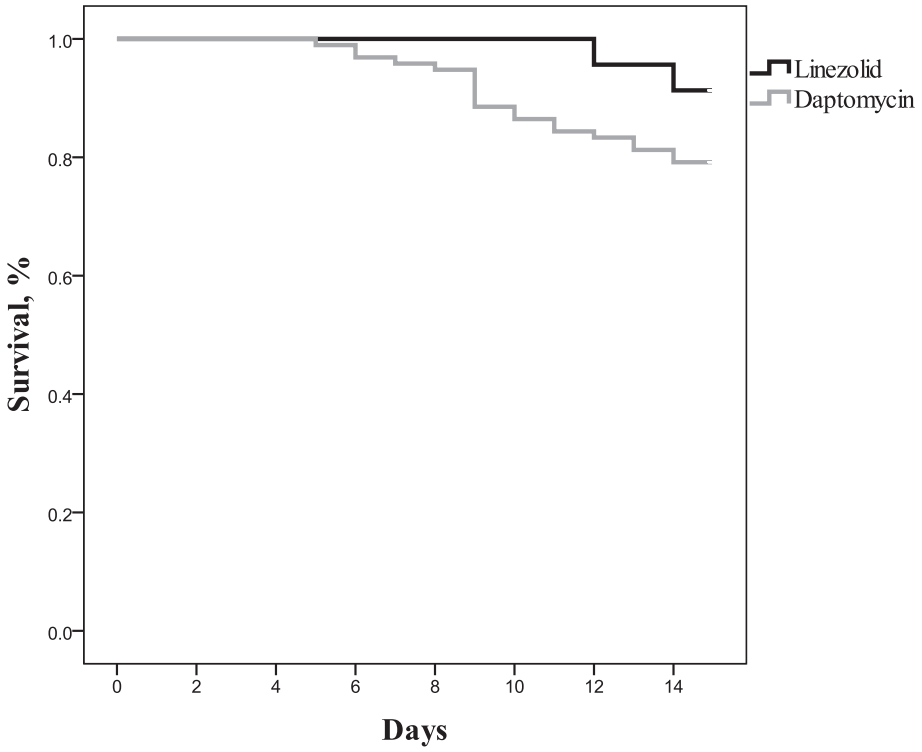

Figure 1. Comparative survival curves of 14-day mortality for linezolid (black line) and daptomycin (gray line) groups; Log-rank test: $P = 0.171$.

Multivariate analyses showed that a high Pitt bacteremia score was an independent risk factor for mortality. Mechanical ventilation and ICU stay were not included in multivariate analyses because these variables had been included in Pitt bacteremia score. In multivariate analyses adjusted for potential confounders and disease severity, linezolid or daptomycin treatment for at least 10 days was an independent protecting factor for mortality.

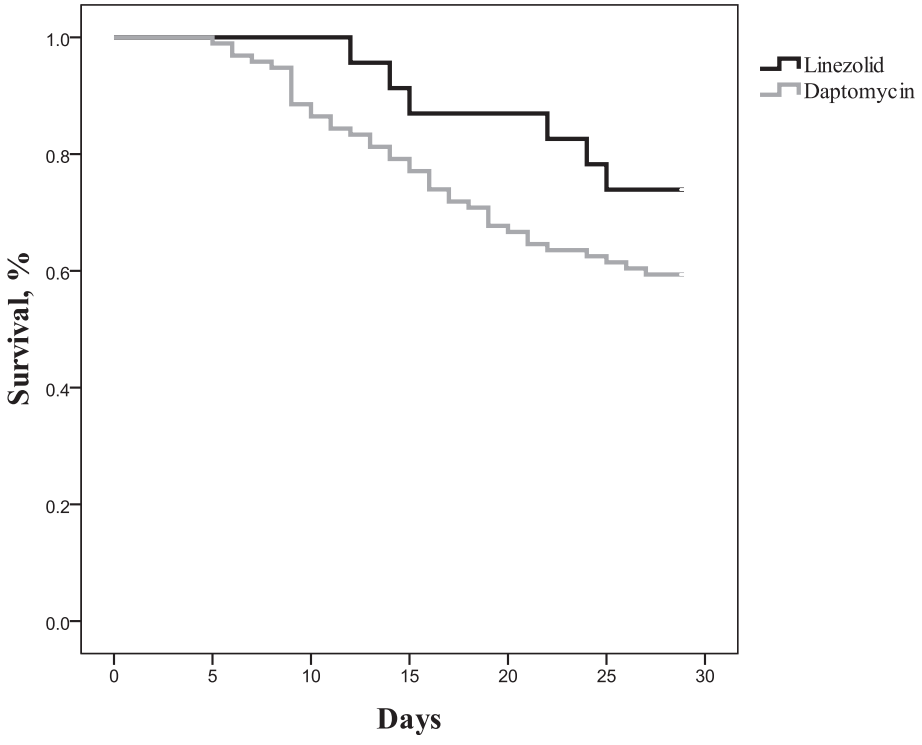

Figure 2. Comparative survival curves of 28-day mortality for linezolid (black line) and daptomycin (gray line) groups; Log-rank test: $P = 0.166$.

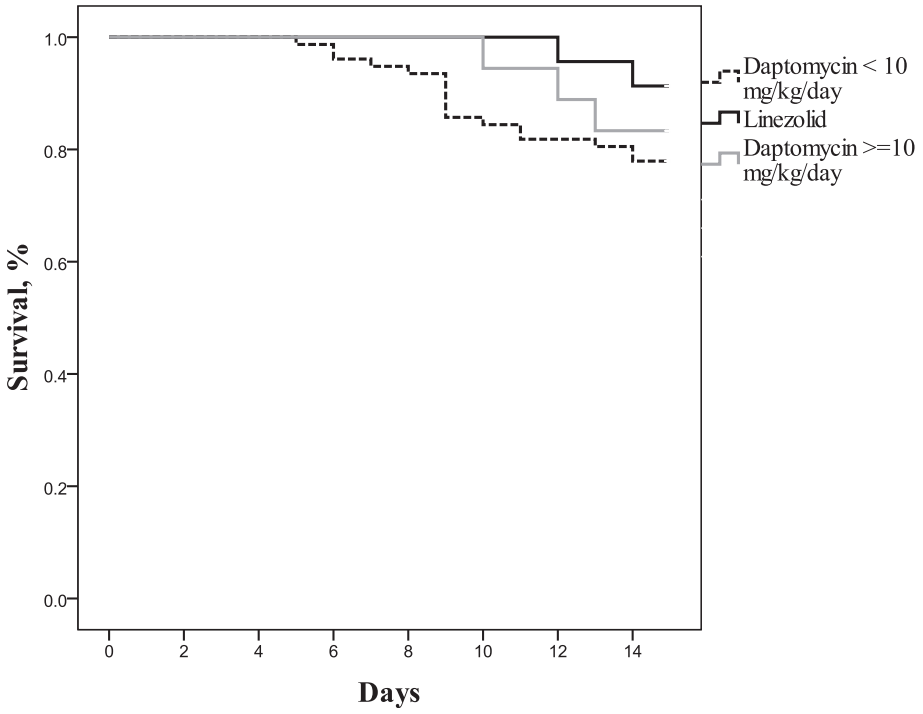

Figure 3. Comparative survival curves of 14-day mortality for linezolid (black line), high-dose daptomycin (gray line), and low-dose daptomycin (dotted line) groups; Log-rank test: $P = 0.315$.

Non-survivors were more likely to have delayed treatment with linezolid or daptomycin (>72 h) after the onset of bacteremia, but the difference was not statistically significant in multivariate analyses. Although the patients who lived longer had several opportunities to receive adequate antimicrobial therapy, the result showed the trend, that early and adequate treatment may prolong survival in VRE-fm bacteremia.

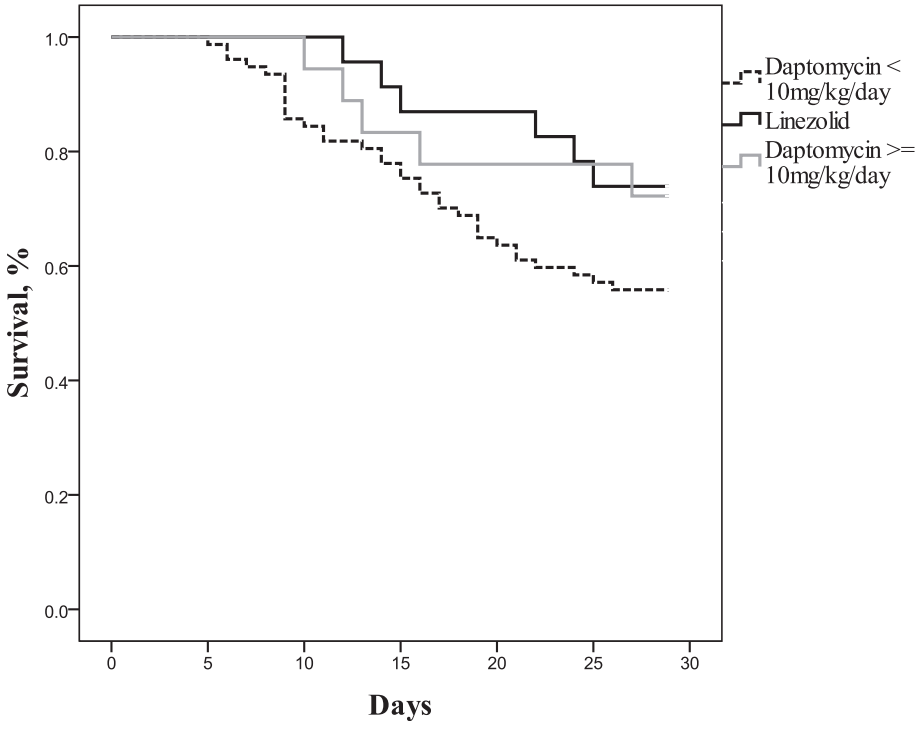

Figure 4. Comparative survival curves of 28-day mortality for linezolid (black line), high-dose daptomycin (gray line), and low-dose daptomycin (dotted line) groups; Log-rank test: $P = 0.152$.

Table 5 Univariate and multivariate analyses of the predictors for microbial eradication.

Variables	No Eradication[a]	Eradication[a]	Univariate	Multivariate[b]	
	N = 114	N = 23	*P*	*P*	aOR (95% CI)
Demographic parameters					
Age, mean ± SD, years	64.2 (16.5)	63.0 (14.5)	0.732		
Male	65 (57.0)	11 (47.8)	0.418		
Concomitant diseases					
Liver cirrhosis	25 (21.9)	2 (8.7)	0.248	0.057	0.178 (0.030–1.051)
Hepatic dysfunction	47 (41.2)	8 (34.8)	0.565		
Requirement for dialysis	36 (31.6)	10 (43.5)	0.270		
Renal insufficiency	64 (56.1)	14 (60.9)	0.676		
Chronic pulmonary disease	13 (11.4)	1 (4.3)	0.464		
Cardiac disease	18 (15.8)	3 (13.0)	1.000		
Diabetes mellitus	49 (43.0)	11 (47.8)	0.669		
Malignancy	42 (36.8)	4 (17.4)	0.072	0.059	0.267 (0.068–1.054)
Clinical conditions					
Pitt bacteremia score, mean ± SD	3.7 (2.9)	3.5 (3.2)	0.687		
Neutropenia	8 (7.0)	1 (4.3)	1.000		
Surgery	17 (14.9)	7 (30.4)	0.128	0.006	6.211 (1.668–23.124)
Liver transplantation	4 (3.5)	1 (4.3)	1.000		
Polymicrobial BSI	46 (40.4)	8 (34.8)	0.618		
Fungemia	5 (4.4)	1 (4.3)	1.000		
Persistent bacteremia	15 (13.2)	3 (13.0)	1.000		
Intensive care unit stay	60 (52.6)	11 (47.8)	0.674		
Mechanical ventilation	53 (46.5)	9 (39.1)	0.518		
VRE-fm growth sites					
Central venous catheter	20 (17.5)	8 (34.8)	0.086	0.145	2.640 (0.715–9.747)
Primary bacteremia	52 (45.6)	5 (21.7)	0.034	0.959	0.964 (0.237–3.919)
Intra-abdominal organ, abscess, or ascites	24 (21.1)	5 (21.7)	1.000		
Skin, soft tissue, and wound	7 (6.1)	1 (4.3)	1.000		
Urinary tract	20 (17.5)	2 (8.7)	0.368		
Multisite	10 (8.8)	1 (4.3)	0.690		
Concurrent infections	65 (57.0)	13 (56.5)	0.965		
Treatment					
Linezolid	24 (21.1)	9 (39.1)	0.064	0.090	2.675 (0.856–8.352)
Daptomycin	74 (64.9)	14 (60.9)	0.712		
Tigecycline	18 (15.8)	2 (8.7)	0.526		
LIN/DAP in 48 h	17 (14.9)	5 (21.7)	0.532		
LIN/DAP in 72 h	43 (37.7)	10 (43.5)	0.605		
LIN/DAP for at least 10 days	78 (68.4)	19 (82.6)	0.172	0.191	0.329 (0.062–1.738)
LIN/DAP use (days)	11.9 (8.5)	19.6 (13.0)	0.002	0.001	1.127 (1.050–1.210)

[a] Categorical data are no. (%) of subject, continuous data are expressed as mean (SD).
[b] All variables included in the final multivariable model are shown.
Abbreviations: VRE-fm, vancomycin resistant *Enterococcus faecium*; aOR, adjusted odds ratio; CI, confidence interval; SD, standard deviation; BSI, bloodstream infection; LIN, linezolid; DAP, daptomycin.

The treatment options for VRE-fm were limited to linezolid and daptomycin. There have been systematic reviews with meta-analysis comparing the two agents for the treatment of VRE bacteremia.[20–22] In one earlier study, there was no significant difference in the microbiologic and clinical cures between the two antibiotics, in spite of a trend toward favorable survival with linezolid usage.[20] Two other studies showed that microbiologic clearance rates were comparable between the two groups, but daptomycin therapy was associated with a higher mortality compared to linezolid therapy.[21,22] While these results suggested a survival benefit of linezolid over daptomycin, the data were not convincing to make comprehensive therapeutic conclusions.[35] In this study, we found that linezolid was associated with higher microbiologic eradication rate, compared to daptomycin. The 14-day and 28-day survival rates were higher for the patients with linezolid or high-dose daptomycin treatment, compared to those with low-dose daptomycin therapy. Although not statistically significant, our findings accord with those of a multicenter, prospective study conducted by Chuang et al. in which survival rate was higher among patients with VRE bacteremia who received linezolid or higher dose of daptomycin (≥9 mg/kg/day).[23] In a retrospective cohort study of 644 hospitalized patients who were treated with standard-(6 mg/kg/day), medium-(8 mg/kg/day), and high-dose

(≥10 mg/kg/day) daptomycin for VRE bacteremia, 30-day mortality was significantly lower among high-dose daptomycin-treated patients, compared to other dosing strategies.[36] Along with our findings, the results also suggest that a higher dose of daptomycin may improve survival and microbiological clearance in VRE bacteremia.

Our findings differ from those of a large-scale, national retrospective cohort study in which linezolid was associated with higher mortality, treatment failure, as well as microbiologic failure rates than daptomycin treatment with a median dose of 5.93 mg/kg, and over 90% of subjects achieved microbiologic clearance, suggesting that this population may not have been as sick as other published cohorts.[24,35]

In this study, we found that longer treatment duration of linezolid or daptomycin (mean days: 19.6 versus 11.9) was independently associated with microbial eradication, but only 137 of the 210 patients (65%) had follow-up cultures for investigation. Fifty-five of the remaining 73 patients (75.3%) without eradication data died within one week after bacteremia occurrence. Linezolid tended to correlate more with favorable outcomes and microbial eradication than daptomycin; however, the results were not statistically significant in comparison and multivariate analyses. The case numbers with linezolid treatment and available data for eradication investigation are relatively small, which may be a limitation to identify the role of regimens in clinical and microbiological outcomes.

There are other limitations to our study. Firstly, this was a single center, retrospective study; therefore, the findings may be not applicable in other settings and should be interpreted cautiously. Secondly, we did not determine the minimum inhibitory concentration (MIC) of daptomycin or linezolid for the isolates. However, a recent national surveillance, in which this hospital participated, discovered that there was no resistant to linezolid or daptomycin in VRE-fm isolates.[30] Thirdly, although therapeutic choices were made with the physicians' discretions, there may be un-investigated variables in the comparison study. Polymicrobial bloodstream infections and concomitant infections other than VRE-fm were common. The clinical impacts of other etiologic pathogens or infections were not evaluated comprehensively. Finally, only 137 of the 210 patients (65%) had follow-up cultures available since 55 of the remaining 73 patients died within one week after bacteremia occurrence. The findings may limit the significance of our data.

In conclusion, higher disease severity and inappropriate treatment were associated with increased mortality. Longer treatment duration of linezolid or daptomycin was associated with microbial eradication for patients with VRE-fm bacteremia. More comparison studies are essential to establish the optimal regimens for VRE-fm bacteremia treatment and to investigate cost-effectiveness of linezolid or daptomycin for VRE-fm eradication.

Acknowledgments

This retrospective study was approved by institutional review boards of CGMH-Linkou (Number: 201700315B0). The ethics committee granted a waiver for informed consent to be obtained. No funding sources had any role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jmii.2017.08.025.