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ORIGINAL ARTICLE

Emergence of vancomycin-resistant *Enterococcus* bloodstream infections in southern Taiwan

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KEYWORDS
Bacteremia;
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Background: An increased incidence of vancomycin-resistant enterococcal bloodstream infections (VRE BSI) in the United States has been noted in recent years. There were a few reports of VRE BSI in Taiwan. This study is intended to show the epidemiology, clinical features and outcomes of VRE BSI at a medical center in southern Taiwan.
Methods: A retrospective study was conducted from January 1, 2005 to December 31, 2010. All patients with VRE BSI episodes were identified and their medical records were reviewed.
Results: A total of 69 episodes of VRE BSI were identified in the study period. The incidence rate increased from 0.01 episodes of VRE BSI/1000 patient-days in 2005 to 0.07 episodes of VRE BSI/1000 patient-days in 2010. The 30-day mortality rate was 52.17% for all patients with VRE BSI. The mortality rate of patients who received *in vitro* active and inactive antimicrobial therapy for VRE BSI was 40% and 100%, respectively ($p < 0.001$). Factors associated with mortality were shock [odds ratio (OR) 24.4, 95% confidence interval (CI) 3.6–163.2, $p = 0.001$], renal failure (OR 90.9, 95% CI 1.9–4404.3, $p = 0.02$), and underlying liver cirrhosis (OR 12.4, 95% CI 1.2–125.8, $p = 0.03$). Use of linezolid for VRE BSI showed a trend for lower 30-day mortality than daptomycin therapy (35.5% *vs.* 56.3%, $p = 0.17$).
Conclusion: VRE BSI is increasingly important in the study hospital and is associated with a significant mortality rate. Appropriateness of antimicrobial therapy has a prognostic impact on patients with VRE BSI.

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Introduction

Vancomycin-resistant enterococci (VRE) emerged in the late 1980s and over the past 20 years the prevalence of VRE has increased rapidly in many countries. In the United States, 14—25% of all clinical enterococci isolates[1—3] and 60% of *Enterococcus faecium* isolates from nosocomial bloodstream infections (BSIs) were resistant to vancomycin.[4] The prevalence of VRE isolates from clinical specimens in our institution was low between 1995 and 2005, accounting for 0.55% of enterococcal isolates, with 61% of VRE isolates identified as *Enterococcus faecalis* with a VanA phenotype, and 39% *E faecium* with a VanB phenotype.[5] BSIs due to VRE have been associated with a poor prognosis. Two meta-analyses have shown that vancomycin resistance was an independent factor for death among patients with enterococcal BSIs.[6,7]

Despite the high mortality of VRE BSIs, the optimal treatment is unclear. Teicoplanin, a glycopeptide available in Europe, Taiwan and other countries, but not in the United States, is generally *in vitro* active against VRE with the VanB phenotype.[8] There were very limited reports about the use of teicoplanin for human VRE infections.[9] A clinical concern is the emergence of resistant mutants during teicoplanin therapy.[10] Quinupristin/dalfopristin and linezolid have been approved by the US Food and Drug Administration (FDA) for VRE infections. Clinical use of quinupristin/dalfopristin was limited by the requirement of a central line for infusion, side effects, and a lack of activity against *E faecalis*. Linezolid has a better tolerability, oral bioavailability and coverage against *E faecalis*; however, its use is associated with bone marrow toxicity and neuropathy. Additionally, VRE isolates that are resistant to linezolid have been identified with subsequent reports of nosocomial transmission in hospitals.[11—13]

Daptomycin has *in vitro* activity against VRE, including strains that exhibit resistance to quinupristin/dalfopristin and linezolid.[14,15] The FDA approved daptomycin for the treatment of complicated skin and soft tissue infections and *Staphylococcus aureus* bacteremia, including right-sided infective endocarditis, but not for VRE infections.[16] Clinical data and treatment outcomes supporting the use of daptomycin in the treatment of VRE infections are limited to a few case reports and case series.[17,18] Thus, the objective of this study is to investigate the epidemiology, clinical features and outcome of VRE BSIs in a tertiary hospital in southern Taiwan, with emphasis on different antimicrobial therapies for VRE BSI and factors associated with mortality.

Material and methods

Study design and source of patients

A retrospective study was conducted at National Cheng Kung University Hospital, a 1000-bed academic tertiary care hospital located in southern Taiwan. Infection control measures, including a real-time laboratory-based reporting system, contact isolation, and VRE surveillance protocols have been launched at this hospital. The list of patients with VRE bacteremia between January 2005 and December 2010 was identified in the database of the Clinical Microbiology Laboratory and Center of Infection Control.

Systematic review of medical records

Medical charts of patients with at least a positive blood culture for VRE during the study period were reviewed. A standardized form was used to systematically collect information regarding demographic, underlying disease and clinical characteristics of each case. Adult patients aged $\geq$18 years with clinically significant VRE BSI occurring between January 2005 and December 2010 were included in the analysis. Clinically significant VRE BSI was defined as the isolation of VRE from two or more separately obtained blood cultures, or isolation of VRE from a single blood culture with clinical features compatible with sepsis.[3] Recurrent VRE BSI was defined as another VRE bacteremic episode at least 30 days apart from completion of antimicrobial therapy for the first VRE BSI episode. Recent invasive procedure was defined as any invasive procedure or surgical intervention within 30 days prior to the VRE bacteremia. Recent hospitalization was defined as admission to the hospital within the previous 30 days. Thirty-day mortality was defined as death due to any cause within 30 days after the onset of VRE BSI. The severity of comorbidity was measured by the Charlson Comorbidity Index (CCI).[19] Prescription of daptomycin and linezolid required the approval from an infectious disease specialist in the study hospital. Appropriate antimicrobial therapy was defined as the receipt of at least one *in vitro* active antimicrobial agent such as linezolid, daptomycin, or teicoplanin against VRE for at least 48 hours. Other regimens were considered as inappropriate therapy. Clinical events associated with organ system failure were assessed by the criteria specified in the organ dysfunction and/or infection score.[20]

VRE identification and antimicrobial susceptibility test

For the laboratory identification of VRE, enterococci were identified by the 6.5% NaCl and bile-esculin test, confirmed by the Vitek Gram-positive identification system (bioMérieux, Marcy l'Etoile, France). Antimicrobial disk susceptibility tests of vancomycin, ampicillin, high-level streptomycin, high-level gentamicin, teicoplanin, and linezolid (Becton Dickinson, Franklin Lakes, NJ, USA) were performed. According to a previous surveillance program, 100% of vancomycin-resistant *E faecalis*, and 99.7% of vancomycin-resistant *E faecium* were susceptible to daptomycin.[21] Susceptibility to daptomycin was not routinely determined for VRE isolates in the study site. If there are concerns regarding the susceptibility of VRE to daptomycin, then the minimal inhibitory concentration (MIC) should be determined using the E-test. The interpretive criteria of the Clinical and Laboratory Standards Institute were used to determine the susceptibilities of the isolates.[22] The interpretive criteria of the European Committee on Antimicrobial Susceptibility Testing were used for teicoplanin susceptibility. [23]

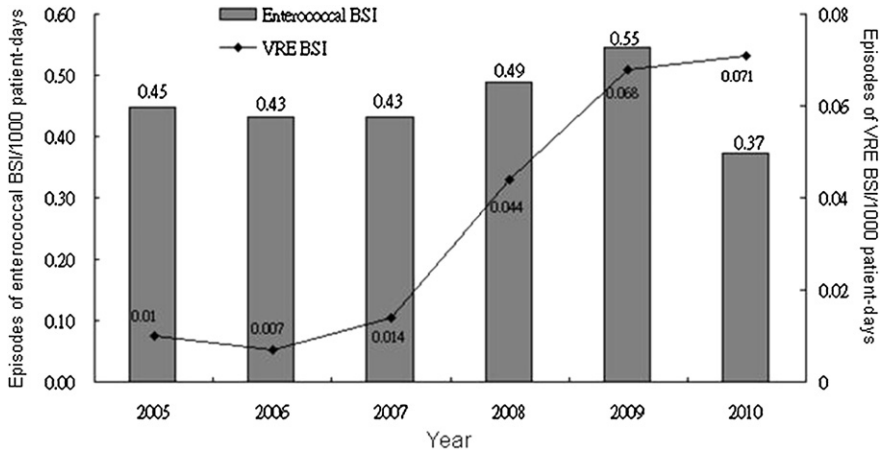

Figure 1. Annual incidence of enterococcal bloodstream infection (BSI) and vancomycin-resistant enterococcal (VRE) BSI/1000 patient-days at National Cheng Kung University Hospital, 2005-2010.

Statistical analysis

SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL, USA), was used for computing statistical tests. The trend in the incidence of VRE BSI over the study period was analyzed with linear regression analysis. Continuous variables were expressed as means ± standard deviations (SD) and evaluated by the Student *t* test. The categorical variables were

Table 1 Comparison of survivors and fatal cases of vancomycin-resistant *Enterococcus* (VRE) bacteremia

Variables[a]	Total (n = 69)	Survivors (n = 33)	Fatal cases (n = 36)	Univariate	Multivariate analysis[b]	
				p	OR (95% CI)	p
Age, mean (SD), y	69.96 (11.67)	69.2 ± 11.7	70.7 ± 11.8	0.601	1.10 (1.00—1.20)	0.048
Male gender	40 (57.97)	20 (60.6)	20 (55.6)	0.671		
Nursing home residency	8 (11.60)	5 (15.2)	3 (8.3)	0.466		
Recent hospitalization	45 (65.22)	21 (63.6)	24 (66.7)	0.792		
Prior VRE colonization	14 (20.29)	6 (18.2)	8 (22.2)	0.677		
Polymicrobial bacteremia	26 (37.68)	12 (36.4)	14 (38.9)	0.829		
Recent invasive procedure	41 (59.42)	18 (54.6)	23 (63.9)	0.43	0.98 (0.25—3.83)	0.978
Charlson Co-morbidity Index	4.19 (2.40)	4.3 ± 2.9	4.0 ± 1.9	0.611		
Pittsburgh Bacteremia Score	4.07 (2.91)	2.2 ± 2.3	5.8 ± 2.2	<0.001	1.83 (1.41—2.38)	<0.001
Comorbidities						
Diabetes mellitus	32 (46.38)	17 (51.5)	15 (41.7)	0.413	1.79 (0.49—6.55)	0.384
Hypertension	34 (49.28)	16 (48.5)	18 (50.0)	0.9		
Malignancy	22 (31.88)	13 (39.4)	9 (25.0)	0.2	1.55 (0.37—6.38)	0.548
Chronic kidney diseases	16 (23.19)	9 (27.3)	7 (19.4)	0.441	1.58 (0.32—7.68)	0.573
Chronic obstructive pulmonary disease	7 (10.14)	4 (12.1)	3 (8.3)	0.702		
Liver cirrhosis	11 (15.94)	3 (9.1)	8 (22.2)	0.137	12.40 (1.23—125.79)	0.033
Immunosuppression	3 (4.35)	1 (3.0)	2 (5.6)	1		
Clinical features						
Mechanical ventilation	38 (55.07)	9 (27.3)	29 (80.6)	<0.001	0.97 (0.08—12.22)	0.981
Concomitant shock	40 (57.97)	8 (24.2)	32 (88.9)	<0.001	24.37 (3.63—163.19)	0.001
Liver failure	23 (33.33)	4 (12.1)	19 (52.8)	<0.001	2.13 (0.23-16.23)	0.468
Renal failure	17 (26.64)	1 (3.0)	16 (44.5)	<0.001	90.92 (1.89-4404.29)	0.023
Appropriate VRE treatment	54 (78.26)	33 (100)	21 (58.3)	<0.001	0.03 (0.01-0.12)	<0.001
Time to appropriate antibiotic[c]	3.60 (1.45)	3.7 ± 1.4	3.5 ± 1.6	0.553		

[a] Data were expressed as cases (%) or means ± standard deviations.
[b] Variables in the univariate analysis with P values <0.5 and age were included in the multivariate analysis.
[c] Time between bacteremia onset to the first dose of appropriate antibiotic against VRE. Only patients who received antibiotic for VRE were included in the analysis.
CI = confidence interval; OR = odds ratio.

evaluated by the Fisher exact test or X^2 test, when appropriate. Multiple regressions were used to determine the effect of comorbidities, clinical features and antimicrobial therapy on mortality while controlling for covariates. The covariates in the analysis included age, male gender, CCI, presence of shock, acute renal and liver failure, mechanical ventilation, and antimicrobial therapy. Adjusted odds ratios and 95% confidence intervals were calculated. A Cox proportional hazards model was used for the survival curve, adjusted for confounding variables. All tests were 2-tailed and a p value <0.05 was considered statistically significant.

Results

Over the 6 years, the rate of VRE BSI in our institution increased significantly. Only 2.29% of *Enterococcus* isolates causing BSI were resistant to vancomycin in 2005, but increased to 19.05% in 2010. The incidence of VRE BSI increased from 0.01 in 2005 to 0.07 VRE BSI/1000 patient-days in 2010 ($p = 0.01$, in trend) as shown in Fig. 1. The incidence of VRE BSI increased significantly since 2008, and the mortality rates from 2008 to 2010 were 71%, 59% and 79%, respectively.

Seventy episodes of VRE BSI were identified. Since a patient had recurrent VRE BSI during the study period, and only the first episode of this patient was included in the analysis, there were 69 episodes included. Seven VRE isolates were not available for species identification, so 52 isolates were identified as *E faecium* and 10 were *Enterococcus gallinarum*. No VRE bacteremic isolates were identified as *E faecalis*. The 30-day mortality rate for *E faecium* and *E gallinarum* were similar, 52% and 50%, respectively. The mean age of patients with VRE-BSI was 70.0 years, and 40% were males. Recent hospitalization and invasive procedures were not infrequent. Diabetes mellitus, hypertension and malignancies were common co-morbid diseases. The mean CCI score was 4.2. The presence of shock or respiratory failure after the onset of bacteremia was noted in more than half of the patients.

Twelve (17.3%) patients received no antibiotic that was active against VRE *in vitro*, and their 30-day mortality rate was 100%. Of 12 fatal cases, 11 died before blood culture results were available. Antibiotics with *in vitro* activity against VRE were prescribed in 57 patients. Ten (14.5%) patients were treated by teicoplanin, 31 (44.9%) linezolid, and 16 (23.2%) daptomycin. None of the VRE isolates were susceptible to ampicillin. The time between bacteremia onset to the first dose of *in vitro* active antibiotic was 3.6 days. The mean CCI score in this study population was 4.2. The 30-day mortality rate of those treated by an *in vitro* effective drug was 42.1% and the overall mortality rate for VRE BSI was 52.17%.

Patient characteristics for survivors and non-survivors are compared in Table 1. Of note, 24 patients had polymicrobial bacteremia, which was not associated with a fatal outcome (14/26, 53.8% vs. 22/43, 51.25, $p = 0.83$). In the univariate analysis, several factors were associated with mortality, including presence of shock (24.2% vs. 83.3%, $p < 0.001$), acute renal failure (3.0% vs. 33.3%, $p = 0.002$), liver failure (12.1% vs. 45.8%, $p = 0.004$), and respiratory failure (27.3% vs. 75.0%, $p < 0.001$). The above factors, in addition to age, gender, presence of liver cirrhosis, malignancy, CCI and appropriateness of antimicrobial therapy for VRE BSI, were analyzed in a multivariable logistic regression model. The presence of liver cirrhosis (OR 12.4, 95% CI 1.2—125.8, $p < 0.03$), shock (OR 24.4, 95% CI 3.6—163.2, $p = 0.001$) and acute renal failure (OR 90.9, 95% CI 1.9—4404.3, $p = 0.02$) at the time of VRE BSI were independently associated with mortality at 30 days (Table 1).

The Cox proportional hazards model was applied after controlling for confounding variables. The result revealed that the survival rate was significantly different between patients with appropriate and inappropriate antimicrobial therapy for VRE BSI ($p < 0.001$) (Fig. 2).

Clinical features of patients receiving either linezolid or daptomycin therapy were compared in Table 2. Platelet counts were lower in patients with daptomycin therapy ($p = 0.001$). Also hepatic failure (50.0% vs. 16.1%, $p = 0.02$) and the use of mechanical ventilation (68.8% vs. 35.5%, $p = 0.03$) at the time of VRE BSI were more common in patients treated with daptomycin. However, there were no differences in patients treated with linezolid or daptomycin in terms of hospitalization days (74.9 vs. 49.9 days, $p = 0.12$) and 30-day mortality rate (35.5% vs. 56.3%, $p = 0.17$). As for teicoplanin therapy, it was used in 10 patients with bacteremia caused by VRE with a VanB phenotype, with a mortality rate of 40%.

Discussion

The first study focusing on VRE bacteremia in Taiwan was published in 2008 and only included 12 patients, with the emphasis on clinical features and outcome but no mention

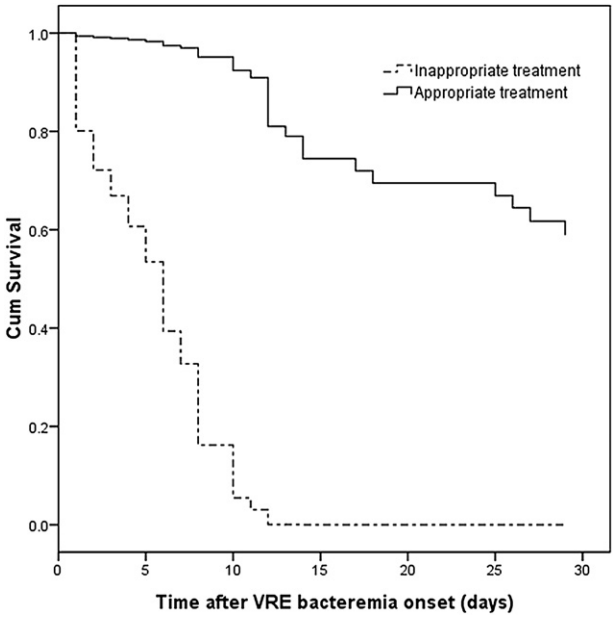

Figure 2. The survival curve for patients with vancomycin-resistant *Enterococcus* bacteremia with appropriate and inappropriate antimicrobial therapy, adjusted for age, gender, Charlson comorbidity index, use of mechanical ventilation, concomitant shock, renal and liver failure (Cox model) ($p < 0.001$).

Table 2 Clinical characteristics of 47 patients with vancomycin-resistant *Enterococcus* (VRE) bacteremia treated by linezolid or daptomycin

Variables[a]	Linezolid ($n = 31$)	Daptomycin ($n = 16$)	p
Age, y	72.2 ± 11.1	68.3 ± 11.8	0.281
Male gender	17 (54.8)	12 (75.0)	0.178
Nursing home residency	7 (22.6)	0	0.078
Recent hospitalization	22 (71.0)	11 (68.8)	1.000
Prior VRE colonization	9 (29.0)	2 (12.5)	0.287
Recent invasive procedure	18 (58.0)	8 (50.0)	0.598
Charlson co-morbidity index	4.3 ± 2.3	4.6 ± 3.2	0.632
Pittsburgh bacteremia score	3.4 ± 2.9	3.9 ± 2.5	0.579
Co-morbidities			
Hypertension	18 (58.1)	9 (56.3)	0.905
Diabetes mellitus	17 (54.8)	8 (50.0)	0.753
Chronic kidney disease	9 (29.0)	5 (31.3)	1.000
Malignancy	7 (22.6)	7 (43.8)	0.182
Chronic obstructive pulmonary disease	5 (16.1)	2 (12.5)	1.000
Liver cirrhosis	3 (9.7)	3 (18.8)	0.395
Immunosuppression	0	1 (6.3)	0.304
Clinical features			
Concomitant shock	14 (45.2)	9 (56.3)	0.471
Mechanical ventilation	11 (35.5)	11 (68.8)	0.030
Liver failure	5 (16.1)	8 (50.0)	0.020
Renal failure	4 (12.9)	3 (18.8)	0.676
Laboratory data			
WBC, /mm^3	12.8 ± 6.5	11.7 ± 8.5	0.637
Platelet count, ×1000/mm^3	185.0 ± 127.7	90.2 ± 64.4	0.001
Serum C-reactive protein, mg/L	91.4 ± 89.7	112.2 ± 80.8	0.451
Serum creatinine, mg/dL	2.2 ± 2.4	2.2 ± 3.0	0.984
Time to appropriate antibiotic,[b] d	3.7 ± 1.3	3.5 ± 1.6	0.709
Hospital stay, d	74.9 ± 60.0	49.9 ± 27.7	0.122
30-d mortality	11 (35.5)	9 (56.3)	0.172

[a] Data were expressed as cases (%) or means ± standard deviations.
[b] Time between bacteremia onset to the first dose of effective antibiotic against VRE. Only patients who received antibiotic for VRE were included in the analysis.

of antimicrobial therapy.[24] The present study is the second study, with more clinical cases in Taiwan investigating clinical characteristics, treatment and outcome of patients with VRE bacteremia. Our findings provide important insights into the epidemiology and management of difficult-to-treat VRE infections. We observed an increasing rate of vancomycin resistance in bacteremic *Enterococcus* isolates during the 6-year study period, increasing from 2.3% in 2005 to 19.1% in 2010, with the incidence increasing from 0.01 to 0.07 VRE BSI/1000 patient-days. This trend in increasing incidence rate of VRE infections was similar in a previous study conducted from 2005 to 2008 in the USA,[25] with an almost three-fold increase in incidence from 0.06 to 0.17 infections/1000 patient-days. This local epidemiology information reflects that VRE BSI is an emerging health-care associated infection in Taiwan, as in the United States.

In this study, the 30-day mortality of patients with VRE BSI was 52.17%. This high mortality rate is comparable to published studies of VRE bacteremia.[24–30] Among all patients with VRE BSI, approximately 60% of patients have concomitant shock and 55% of patients need mechanical ventilation at the time of VRE BSI. Moreover, a long hospital stay, up to 62 days, was found. This suggests that patients with VRE bacteremia had poor clinical conditions at the time of VRE BSI, as reflected by high Pittsburg bacteremia scores. All these factors may contribute to a high mortality rate. Several host factors such as severe underlying disease, shock, renal and liver failure at the time of VRE BSI, and mechanical ventilation, have been recognized to be independent predictors of mortality in patients with VRE bacteremia.[29,31,32] Our study confirmed previous findings as we found a significant association between shock ($p = 0.001$), renal failure ($p = 0.02$) and mortality. Moreover, in the current study, an amendable factor to improve clinical outcome is noted, and that is administration of adequate *in vitro* active antimicrobial therapy for VRE BSI.

To date, the optimal treatment for VRE BSI is still unclear. To conduct a prospective, double-blinded, randomized, placebo-controlled trial to compare the efficacy of daptomycin and linezolid for VRE BSI will be difficult due to the rarity of VRE BSI in the real world. Currently, clinical choices

of teicoplanin, daptomycin or linezolid will be influenced by the resistance profiles of VRE isolates, preference of attending clinicians, or more importantly the patients' underlying conditions, such as platelet count, renal function, serum creatine kinase, or a history or current evidence of myositis. There were few retrospective studies comparing the treatment outcome of daptomycin and linezolid for VRE BSI. Mave et al[25] reported 98 patients with VRE bacteremia. Sixty-eight patients were treated by linezolid and 30 by daptomycin, with a corresponding mortality rate of 20.6% and 26.7%, respectively. However, daptomycin therapy has been associated with a higher relapse rate (2.9% vs. 6.7%). Similar results were found in a multicenter cohort study involving 101 patients with VRE BSI, in-hospital mortality was 46.3% for those treated by daptomycin and 29.4% by linezolid ($p = 0.10$).[26] The latest study by McKinnell et al indicated there was a higher microbiological failure rate (29.0% vs. 17.5%) or mortality rate (37.2% vs. 28.0%) for VRE BSIs treated by daptomycin than those by linezolid.[27] All studies were done in the United States, and a trend towards a higher mortality rate among individuals with daptomycin therapy was found. However the difference did not reach statistical significance. Concordantly, we found a similar trend. However, such a result should not be considered to be conclusive, as the poor prognosis was possibly influenced by more cases of respiratory failure requiring mechanical ventilation and liver failure in the daptomycin group. These observations suggest that patients with poorer clinical conditions were more likely to receive daptomycin and have a grave prognosis.

The current study has several limitations. First, this is a retrospective study with a small number of cases analyzed, and the study population was heterogeneous. Second, our study did not evaluate the type and appropriateness of medical therapy for concurrent pneumonia. As daptomycin will be inhibited by surfactants, there may be a greater likelihood of a grave outcome in pulmonary infections treated by daptomycin, which not found by our retrospective study. Third, a significant number of patients with concurrent bloodstream infections were observed. Although the majority of patients also received appropriate therapy for concurrent pathogens others than VRE, those co-existing pathogens were heterogeneous, which may variably influence the outcome.

In conclusion, VRE BSIs may become a challenge in the near future due to increasing incidence and a high mortality rate. Appropriateness of antimicrobial therapy may improve survival, and more prospective studies are needed to define the optimal treatment for VRE BSI.

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