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Clinical Characteristics and Low Susceptibility to Daptomycin in *Enterococcus faecium* Bacteremia

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Enterococcus faecium has high levels of resistance to multiple antibiotics, and the mortality due to *E. faecium* bacteremia is high. Accordingly, *E. faecium* strains with low susceptibility to daptomycin are a concern in clinical practice. This study assessed the predictive factors and prognosis of patients with bacteremia due to *E. faecium* as well as the antimicrobial susceptibility, particularly to daptomycin, among *E. faecium* isolates. The medical records of patients admitted to Osaka City University Hospital with *E. faecalis* (n = 60) and *E. faecium* (n = 48) bacteremia between January 2011 and March 2016 were retrospectively reviewed. The *E. faecalis* group (mean age: 62.0 years) included 22 women, and the *E. faecium* group (mean age: 59.1 years) included 19 women. Predictive factors for infection, prognosis, and isolate antimicrobial susceptibilities were evaluated. The mean Sequential Organ Failure Assessment score and mortality rate did not differ between the two groups. The independent predictors of *E. faecium* bacteremia in multivariate analysis included quinolone use (p = 0.025), malignancy (p = 0.021), and prolonged hospitalization (p = 0.016). Cardiovascular disease was associated with a reduced risk of *E. faecium* bacteremia (p = 0.015). Notably, the percentage of *E. faecium* isolates with low daptomycin susceptibility was higher than that of *E. faecalis* (8.5% vs. 0%, p = 0.036). Thus, *E. faecium* should be considered when administering antibiotic therapy to patients with a history of these predictors. Furthermore, the use of daptomycin should be avoided in case of *E. faecium* with low susceptibility to daptomycin.

Keywords: bacteremia; daptomycin; *Enterococcus faecalis*; *Enterococcus faecium*; low susceptibility
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Introduction

Enterococci, gram-positive bacteria occurring as pairs or short chains, are generally considered to be commensal organisms within the human gastrointestinal tract. Enterococci cause urinary tract, hepatobiliary, catheter-related bloodstream, and surgical wound infections, as well as infective endocarditis and bacteremia (Kajihara et al. 2015). The in-hospital mortality rate of patients with enterococcal bacteremia is high, ranging from 19%-30% (Noskin et al. 1995; Patterson et al. 1995; McBride et al. 2010; Conde-Estévez et al. 2011); thus, enterococci are considered a clinically important pathogen.

The two major species associated with enterococcal infections in humans are *Enterococcus faecalis* and *E. faecium*. In particular, *E. faecium* has high levels of resistance to multiple antibiotics and the mortality due to *E. faecium* bacteremia is higher than that of *E. faecalis* (Noskin et al. 1995; McBride et al. 2010; Conde-Estévez et al. 2011). The differential diagnosis of *E. faecalis* or *E. faecium* is important when treating enterococcal infections in clinical practice. Furthermore, the emergence and spread of resistant enterococci are of particular concern worldwide. The prevalence of vancomycin-resistant *E. faecium* isolates is 14.1% in the Asia/Pacific region, 31.5% in Europe, 48.1% in Latin America, and 76% in North America (Putnam et al. 2010; Cattoir and Leclercq 2013). Although the prevalence of vancomycin-resistant enterococci is currently very low

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in Japan, it is expected to increase due to increasing contact between Europe and the United States, with a higher prevalence of vancomycin-resistant enterococci, and Japan.

Daptomycin is a cyclic lipopeptide used for the treatment of severe infections by Gram-positive organisms and has become a key antibiotic for the treatment of serious enterococcal infections. The 2016 Clinical and Laboratory Standards Institute (CLSI) defines the daptomycin breakpoint for enterococci as 4 μg/mL (Clinical and Laboratory Standards Institute 2016). However, Shukla et al. (2016) recently reported daptomycin minimum inhibitory concentrations (MICs) of 3-4 μg/mL in initial *E. faecium* blood isolates, values which forecast the microbiological failure of daptomycin treatment and suggest the need to revise the daptomycin breakpoint for enterococci.

The present study investigated the clinical characteristics of patients with bacteremia due to vancomycin-susceptible *E. faecalis* and *E. faecium* in a tertiary hospital, including the predictive factors for infection; patient prognosis; and isolate antimicrobial susceptibility, particularly to daptomycin.

Materials and Methods

The medical records of patients admitted to Osaka City University Hospital between January 2011 and March 2016 for *E. faecalis* (n = 60) or *E. faecium* (n = 48) bacteremia were retrospectively reviewed. Patient age, sex, underlying disease, clinical features, medication, and prognosis were evaluated. If *E. faecalis* or *E. faecium* were isolated on multiple occasions within a five-year period in the same patient, only the first episode of was reviewed. This study was approved by the Ethics Committee of Osaka City University, and the thesis was approved on December 27, 2016 (approval number 3646).

Definition of bacteremia and its source

Bacteremia was defined as one or more positive blood cultures from patients with clinical signs of infection, including fever, shaking chills, and sweats with or without local signs and symptoms (Yamada et al. 2011). *E. faecalis* or *E. faecium* urinary tract infection was defined as clinical and diagnostic findings including two more of following: 1) *E. faecalis* or *E. faecium* identified in a urine specimen, 2) clinical manifestations suggestive of urinary tract infection, and 3) imaging findings suggestive of pyelonephritis. The symptoms and urinary findings characteristic of urinary tract infection include dysuria, suprapubic pain, hematuria, flank pain, costovertebral-angle tenderness, nausea or vomiting, and pyuria or bacteriuria (Hooton 2012). Imaging findings including perinephric stranding, renal swelling, thickening of Gerota's fascia, and segmental poor enhancement region are characteristic of pyelonephritis (Hammond et al. 2012). *E. faecalis* or *E. faecium* biliary tract infection was diagnosed when the clinical and diagnostic findings included three or more of the following: 1) fever and/or shaking chills or laboratory evidence of an inflammatory response, 2) jaundice or abnormal liver chemistry findings, 3) biliary dilation or evidence of an etiology observed in imaging, and 4) *E. faecalis* or *E. faecium* isolated from a bile specimen. *E. faecalis* or *E. faecium* catheter-related bloodstream infection was diagnosed based on clinical and diagnostic findings including one or more of the following: 1) *E. faecalis* or *E. faecium* growth in at least one percutaneous blood and catheter tip culture and 2) *E. faecalis* or *E. faecium* growth in a blood sample drawn from a catheter hub at least two hours before the growth of *E. faecalis* or *E. faecium* was detected in a peripheral vein blood sample (Mermel et al. 2009). Infective endocarditis was defined according to previous literature (Li et al. 2000).

Definition of nosocomial bacteremia

Bacteremia that occurred after 48 hours of hospitalization was defined as nosocomial bacteremia.

Assessment of laboratory data

If the initial blood culture was positive, then the leukocyte count, C-reactive protein levels, and albumin levels were recorded within two days of the culture.

Identification of bacteria

All *E. faecalis* and *E. faecium* isolates were identified by colony morphology analysis and gram staining. Isolate identification was confirmed using a MicroScan WalkAway-96 SI (Beckman Coulter, Inc., Brea, CA, USA). The MICs were determined using a dilution antimicrobial susceptibility test according to the manufacturer's instructions (Eiken Chemical, Japan). Daptomycin sensitivity was assessed using Mueller-Hinton broth supplemented with 50 μg/mL calcium. All plates were incubated overnight at 35°C (vancomycin: 24 h, others: 16-20 h). The results were interpreted according to the 2016 CLSI breakpoints.

Antimicrobial treatments

The attending physicians determined the initial antimicrobial treatment regimens. The antimicrobial treatment administrated from the sixth day after bacteremia onset was defined as the definitive therapy (Lee et al. 2013). The definitive treatment was considered appropriate if the attending physician prescribed an antibiotic to which the isolate was susceptible.

Statistical analysis

Patient characteristics, outcomes, and isolate antimicrobial susceptibility were compared between the *E. faecalis* and *E. faecium* groups. Fisher's exact tests were used for univariate comparisons of categorical data. Variables with p-values < 0.05 in the univariate analyses were included in the backward, stepwise, multivariate logistic regressions using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.3.1), in order to determine the independent predictors of *E. faecalis* and *E. faecium* infections. EZR is a modified version of R commander (version 2.3-0) that includes the statistical functions frequently used in biostatistics. P-values < 0.05 indicated statistically significant differences.

Results

Patient clinical characteristics and laboratory findings

The clinical characteristics and laboratory findings of patients with *E. faecalis* or *E. faecium* bacteremia are summarized in Table 1. The 60 patients with *E. faecalis* bacteremia include 38 men and 22 women with a mean age of 62.0 years. The 48 patients with *E. faecium* bacteremia

Table 1. Clinical characteristics and laboratory findings of *E. faecalis* and *E. faecium* bacteremia and univariate analysis of predictive factors associated with *E. faecium* bacteremia.

Variables	*E. faecalis* (n = 60)	*E. faecium* (n = 48)	p-value[a]
Male sex	38 (63.3%)	29 (60.4%)	0.84
Age ≥ 70 years	22 (36.7%)	12 (20.0%)	0.22
Underlying disease			
Malignancy	29 (48.3%)	40 (83.3%)	< 0.001
Hematologic	9 (15.0%)	21 (43.8%)	0.001
Gastrointestinal	14 (23.3%)	16 (33.3%)	0.28
Immunosuppressive drug or corticosteroid use	16 (26.7%)	24 (50.0%)	0.016
Diabetes mellitus	13 (21.7%)	10 (20.8%)	1.00
Cardiovascular disease	19 (31.7%)	4 (8.3%)	0.004
Autoimmune disease	4 (6.7%)	2 (4.2%)	0.69
Respiratory disease	3 (5.0%)	7 (14.6%)	0.11
Digestive disease	8 (13.3%)	6 (12.5%)	1.00
Chronic renal failure	12 (20.0%)	3 (6.3%)	0.05
Central nervous system disease	7 (11.7%)	4 (8.3%)	0.75
Urologic disease	2 (3.3%)	3 (6.3%)	0.65
Trauma	4 (6.7%)	2 (4.2%)	0.69
Neutrophil count < 500 (/μL)	6 (10.0%)	17 (35.4%)	0.002
Albumin ≤ 2.5 (g/dL)	21 (35.6%)	16 (33.3%)	0.84
SOFA score ≥ 5	25 (41.7%)	18 (37.5%)	0.70
Antibiotic use prior to isolation			
Second-generation cephalosporins	3 (5.0%)	2 (4.2%)	1.00
Third-generation cephalosporins	11 (18.3%)	11 (22.9%)	0.63
Fourth-generation cephalosporins	10 (16.7%)	19 (39.6%)	0.009
Sulbactam/ampicillin	5 (8.3%)	0 (0%)	0.06
Tazobactam/piperacillin	9 (15.0%)	14 (29.2%)	0.10
Quinolones	12 (20.0%)	24 (50.0%)	0.002
Carbapenems	11 (18.3%)	20 (41.7%)	0.01
Anti-MRSA agents	5 (8.3%)	12 (25.0%)	0.03
Nosocomial infection	48 (80.0%)	46 (95.8%)	0.02
Operation within 30 days	14 (23.3%)	8 (16.7%)	0.47
Hospitalization within 90 days	16 (26.7%)	25 (52.1%)	0.009
Hospital stay ≥60 days	6 (10.0%)	13 (27.1%)	0.02
Urinary catheter	25 (41.7%)	15 (31.3%)	0.32
Central venous catheter	26 (43.3%)	29 (60.4%)	0.09
Intraperitoneal drain	8 (13.3%)	11 (22.9%)	0.21
Infection site			
Urinary tract	6 (10.0%)	2 (4.2%)	0.30
Biliary tract	6 (10.0%)	10 (20.8%)	0.17
Intravascular device	4 (6.7%)	4 (8.3%)	1.00
Endocardium	6 (10.0%)	0 (0%)	0.03
Others	3 (5.0%)	5 (10.4%)	0.46
Unknown	35 (58.3%)	27 (56.3%)	0.85
Mortality	11 (18.3%)	11 (22.9%)	0.63

[a]Fisher's analysis.

E. faecium, *Enterococcus faecium*; MRSA, methicillin-resistant *Staphylococcus aureus*; SOFA, Sequential Organ Failure Assessment.

included 29 men and 19 women with a mean age of 59.1 years. Of the patients with *E. faecalis* bacteremia, 29 (48.3%) had malignancy including hematologic malignancy (n = 9, 15.0%); 19 (31.7%) had cardiovascular disease; 12 (20.0%) had received quinolones; and 48 (80.0%) had nosocomial bacteremia. In comparison, of the 48 patients with *E. faecium* bacteremia, 40 (83.3%) had malignancy, including hematologic malignancy in 21 (43.8%) patients; 4 (8.3%) had cardiovascular disease; 24 (50.0%) had received quinolones; and 46 (95.8%) had nosocomial bacteremia. The occurrence of neutropenia was significantly higher in patients with bacteremia due to *E. faecium* than that in patients with bacteremia due to *E. faecalis* (35.4% vs. 10.0%, p = 0.002). The male-to-female ratio, mean age, and albumin level (≤ 2.5 g/dL) did not differ between the bacteremia groups. The mean Sequential Organ Failure Assessment (SOFA) scores for patients with *E. faecalis* and *E. faecium* bacteremia were 4.5 and 4.9, respectively. Furthermore, the 30-day mortality rates did not differ between groups. Urinary tract, biliary tract, and intravascular device infections were the presumed source of *E. faecalis* bacteremia in six (10.0%), six (10.0%), and four (6.7%) patients, respectively and in two (4.2%), 10 (20.8%), and four (8.3%) patients, respectively, with *E. faecium* bacteremia. Infective endocarditis was the presumed source of *E. faecalis* bacteremia in six patients (10.0%), but was not the source of *E. faecium* bacteremia in any patient.

Treatment

The definitive therapies against *E. faecalis* and *E. faecium* bacteremia are summarized in Table 2. Penicillin antibiotics were administered to 25 patients (44.6%) in the *E. faecalis* bacteremia group. In addition, 18 patients (32.1%) in the *E. faecalis* bacteremia group received anti-MRSA agents as definitive therapy. In contrast, 37 patients (80.4%) in the *E. faecium* bacteremia group received anti-MRSA agents. The proportions of appropriate definitive therapy did not differ between the bacteremia groups (89.3% vs. 80.4%, p = 0.27).

Predictive factors of E. faecalis and E. faecium bacteremia

The independent predictors associated with *E. faecium* bacteremia in the multivariate analysis included the use of quinolones (odds ratio [OR], 2.97; p = 0.025), malignancy (OR, 3.32; p = 0.021), and prolonged hospitalization (OR, 5.82; p = 0.016). Cardiovascular disease was the opposite predictor (p = 0.015) (Table 3).

Antimicrobial susceptibility

The MIC_{50} and MIC_{90} values of the various antimicrobial agents against *E. faecalis* and *E. faecium* are shown in Table 4. Fig. 1 shows the distributions and daptomycin MICs of the *E. faecalis* and *E. faecium* isolates. Notably, the percentage of *E. faecium* isolates with low susceptibility to daptomycin (MIC ≥ 3 μg/mL) was higher than the percentage of *E. faecalis* with low susceptibility to daptomycin (8.5% vs. 0%, p = 0.036).

Discussion

The results of our study revealed the following. First,

Table 2. Definitive therapies for *E. faecalis* and *E. faecium* bacteremia.

Variables	Definitive therapy	
	E. faecalis (n = 56)[a]	*E. faecium* (n = 46)[b]
Ampicillin	9 (16.1%)	0 (0%)
Sulbactam/ampicillin	6 (10.7%)	0 (0%)
Tazobactam/piperacillin	10 (17.9%)	2 (4.3%)
Third-generation cephalosporins	5 (8.9%)	0 (0%)
Fourth-generation cephalosporins	0 (0%)	3 (6.5%)
Quinolones	1 (1.8%)	1 (2.2%)
Carbapenems	18 (32.1%)	3 (6.5%)
Vancomycin	5 (8.9%)	13 (27.1%)
Teicoplanin	11 (19.6%)	19 (41.3%)
Linezolid	2 (3.6%)	4 (8.7%)
Daptomycin	0 (0%)	1 (2.2%)
Others	6 (10.7%)	0 (0%)
None	2 (3.6%)	0 (0%)
Appropriate treatment	50 (89.3%)	37 (80.4%)

These data include combination therapy.

[a]Three patients died and one patient was transferred to a different hospital before definitive therapy.

[b]One patient died and one patient was transferred to a different hospital before definitive therapy.

E. faecalis, *Enterococcus faecalis*; *E. faecium*, *Enterococcus faecium*.

Table 3. Multivariate analysis of predictive factors associated with *E. faecium* bacteremia.

Predictive factor	OR (95% CI)	p-value
Quinolones	2.97 (1.15-7.72)	0.025
Malignancy	3.32 (1.20-9.18)	0.021
Hospital stay ≥ 60 days	5.82 (1.38-24.5)	0.016
Cardiovascular disease	0.15 (0.03-0.69)	0.015

CI: confidence interval; *E. faecium*, *Enterococcus faecium*; OR, odds ratio.

Table 4. Minimum inhibitory concentrations of six antibiotics in *E. faecalis* and *E. faecium* isolates.

Variables		*E. faecalis* (n = 59)[a]		*E. faecium* (n = 47)[b]	
	MIC range (μg/mL)	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Ampicillin	≤ 0.5-≥ 16	1	2	≥ 16	≥ 16
Imipenem	≤ 1-≥ 16	≤ 1	2	≥ 16	≥ 16
Vancomycin	≤ 0.5-4	1	2	1	1
Teicoplanin	≤ 0.5-2	≤ 0.5	≤ 0.5	≤ 0.5	1
Linezolid	≤ 1-4	2	4	2	4
Daptomycin	≤ 0.12-4	0.5	1.5	1.5	2

[a]One strain was not preserved.
[b]One strain was not preserved.
MIC_{50}: Minimum inhibitory concentration required to inhibit the growth of 50% of organisms.
MIC_{90}: Minimum inhibitory concentration required to inhibit the growth of 90% of organisms.
E. faecalis, *Enterococcus faecalis*; *E. faecium*, *Enterococcus faecium*; MICs, minimum inhibitory concentrations.

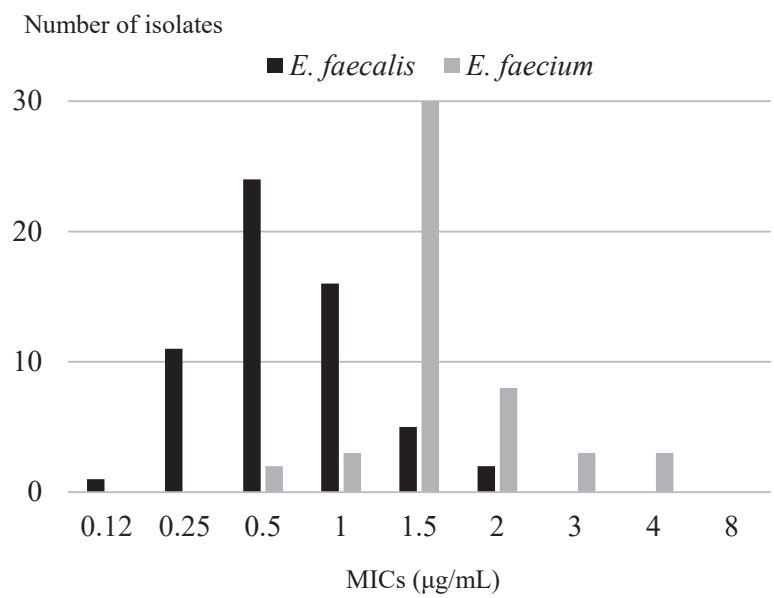

Fig. 1. Distributions of daptomycin minimum inhibitory concentrations in *E. faecalis* and *E. faecium* isolates.
E. faecalis, Enterococcus faecalis; E. faecium, Enterococcus faecium; MICs, minimum inhibitory concentrations.

the use of quinolones, malignancy, and prolonged hospitalization were independent predictors of *E. faecium* bacteremia. Second, the mortality rates did not differ between patients with *E. faecalis* and *E. faecium* bacteremia. Third, there were more *E. faecium* than *E. faecalis* isolates with low susceptibility to daptomycin.

Previous reports showed that hospitalized patients experienced enterococci intestinal overgrowth (Ruiz-Garbajosa et al. 2012), which appears to be important for bacterial translocation and the development of bacteremia (Ubeda et al. 2010). Weisser et al. (2012) reported that hospitalized patients had increased *E. faecium* colonization. Furthermore, Top et al. (2007) reported that the use of quinolones was an independent risk factor of *E. faecium* colonization. These findings suggest that patients receiving quinolones are at an increased risk of *E. faecium* acquisition

and bacteremia.

Conde-Estévez et al. (2011) reported a potential relationship between *E. faecium* bacteremia and cancer. Other reports showed that the use of carbapenems is an independent predictor of *E. faecium* bacteremia (Gudiol et al. 2013; Hamada et al. 2015). The use of broad-spectrum β-lactams including carbapenems in cancer patients is common in clinical practice. In the present study, the percentage of patients with malignancy and bacteremia due to *E. faecium* was significantly higher than that in patients with malignancy and bacteremia due to *E. faecalis* (83.3% vs. 48.3%, $p < 0.001$). Furthermore, univariate analysis revealed that the use of carbapenems in patients with bacteremia due to *E. faecium* was higher than that in patients with bacteremia due to *E. faecalis*. (41.7% vs 18.3%, $p = 0.01$). These findings suggest that any malignancy increases the risk for *E. faecium* bacteremia.

A previous report showed that enterococcal bacteremia is associated with a prolonged stay in the medical intensive care unit (Moses et al. 2012). There are many opportunities for exposure to multiple antimicrobial agents among long-term inpatients; thus, the prescription of antimicrobial agents for more than 10 days and a prolonged stay are associated with the selection of ampicillin-resistant enterococci (Harthug et al. 2000). In the present study, the incidence of hospital stays ≥ 60 days was higher in patients with bacteremia due to *E. faecium* than that in those with *E. faecalis* bacteremia (27.1% vs. 10.0%, $p = 0.02$). Furthermore, the use of antibiotics for more than four days prior to isolation in patients with bacteremia due to *E. faecium* was significantly higher than that in patients with bacteremia due to *E. faecalis* (89.6% vs. 55.0%, $p < 0.001$). These findings suggest that a prolonged stay increases the risk of *E. faecium* acquisition and bacteremia.

Although previous studies have identified various predictors associated with *E. faecium* bacteremia, the association with cardiovascular disease observed in multivariate analysis in the present study is an unusual finding. A previous report showed that cardiovascular disease, especially valvular disease, is an important risk factor of infective endocarditis (Hoen and Duval 2013). Bouza et al. (2015) reported that 4.3% of patients with enterococcal bacteremia also had infective endocarditis. Notably, 86.2% and 10.8% of patients with infective endocarditis developed *E. faecalis* and *E. faecium* bacteremia, respectively. Therefore, enterococcal bacteremia, especially that due to *E. faecalis*, increases the risk of infective endocarditis. In the present study, of the 60 patients with *E. faecalis* bacteremia, 19 (31.7%) had cardiovascular disease, including seven (12.0%) with valvular disease. In contrast, of the 48 patients with *E. faecium* bacteremia, four (8.3%) had cardiovascular disease and none had valvular disease. Furthermore, infective endocarditis was the presumed source of *E. faecalis* bacteremia in six patients (10.0%) and none of the patients with *E. faecium* bacteremia (0%). Although the cause is not clear, these findings suggest that cardiovascular disease may be associated with a reduced risk of *E. faecium* bacteremia. Although the results of the present study indicate a relationship between *E. faecium* bacteremia and quinolone use, malignancy, and prolonged hospitalization, more cases should be studied in order to confirm this relationship.

Increased mortality among patients with *E. faecium* bacteremia compared to that among those with *E. faecalis* bacteremia has been reported (Noskin et al. 1995; McBride et al. 2010; Conde-Estévez et al. 2011). However, similar in-hospital mortalities for *E. faecium* and *E. faecalis* infections (5.3% vs. 9.0%) have also been reported (Kajihara et al. 2015). In our study, the 30-day mortality did not differ between patients with *E. faecalis* and those with *E. faecium* bacteremia (18.3% vs. 22.9%). The likely reasons for this are as follows. There was no significant difference in SOFA scores between the two groups (4.5 vs. 4.9). Similarly, the use of inappropriate definitive therapy did not differ between these groups (10.7% vs. 19.6%). Suppli et al. (2011) reported that the use of inappropriate antibiotics against enterococcal bacteremia was an independent risk factor for mortality.

According to the 2016 CLSI, the daptomycin breakpoint for enterococci is 4 μg/mL (Clinical and Laboratory Standards Institute 2016). However, in vitro data from Diaz et al. underscore the need to re-assess this breakpoint (Diaz et al. 2014). In clinical data, Munita et al. (2014) reported that daptomycin monotherapy should be used with caution against daptomycin-susceptible *E. faecium* strains with MICs > 2 μg/mL. More recently, Shukla et al. (2016) reported that daptomycin MICs of 3-4 μg/mL in the initial *E. faecium* blood isolate forecasted the microbiological failure of daptomycin treatment, also indicating the need to revise the daptomycin breakpoint for enterococci. The proportions of vancomycin-susceptible *E. faecium* with low susceptibility to daptomycin are 10.9% in Europe and 12.8% in the United States (Sader et al. 2015). In the present study, 4 (8.5%) *E. faecium* isolates exhibited low susceptibility to daptomycin (MICs ≥ 3 μg/mL). None of the corresponding patients received daptomycin treatment and none died from *E. faecium* bacteremia. Although daptomycin should be administered for bacteremia caused by vancomycin-susceptible *E. faecium* strains with MICs ≤ 2 μg/mL, the findings of previous reports suggest that the administration of daptomycin should be avoided against *E. faecium* strains with low susceptibility to daptomycin.

Our study had several limitations. First, we assessed only *E. faecalis* and *E. faecium* bacteremia. It is necessary to determine the numbers of patients with bacteremia caused by other *Enterococcus* spp. such as *E. avium*, *E. casseliflavus*, and *E. gallinarum* in addition to *E. faecalis* and *E. faecium*. Second, as this study was conducted only in patients in a tertiary hospital, there was a selection bias. Future studies are necessary to determine the numbers of patients with bacteremia caused by *Enterococcus* spp. in a community hospital setting. Third, we conducted this retro-

spective study primarily with the aim of investigating the predictive factors of bacteremia caused by *E. faecium*. Future prospective studies are necessary to compare daptomycin and linezolid for the treatment of bacteremia caused by *Enterococcus* spp.

In conclusion, the results of our study showed that the mortality rates did not differ between patients with *E. faecalis* and *E. faecium* bacteremia. Quinolone use, malignancy, and prolonged hospitalization were independent predictors of *E. faecium* bacteremia. It is necessary to consider the presence of *E. faecium* when administering antibiotic therapy to patients with a history of these predictors. Although daptomycin should be administered for bacteremia caused by vancomycin-susceptible *E. faecium* strains with MICs ≤ 2 μg/mL, the administration of daptomycin should be avoided against *E. faecium* strains with low susceptibility to daptomycin (MICs ≥ 3 μg/mL).

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Conflict of Interest

The authors declare no conflict of interest.

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