

# Observational study of the epidemiology and outcomes of vancomycin-resistant *Enterococcus* bacteraemia treated with newer antimicrobial agents

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## SUMMARY

Vancomycin-resistant *Enterococcus* bloodstream infections (VRE-BSI) are a growing problem with few clinical trials to guide therapy. We conducted a retrospective study of management and predictors of mortality for VRE-BSI at a tertiary-care centre from January 2005 to August 2008. Univariate and multivariable analyses examined the relationship of patient characteristics and antibiotic therapy with 30-day all-cause mortality. Rates of VRE-BSI increased from 0·06 to 0·17 infections/1000 patient-days ( $P=0\cdot03$ ). For 235 patients, 30-day mortality was 34·9%. Patients were primarily treated with linezolid (44·2%) or daptomycin (36·5%). Factors associated with mortality were haemodialysis [odds ratio (OR) 3·2, 95% confidence interval (CI) 1·6–6·3,  $P=0\cdot007$ ], mechanical ventilation (OR 3·7, 95% CI 1·3–10·4,  $P=0\cdot01$ ), and malnutrition (OR 2·0, 95% CI 1·0–4·0,  $P=0\cdot046$ ). Use of linezolid, but not daptomycin ( $P=0\cdot052$ ) showed a trend towards an association with survival. In conclusion, VRE-BSI is a growing problem, associated with significant 30-day mortality. Multiple factors were associated with poor outcomes at our hospital.

**Key words:** Antibiotic resistance, antibiotics, *Enterococcus*, hospital-acquired (nosocomial) infections.

## INTRODUCTION

Enterococci are the second most common cause of nosocomial bloodstream infections in the USA [1] and vancomycin resistance occurs in nearly one third of isolates. Vancomycin-resistant *Enterococcus*

bloodstream infections (VRE-BSI) are associated with increased morbidity, mortality, and healthcare expenditures for hospitalized patients [2–12]. Fortunately, novel antimicrobials with activity against VRE (daptomycin, linezolid, quinupristin-dalfopristin, tigecycline) provide a therapeutic option for physicians.

The impact of newer antimicrobial agents on predictors of mortality from VRE-BSI needs further investigation [5, 13–16]. While previous research has

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identified factors associated with poor outcomes from VRE-BSI [Charlson comorbidity index (CCI), the number of positive blood cultures, parenteral nutrition, severity of illness, renal function, liver disease, malignancy, prior VRE infection] [4, 5, 7, 16–18], most of these studies were conducted prior to widespread use of novel antimicrobials with activity against VRE. Herein, we explore outcomes of patients with VRE-BSI at a tertiary-care medical centre, focusing on antimicrobial therapy and factors associated with mortality for VRE-BSI.

## PATIENTS AND METHODS

### Clinical data

We conducted a retrospective study of patients with nosocomial VRE-BSI at University Hospital in Birmingham, Alabama between 1 January 2005 and 1 August 2008. All patients who met CDC criteria for nosocomial bloodstream infections with vancomycin-resistant *Enterococcus* spp. were included in the study [19]. All blood cultures were analysed with an automated culture system (BacT/ALERT, bioMérieux Industries, USA) and automated susceptibility testing (Microscan Walkaway 96 SI, Siemens Healthcare Diagnostics, USA). Rates of VRE-BSI were calculated as number of patients with bacteraemia/1000 patient-days of care.

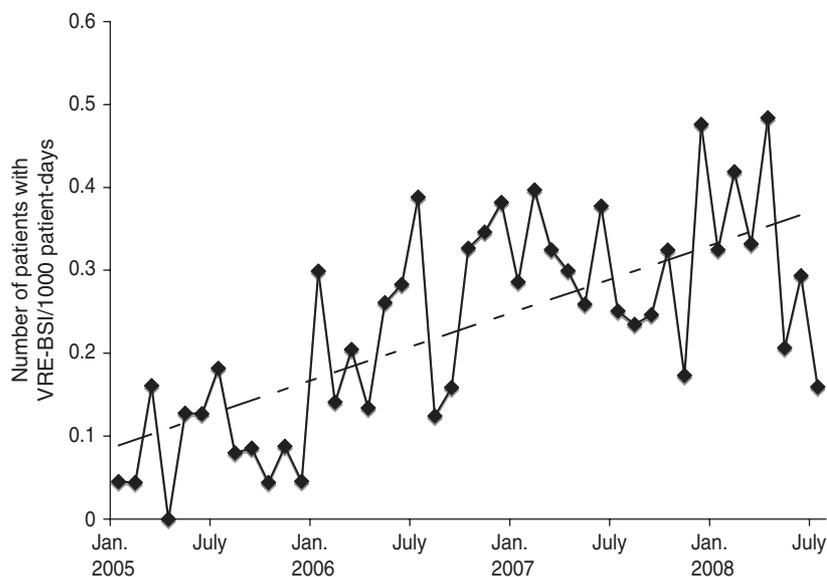
Medical records were reviewed for demographic information, presence of comorbidities, laboratory data, antimicrobial treatment, and outcomes. The following definitions were used: cancer (any active malignancy); liver disease (cirrhosis due to any cause, chronic viral hepatitis, or transaminase levels at least four times the upper limit of normal); recent surgery (surgery within the previous 60 days); transplant (receipt of a haematopoietic stem cell or solid organ transplant); leukocytosis [white blood cell (WBC) count  $>20\,000$  cells/mm<sup>3</sup>]; neutropenia (absolute neutrophil count  $<500$  neutrophils/mm<sup>3</sup>); malnutrition (serum albumin  $<2.0$  mg/dl); concurrent bloodstream infection (positive blood culture for bacteria or fungi with associated findings of infection within 14 days before or after the first positive VRE culture). Renal insufficiency was defined as creatinine  $>2$  g/dl or haemodialysis at time of VRE culture. Immunosuppression was defined as receipt of any immunosuppressive medication, excluding anti-neoplastic agents for the treatment of cancer, during the index hospitalization. Corticosteroid doses

equivalent to  $<10$  mg prednisone were not included as immunosuppression. An aggregate measure of underlying illness was measured using the CCI [20]. The CCI is predictive of mortality for a patient who may have a range of comorbid conditions such as heart disease, HIV/AIDS, or cancer (a total of 22 conditions). Each condition is assigned a score from 1 to 6 depending on the risk of dying associated with the condition. The CCI is the sum of these scores and a higher score is associated with a greater likelihood of death.

Primary antimicrobial therapy for VRE was defined as receipt of daptomycin, linezolid, quinupristin-dalfopristin, or tigecycline for at least 3 days of the initial 4 days of VRE treatment. Time to initiation of antibiotics was determined from collection of the first blood culture that subsequently grew VRE to the start date of antibiotics, measured in days. Microbiological failure was defined as persistently positive blood cultures while on appropriate therapy for at least 24 h or recurrence of positive blood cultures within 1 week of completing therapy. Antimicrobial stewardship guidelines were in place throughout the hospital for the entire course of the study. Daptomycin and linezolid were unrestricted for the treatment of VRE, but quinupristin-dalfopristin and tigecycline required verbal approval from an infectious disease (ID) specialist. ID consultation was recommended, but not required for all VRE infections. The primary outcome of interest was all-cause mortality at 30 days following the first positive culture for VRE.

### Statistical analyses

Frequencies of categorical variables and means, medians and standard deviations of continuous variables were calculated for the overall population and for patients who received appropriate treatment. For analysis of the relationships of variables to survivors and non-survivors, univariate analyses were performed using  $\chi^2$  or Fisher's exact methods for categorical variables and Student's *t* test or the Wilcoxon rank sum test for continuous variables. The primary model for factors associated with mortality was created using stepwise multiple logistic regression analysis. Models using all-cause mortality as the dependent variable were determined for the overall population, and then for patients who received appropriate treatment. All variables significant at  $\alpha=0.20$  in univariate analyses were considered as possible predictor variables for the multivariable



**Fig. 1.** The number of patients with vancomycin-resistant *Enterococcus* bloodstream infections (VRE-BSI)/1000 patient-days of care plotted per month at the University Hospital in Birmingham, Alabama. Linear trend added.

analyses. Age was entered into the final model as a continuous variable. The criterion for entry into the models was significance at  $\alpha = 0.20$ , while the criterion for remaining in the model was significance at  $\alpha = 0.05$ . Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated. Model fit was assessed using the Hosmer–Lemeshow goodness-of-fit statistic, and it was determined that all models fit the data well. A potential interaction between intensive-care unit (ICU) stay and ventilator use was evaluated by incorporating an interaction term into the final model. In addition to the primary models, where comorbidities were entered individually, models were constructed using the CCI as a continuous variable.

All statistical tests were two-tailed and were performed using a 0.05 significance level. Statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., USA). This study was approved by the University of Alabama at Birmingham Institutional Review Board.

## RESULTS

Of 237 patient episodes of VRE-BSI that occurred during the study period, 235 had outcome data available and were included in analyses. Over the study period, rates of VRE-BSI increased significantly from a baseline of 0.06 infections/1000 patient-days to 0.17 infections/1000 patient-days ( $P = 0.03$ , Fig. 1). Mean age of patients with VRE-BSI was 53.7 years and 42.3% were male. *Enterococcus faecium* caused

227 (96.6%) VRE-BSI, with the remainder due to *E. faecalis*. Patient characteristics for survivors and non-survivors are shown in Table 1. Frequent underlying illnesses present at the time of VRE-BSI included malnutrition (50.2%), concurrent bloodstream infection (51%), renal insufficiency (48.5%), mechanical ventilation (29.3%), and cancer (30.2%). More than one third (39.2%) of patients were located in an ICU when the index blood cultures were drawn. Medical comorbidities in patients were common; with a CCI score  $\geq 6$  in 149 (63.4%) patients.

All-cause mortality at 30 days was 34.9% (82/235). Significant differences between survivors and non-survivors in univariate analysis included presence of mechanical ventilation (20.3% vs. 46.3%,  $P < 0.001$ ); ICU location (32.0% vs. 52.4%,  $P = 0.002$ ); renal insufficiency (39.2% vs. 65.9%,  $P < 0.001$ ); malnutrition (41.8% vs. 64.6%,  $P = 0.01$ ); receipt of antibiotics active against the VRE isolate (85.0% vs. 73.2%,  $P = 0.03$ ); and mean CCI (5.15 vs. 6.14,  $P = 0.03$ ).

## Independent predictors of mortality

Predictors of mortality in the overall population were explored in a multivariable logistic regression model (Table 2). Factors independently associated with 30-day mortality included mechanical ventilation (OR 3.32, 95% CI 1.7–6.6,  $P = 0.007$ ), renal insufficiency (OR 3.2, 95% CI 1.6–6.3,  $P = 0.007$ ) and malnutrition (OR 2.0, 95% CI 1.0–4.0,  $P = 0.046$ ). There was an association with receipt of VRE-active

Table 1. Characteristics of 235 patients with vancomycin-resistant *Enterococcus* bloodstream infections with comparison of survivors vs. non-survivors using *t* test or  $\chi^2$  analysis

Characteristic	Total <i>n</i> (%) ( <i>n</i> = 235)	Survivors ( <i>n</i> = 153)	Non-survivors ( <i>n</i> = 82)	<i>P</i>
Age (mean $\pm$ s.d.)	53.7 $\pm$ 14.3	52.6 $\pm$ 14.4	55.9 $\pm$ 13.9	0.09
Male sex	99 (42)	68 (44)	31 (38)	0.31
Black race	115 (49)	72 (47)	43 (52)	0.43
Cancer	71 (30)	44 (29)	27 (33)	0.31
Recent surgery	87 (37)	54 (35)	33 (40)	0.43
Leukocytosis	52 (22)	30 (20)	22 (27)	0.20
Mechanical ventilation	69 (29)	31 (20)	38 (46)	<0.001
Intensive-care unit	92 (39)	49 (32)	43 (52)	0.002
Renal insufficiency	114 (49)	60 (39)	54 (66)	<0.001
Liver disease	53 (23)	30 (20)	23 (28)	0.27
Malnutrition	117 (50)	64 (42)	53 (64)	0.01
Diabetes mellitus	82/228 (36)	53/149 (36)	29/79 (37)	0.86
Immunosuppression	52 (22)	35 (23)	17 (21)	0.68
Neutropenia	36 (15)	24 (16)	12 (15)	0.83
Transplant recipient	37 (16)	28 (18)	9 (11)	0.14
Concurrent bloodstream infection	121 (51)	80 (52)	41 (50)	0.73
HIV/AIDS	7 (3)	6 (4)	1 (1)	0.24
ID consultation	34 (15)	27 (18)	7 (9)	0.06
No antibiotic therapy	45 (19)	23 (15)	22 (27)	0.03
Daptomycin therapy	86/190 (45)	54/130 (42)	32/60 (53)	0.14
Linezolid therapy	104/190 (55)	76/130 (58)	28/60 (47)	0.10
Tigecycline therapy	2/190 (1)	2/130 (2)	0/60 (0)	0.56
<i>Enterococcus faecium</i>	227 (97)	147 (96)	80 (98)	0.55
Timing of antibiotics (mean $\pm$ s.d.)	2.65 $\pm$ 1.6	2.78 $\pm$ 1.7	2.36 $\pm$ 1.4	0.17
CCI (mean $\pm$ s.d.)	5.5 $\pm$ 2.9	5.15 $\pm$ 2.9	6.14 $\pm$ 2.7	0.03

CCI, Charlson comorbidity index, HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; ID, infectious diseases; s.d., standard deviation.

Table 2. Multivariable logistic regression analysis\* of factors related to 30-day mortality in the overall population (*n* = 235)

Variable	Univariate		Multivariable†	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Age	1.0 (0.9–1.04)	0.09		
Male sex	0.8 (0.4–1.3)	0.31		
Black race	1.2 (0.7–2.1)	0.43		
Ventilator	3.4 (1.9–6.1)	<0.001	3.32 (1.7–6.6)	0.007
Intensive-care unit location	2.3 (1.4–4.1)	0.003		
Renal insufficiency	3.0 (1.7–5.2)	<0.001	3.2 (1.6–6.3)	0.007
Malnutrition	2.2 (1.2–4.1)	0.01	2.0 (1.0–4.0)	0.046
Antibiotic treatment (vs. no antibiotic treatment)	0.5 (0.25–0.93)	0.03	0.53 (0.2–1.2)	0.13
ID consultation	0.4 (0.2–1.05)	0.06	0.4 (0.2–1.2)	0.06
Transplant	0.5 (0.2–1.2)	0.14		

OR, Odds ratio; CI, confidence interval.

\* Logistic regression analysis. Variables with *P* < 0.20 on univariate analysis were included in a multivariable stepwise regression model in addition to variables for race and sex. Results are listed for variables with *P* < 0.20. *P* values obtained are two-tailed.

† Each of the multivariable odds ratios are adjusted for all of the other variables remaining in the final model.

Table 3. *Multivariable logistic regression analysis of factors related to 30-day mortality in patients who received vancomycin-resistant Enterococcus-active therapy (n = 190)\*†*

Variable	Univariate OR (95% CI)	P	Multivariable‡ OR (95% CI)	P
Age	1.01 (0.99–1.03)	0.40		
Male sex	0.9 (0.5–1.6)	0.67		
Black race	1.4 (0.7–2.5)	0.32		
Ventilator	3.1 (1.6–6.0)	<0.001	3.4 (1.5–7.7)	0.003
Intensive-care unit	2.2 (1.2–4.1)	0.01		
Renal insufficiency	3.2 (1.7–6.0)	<0.001	4.1 (1.9–9.1)	0.004
Malnutrition	1.8 (0.9–3.7)	0.01		
Daptomycin (vs. linezolid)	1.6 (0.87–3.0)	0.13	2.1 (0.99–4.7)	0.052
Liver disease	1.7 (0.8–3.6)	0.16		
Timing of antibiotics	0.8 (0.7–1.0)	0.09	0.8 (0.55–1.0)	0.051
Transplant	0.4 (0.15–1.1)	0.07	0.2 (0.06–0.8)	0.027

OR, Odds ratio; CI, confidence interval.

\* Logistic regression analysis. Variables with  $P < 0.20$  on univariate analysis were included in a multivariable stepwise regression model in addition to variables for age, sex and race. Results are listed for variables with  $P < 0.10$ .  $P$  values obtained are two-tailed.

† Due to limited sample size two patients treated with tigecycline were not included in this analysis.

‡ Each of the multivariable odds ratios are adjusted for all of the other variables remaining in the final model.

antibiotics and increased survival (OR 0.53, 95% CI 0.2–1.2,  $P = 0.13$ ), but this was not statistically significant. In a model with age, sex, race, timing of antibiotics, transplant and CCI (instead of individual comorbidities), CCI was an independent predictor of mortality (OR 1.13, 95% CI 1.03–1.25,  $P = 0.01$ ).

### VRE antimicrobial therapy

Linezolid was the primary therapy for VRE-BSI in 104 (44%) patients, daptomycin in 86 (37%) patients and tigecycline in two (1%) patients. No patient received quinupristin-dalfopristin. The remaining 43 (18%) did not receive VRE-specific therapy. Of those who did not receive specific antimicrobial therapy, 22 (51%) out of 43 died by day 30. Eighteen (42%) out of 43 died before blood culture results were identified as VRE.

Microbiological failure occurred in 18 (17.5%) patients treated with linezolid and 25 (29%) patients treated with daptomycin. No failure occurred in two patients treated with tigecycline. There were 28 (27%) deaths in patients treated with linezolid, 32 (37.2%) deaths in patients treated with daptomycin and no deaths in patients treated with tigecycline. Concurrent bloodstream infection was noted in 50/86

(58%) patients in the daptomycin group and 54/104 (52%) patients in the linezolid group.

A multivariable logistic regression analysis was conducted to identify independent predictors of mortality for those patients who received VRE-active therapy (Table 3). Patients treated with tigecycline were excluded from the analysis because of limited sample size. In this population of 190 patients, mechanical ventilation (OR 3.4, 95% CI 1.5–7.7,  $P = 0.003$ ) and renal insufficiency (OR 4.1, 95% CI 1.9–9.1,  $P < 0.001$ ) were predictors of increased mortality. Receipt of a solid organ or stem cell transplant was associated with improved survival (OR 0.2, 95% CI 0.06–0.8,  $P = 0.027$ ). Delayed administration of antibiotics was associated with decreased mortality (OR 0.8, 95% CI 0.55–1.00,  $P = 0.051$ ), but this was not significant. In addition, there was an association of daptomycin therapy and increased mortality (OR 2.1, 95% CI 0.99–4.7,  $P = 0.052$ ), but this did not reach statistical significance. In a model with age, sex, race, timing of antibiotics, transplant and CCI (instead of individual comorbidities), only CCI was an independent predictor of mortality (OR 1.13, 95% CI 1.00–1.29,  $P = 0.03$ ).

Characteristics of patients receiving either linezolid or daptomycin were compared in a sub-analysis

Table 4. Characteristics of patients treated with linezolid ( $n=104$ ) or daptomycin ( $n=86$ )

Characteristic	Linezolid $n=104$ (%)	Daptomycin $n=86$ (%)	<i>P</i>
Age, mean $\pm$ s.d.	54.5 $\pm$ 14.3	50.1 $\pm$ 13.5	0.52
Male sex	42 (40)	41 (48)	0.28
Black race	47(45)	41 (48)	0.73
Cancer	28 (27)	32 (37)	0.11
Recent surgery	47 (45)	28 (33)	0.09
Leukocytosis	28 (27)	15 (17)	0.12
Ventilator	30 (29)	24 (28)	0.90
Intensive-care unit	43 (41)	33 (38)	0.67
Renal insufficiency	48 (46)	42 (49)	0.71
Liver disease	25/84 (30)	14/76 (18)	0.10
Malnutrition	51/82 (62)	41/74 (55)	0.39
Diabetes	38 (37)	32 (37)	0.80
Immunosuppressives	25 (24)	19 (22)	0.80
Neutropenia	8 (8)	25 (29)	<0.001
Transplant	15 (15)	14 (16)	0.70
Concurrent bloodstream infection	54 (52)	50 (58)	0.43
ID consultation	25 (24)	7 (8)	0.003
HIV/AIDS	2 (2)	3 (3)	0.50
<i>Enterococcus faecium</i>	101 (99)	85 (99)	0.41
Timing of antibiotics (mean $\pm$ s.d.)	2.38 $\pm$ 1.7	2.25 $\pm$ 1.5	0.58
CCI (mean $\pm$ s.d.)	5.0 $\pm$ 2.8	4.6 $\pm$ 2.8	0.4

CCI, Charlson comorbidity index, HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; ID, infectious diseases; s.d., standard deviation.

(Table 4). Neutropenia was more common in patients who received daptomycin (29% vs. 7.7%,  $P<0.001$ ); and ID consultation was more common in patients who received linezolid (24.0% vs. 8.1%,  $P=0.003$ ). Overall duration of therapy was a median of 11 days (range 3–47 days), and was not significantly different between the two groups.

## DISCUSSION

This retrospective cohort study of 235 patients represents one of the largest published investigations of nosocomial VRE-BSI. Our findings provide important insights into the epidemiology and management of this growing health problem. For example, we observed an almost threefold increase in VRE-BSI incidence during the 2.5-year study period. We also report a 30-day all-cause mortality of 35%, consistent with previous observations [2–12]. These data provide ‘real world’ evidence that VRE-BSI is a growing problem for hospitalized patients in the USA [2, 3, 21, 22].

A crucial component of the epidemiology of VRE-BSI is the identification of factors that relate to patient outcomes. Previous studies found CCI,

number of positive blood cultures, parenteral nutrition, severity of illness, decreased renal function, liver disease, malignancy, and prior VRE infection to be associated with poor outcomes in cases of VRE infection [4, 5, 7, 16–18]. Most of these studies were conducted when there were relatively limited treatment options for VRE. Our study confirmed several previous findings. In both the overall population and those receiving antibiotics, renal insufficiency and mechanical ventilation were independent predictors of increased mortality [5, 7, 17, 23]. Similarly to the recent study from Camins and colleagues [17], we also observed that CCI was a significant predictor of mortality. Previous studies have not specifically addressed lack of antibiotics and mortality. In our cohort, treatment with a VRE-active antimicrobial was associated with improved survival in univariate analysis ( $P=0.03$ ). Although these findings did not reach statistical significance in multivariable analysis ( $P=0.13$ ), we favour treatment for patients with VRE-BSI.

Providers at our institution prescribed daptomycin and linezolid frequently; prescribed tigecycline infrequently; and did not use quinupristin-dalfopristin.

Antimicrobial stewardship guidelines during the study period required ID consultation or specific approval prior to use of quinupristin-dalfopristin and tigecycline, which probably led to decreased use of these agents. However, the lack of consensus on treatment strategy is also probably related to lack of published data to guide therapy. To date, there are few retrospective observational investigations comparing treatment options for VRE-BSI [5, 16]. Furthermore, most data supporting the use of newer agents with *in vitro* activity against VRE, i.e. daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline, are based on case series and case reports [5, 13–16, 24–31]. Additional research, preferably an adequately powered randomized controlled trial, is needed to determine optimal selection of antimicrobial therapy in this context.

When limiting our analysis to patients who received VRE-active antimicrobial therapy, use of daptomycin showed a trend towards an association with mortality, but was not significant in multivariable analysis ( $P=0.052$ ). Our observations that daptomycin therapy may be associated with poorer outcomes when compared to linezolid were unexpected; however, ours is the second investigation to suggest a potential difference. In a retrospective study of 98 patients with VRE bacteraemia, Mave and colleagues [16] demonstrated a trend towards higher mortality with daptomycin when compared to linezolid. Our observations, while similar, should not be considered conclusive, as they are possibly influenced by several important factors. First, when we forced the CCI into the multivariable model (data not shown), the association of daptomycin and mortality was less pronounced (OR 1.7), suggesting that ‘sicker’ people received daptomycin therapy. Second, there were important differences in patients who received daptomycin or linezolid therapy, including neutropenia and number of ID consultations. Differences in ID consultation may be relevant, as published reports demonstrate decreased mortality in patients with candidaemia and staphylococcal bacteraemia in patients who received ID consultation [32, 33]. Last, our finding that transplant patients had a lower mortality is probably spurious and suggests confounding in this investigation. Although our data are limited by being observational in nature, further research into the comparative effectiveness of these two agents is warranted.

Our study has several other limitations. A high number of concurrent bloodstream infections ( $n=120$ ) was observed. The high frequency of

bloodstream infection (51%) is probably the result of our generous time-frame for concurrent infection ( $\pm 14$  days). Although the majority of patients in our cohort received effective therapy for concurrent bloodstream infection ( $>90\%$ ), the bloodstream isolates were heterogeneous in grade of bacteraemia (number of positive cultures) and causative organism, e.g. *Klebsiella*, *Candida*, *Staphylococcus*, and other species. Future studies should consider a different time interval ( $+7/-2$  days) and make specific adjustments for type and grade of bloodstream infection. Although this represents a large cohort of VRE-BSI patients, some analyses were limited by small variable frequencies. Our study did not evaluate treatment of concurrent pneumonias. As daptomycin has limited efficacy in lung parenchyma, there may have been increased mortality due to pulmonary infections not captured. We were unable to determine appropriate dosing or levels of daptomycin in patients on haemodialysis. As this was a retrospective study, we were unable to collect robust severity-of-illness data such as APACHE scores.

In conclusion, this investigation confirms that VRE-BSI continue to be a challenging problem and are associated with increased mortality. Our observations on ‘real-world’ management of VRE-BSI indicate that limited clinical trial data has led to treatment equipoise. Given the growing burden of disease and the serious consequences of infection, there is a pressing need to understand optimal management of VRE-BSI, especially the impact of newer antimicrobial therapy. Identifying predictors of mortality in VRE-BSI patients treated with newer antimicrobial agents may aid in future study design.

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## DECLARATION OF INTEREST

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