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Clinical epidemiology of vancomycin-resistant *Enterococcus gallinarum* and *Enterococcus casseliflavus* bloodstream infections

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Abstract

This study aimed to evaluate the clinical outcomes of vancomycin-resistant enterococcal bloodstream infections (VRE BSI) caused by *Enterococcus gallinarum* or *Enterococcus casseliflavus*. Variables associated with treatment failure were determined and treatment options were compared. This was a national retrospective study of hospitalised Veterans Affairs patients with non-*faecium*, non-*faecalis* VRE BSI. The primary outcome was treatment failure, defined as a composite of: (i) 30-day all-cause mortality; (ii) microbiological failure; and (iii) 30-day VRE BSI recurrence. Stepwise Poisson regression was conducted to determine variables associated with treatment failure. In total, 48 patients were included, with 29 cases (60.4%) caused by *E. gallinarum* and 19 cases (39.6%) caused by *E. casseliflavus*. Among these cases, 20 (41.7%) were treated with an anti-VRE agent (linezolid or daptomycin) and 28 (58.3%) were treated with an anti-enterococcal β-lactam. Overall, 30-day mortality was 10.4% (5/48) and composite treatment failure was 39.6% (19/48). In multivariate analysis, treatment with an anti-enterococcal β-lactam was associated with increased treatment failure in comparison with anti-VRE therapy (adjusted risk ratio = 1.73, 95% confidence interval 1.06–4.97; $P = 0.031$). Overall, treatment with linezolid or daptomycin for vancomycin-resistant *E. gallinarum or E. casseliflavus* BSI resulted in improved clinical outcomes in comparison with anti-enterococcal β-lactam treatment.

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Ethical approval: This study was approved by the Kansas City Veterans Affairs Institutional Review Board (Kansas City, KS) [study #00766], and a waiver of informed consent was obtained.

Keywords

Vancomycin-resistant enterococci; Bloodstream infection; Daptomycin; Linezolid

1. Introduction

Vancomycin-resistant enterococci (VRE) are becoming an increasingly important cause of invasive infection in the USA [1,2]. The most common type of enterococcal vancomycin resistance is high-level resistance associated with acquisition of the *vanA* and *vanB* genes, typically observed in *Enterococcus faecium* and *Enterococcus faecalis* isolates [3]. These isolates comprise the majority of VRE bloodstream infection (BSI) isolates and are associated with significant mortality [4]. Conversely, the *vanC* genotype is associated with constitutive low-level vancomycin resistance and is intrinsic to *Enterococcus gallinarum* and *Enterococcus casseliflavus* [5]. Whilst these strains exhibit resistance to vancomycin, ampicillin susceptibility is typically retained [5]. Treatments options also include linezolid, which is bacteriostatic against *E. gallinarum* and *E. casseliflavus*, as well as daptomycin, which exhibits bactericidal activity against *vanC*-type enterococci [6].

Non-*faecium*, non-*faecalis* VRE are implicated in only 1–2% of VRE BSI cases [7,8]. However, the prevalence of these infections is likely underestimated due to limitations in detection and identification [9]. Motility and pigmentation tests may help differentiate between *Enterococcus* spp., although these methods are not always reliable [9,10]. Molecular identification methods such as multiplex PCR have been developed to better identify *Enterococcus* spp., but these assays are complex and are not available in the majority of clinical microbiology laboratories [10].

The clinical significance of non-*faecium*, non-*faecalis* VRE BSI is unclear. Although these infections remain relatively rare, they have been associated with severe invasive disease [5,7,11]. Little is known about the clinical epidemiology of non-*faecium*, non-*faecalis* VRE BSI. In a recent study, only immunocompromised status was a significant predictor of mortality in patients with these infections [11]. Still less is known about the optimal treatment of non-*faecium*, non-*faecalis* VRE BSI. To our knowledge, there are no comparative data investigating available treatment options for such infections.

Therefore, the objectives of this study were to describe the clinical outcomes of vancomycin-resistant *E. gallinarum* and *E. casseliflavus* BSIs, to determine variables associated with treatment failure and to compare clinical outcomes between treatment strategies.

2. Materials and methods

2.1. Population

This was a national retrospective cohort study of hospitalised patients admitted to any Veterans Affairs Medical Center (VAMC) between 1 January 2010 and 1 January 2013. All adult patients with at least one blood culture positive for *E. gallinarum* or *E. casseliflavus* with a susceptibility profile consistent with the *vanC* genotype [vancomycin minimum

inhibitory concentration (MIC) of 4–32 μg/mL plus ampicillin susceptibility] were eligible for inclusion. Because corresponding clinical isolates were not available for additional in vitro analysis or genotyping, the susceptibility profile was used as an indicator of the *vanC* genotype. Patients treated with an anti-VRE agent (daptomycin or linezolid) or an intravenous anti-enterococcal β-lactam (ampicillin, ampicillin/sulbactam, imipenem/cilastatin, ticarcillin/clavulanic acid or piperacillin/tazobactam) for <72 h or those treated with sequential therapy were excluded. In recurrent VRE BSI, only the first case encountered in the study period was analysed. This study was approved by the Kansas City VAMC Institutional Review Board (Kansas City, KA), and a waiver of informed consent was obtained.

2.2. Data sources

National clinical databases comprised of inpatient, outpatient and administrative data were queried to identify patients meeting the study criteria. Data extracted from these databases included patient demographics, facility information, laboratory and microbiology data, vital signs, antimicrobial treatment data, co-morbidities and admission records. In addition, retrospective review of the electronic medical record was conducted to determine the source of infection as documented by a treating physician and categorised according to site (line, genitourinary, abdominal/biliary). If no source was discernible from review of the electronic medical record, the source was designated as undocumented. Bacterial identification and susceptibility to antimicrobial agents were determined during routine clinical care.

2.3. Outcomes

The primary outcome was treatment failure, defined as the occurrence of any of the following: (i) 30-day all-cause mortality; (ii) microbiological failure (lack of microbiological clearance among those with at least one follow-up blood culture during the antimicrobial treatment period); and (iii) recurrence of VRE BSI within 30 days of therapy completion. Secondary outcomes were hospital mortality and time to microbiological cure. Microbiological cure was defined as microbiological clearance among those with at least one follow-up blood culture. Hospital mortality was defined as death while hospitalised for non-*faecium*, non-*faecalis* VRE BSI.

2.4. Statistical analysis

Baseline categorical variables were compared by χ^2 or two-tailed Fisher's exact test and continuous variables were compared by Mann–Whitney *U*-test. Treatment for non-*faecium*, non-*faecalis* VRE BSI was categorised as either: (i) anti-VRE therapy (linezolid or daptomycin); or (ii) anti-enterococcal β-lactam therapy. Variables that were associated with treatment classification or composite treatment failure ($P < 0.2$) were entered into a forward stepwise Poisson regression model with robust variance estimates. In contrast to logistic regression, Poisson regression provides an accurate estimation of risk when the study outcome is common (>10%). A time-to-event analysis was conducted for microbiological cure using the Kaplan–Meier method, with differences in outcome distributions for treatment groups compared using the log-rank test. Forward stepwise Cox regression analysis was also performed. For time-dependent analyses, cases that did not experience microbiological cure were right-censored at the end of treatment. All statistical analyses

were performed using SAS v.9.3 (SAS Institute Inc., Cary, NC) with statistical significance designated as a two-tailed *P*-value of <0.05.

3. Results

A total of 86 cases of non-*faecium*, non-*faecalis* VRE BSI met the inclusion criteria during the study period. Of those cases, patients were excluded due to treatment <72 h ($n = 28$) or recurrent infection ($n = 10$). Thus, 48 patients were included in the final analysis, with 29 cases (60.4%) caused by *E. gallinarum* and 19 cases (39.6%) caused by *E. casseliflavus*. Of these cases, 20 (41.7%) were treated with an anti-VRE agent and 28 (58.3%) were treated with an anti-enterococcal β-lactam. Among patients treated with an anti-VRE agent, 8 (40.0%) were treated with linezolid and 12 (60.0%) were treated with daptomycin. All patients treated with linezolid were given 600 mg doses twice daily. The median daptomycin dose was 6.12 mg/kg (interquartile range 5.40–6.54 mg/kg). No patients were treated with daptomycin doses >8 mg/kg. Anti-enterococcal β-lactam agents utilised included ampicillin ($n = 6$), ampicillin/sulbactam ($n = 3$), imipenem/cilastatin ($n = 1$), ticarcillin/clavulanic acid ($n = 1$) and piperacillin/tazobactam ($n = 17$). No patients received synergistic aminoglycoside therapy.

Individuals in this study were treated at 23 distinct VAMCs across 20 US states. All corresponding isolates were susceptible to ampicillin, linezolid and daptomycin. In this cohort, treatment failure occurred in 19 (39.6%) of 48 cases. Mortality within 30 days was relatively rare, occurring in only 5 cases (10.4%). A comparison of factors associated with treatment failure is included in Table 1. As can be seen, anti-enterococcal β-lactam treatment, polymicrobial bacteraemia and abdominal/biliary source of infection were significantly associated with treatment failure in univariate analysis. Conversely, undocumented source of infection was associated with successful treatment.

Baseline characteristics were also compared by treatment classification (Table 2). In unadjusted analysis, patients treated with an anti-VRE agent were significantly more likely to have a line source of infection, whilst patients treated with an anti-enterococcal β-lactam were more likely to have an abdominal/biliary source of infection. There was a trend toward more intensive care unit admissions among patients treated with an anti-VRE agent, and more co-morbid diabetes mellitus (uncomplicated) in patients treated with an anti-enterococcal β-lactam.

A comparison of clinical outcomes by treatment classification is included in Table 3 (reference group, β-lactam treatment). As shown, the increased composite treatment failure associated with anti-enterococcal β-lactam treatment was driven primarily by differences in microbiological failure and 30-day recurrence. No differences in 30-day all-cause or hospital mortality were observed between treatment groups. Variables that were selected in the final parsimonious Poisson regression model for treatment failure included anti-enterococcal β-lactam treatment, abdominal/biliary source of infection and polymicrobial bacteraemia. The relationship between increased failure among those treated with an anti-enterococcal β-lactam persisted in this model (Supplementary Table S1) [adjusted risk ratio = 1.73, 95% confidence interval (CI) 1.06–4.97; $P = 0.031$]. In comparison with anti-enterococcal β-

lactam treatment, treatment with linezolid or daptomycin also resulted in significantly reduced time to microbiological cure (log-rank $P = 0.048$). This association persisted in stepwise Cox regression after adjusting for polymicrobial bacteraemia (adjusted hazard ratio = 2.27, 95% CI 1.03–4.98; $P = 0.041$).

4. Discussion

The present study aimed to describe clinical outcomes among patients with vancomycin-resistant *E. gallinarum* or *E. casseliflavus* BSIs, to determine variables associated with these outcomes and to compare treatment options. To our knowledge, this is the first nationwide study from the USA investigating non-*faecium*, non-*faecalis* VRE BSI and the first to provide data comparing treatments. Consistent with previous research, mortality associated with non-*faecium*, non-*faecalis* enterococcal BSI was relatively low [8,11]. Although the present study included only cases of enterococcal BSI caused by species intrinsically resistant to vancomycin, the mortality rate observed was not profoundly different from studies including vancomycin-susceptible cases of non-*faecium*, non-*faecalis* enterococcal BSI [12]. Overall, 30-day mortality in non-*faecium*, non-*faecalis* VRE BSI appears to be much less than proportions reported in studies of VRE BSI caused by *E. faecium* or *E. faecalis* [12,13]. Treatment failure also appears to occur less frequently, suggesting lower virulence relative to *E. faecium* and *E. faecalis* strains [12]. However, additional host–pathogen interactions and patient-specific factors should be considered, as the overall co-morbidity burden and severity of illness were lower in this cohort than in previous studies of VRE BSI caused by *E. faecium* and *E. faecalis* [13].

Consistent with previous studies, abdominal/biliary source of infection was frequent [5,12]. Although abdominal/biliary source was associated with increased treatment failure, it was not associated with greater time to microbiological cure in Cox regression. Anti-enterococcal β-lactam treatment and polymicrobial bacteraemia were consistently associated with poorer outcomes in multivariate analyses. The increased treatment failure observed in patients treated with an anti-enterococcal β-lactam was partially driven by differences in microbiological cure rates. Not only did microbiological clearance occur more frequently among patients treated with an anti-VRE agent, it also occurred sooner in the course of therapy. Treatment with an anti-VRE agent also resulted in less 30-day recurrence of VRE BSI. The reason for these differences in clinical outcomes is uncertain. Anti-enterococcal β-lactam monotherapy and linezolid are bacteriostatic against *Enterococcus* spp., whilst daptomycin is typically bactericidal. Bactericidal activity can be achieved with β-lactams through the use of low-dose aminoglycoside therapy synergy; however, this strategy was not utilised for any patients in the present study. It has previously been hypothesised that bactericidal activity may result in improved outcomes in VRE BSI, but this has not yet been demonstrated in clinical studies. Among patients treated with an anti-VRE agent, treatment failure did not differ significantly between daptomycin- and linezolid-treated subjects [23.1% (3/13) vs. 14.3% (1/7)]. Therefore, the improved clinical outcomes observed cannot be attributed to bactericidal activity alone.

Another possible explanation for the observed treatment difference is that in vitro ampicillin activity was not wholly predictive of activity to other anti-enterococcal β-lactams. Clinically,

ampicillin susceptibility is commonly used as a surrogate marker for susceptibility to other anti-enterococcal β-lactams [14]. Indeed, this was the case for the present investigation, as only 9 (32.1%) of 28 patients treated with an anti-enterococcal β-lactam were given an ampicillin-containing antibiotic. Newer evidence suggests that ampicillin activity may not be predictive of carbapenem or piperacillin/tazobactam activity in certain strains of *E. faecalis* [14]. To our knowledge, there are no such data with *vanC*-type enterococci; however, we believe this warrants future investigation.

This study has a number of noteworthy limitations. The difference in composite treatment failure observed was largely driven by differences in microbiological cure rate, which is dependent on the frequency of follow-up blood cultures. This practice may vary between practitioners and cannot be adequately controlled in a retrospective observational study. In addition, multiple antimicrobial agents were grouped into treatment classification groups. Owing to the limited number of patients in this study, we were unable to compare individual antimicrobial agents within these classifications. Therefore, we are unable to determine a treatment of choice for non-*faecium*, non-*faecalis* VRE BSI based on the results of this study alone, and further research in this area is warranted. Standard 6 mg/kg doses of daptomycin were used in all cases treated with this agent. There is increasing evidence to support the use of high-dose daptomycin in the treatment of *E. faecium* and *E. faecalis* VRE BSI, but there are limited data investigating the use of these doses against non-*faecium*, non-*faecalis* VRE isolates [15]. Owing to the retrospective nature of this study, corresponding blood isolates were not available for *van* genotyping or assessment of overall MIC distribution. Lastly, owing to the limited number of patients in this study, we were left underpowered to evaluate differences in some secondary outcomes, including hospital mortality.

Whilst increased use of daptomycin or linezolid for the treatment of non-*faecium*, non-*faecalis* VRE BSI may provide selective pressure for resistance to these agents among other VRE species and Gram-positive pathogens, we do not anticipate this would have a large public health impact owing to the relative rarity of these infections. Because aminoglycosides were not utilised for β-lactam synergy in this study, we cannot exclude the possibility that clinical outcomes may be comparable between such a strategy and anti-VRE therapy without increasing the overall use of daptomycin and linezolid in clinical practice.

4.1. Conclusions

In summary, 30-day all-cause mortality was 10.4% and composite treatment failure was 39.6% among cases of vancomycin-resistant *E. gallinarum* and *E. casseliflavus* BSI in a national observational study. In multivariate analysis, treatment with an anti-enterococcal β-lactam agent rather than anti-VRE therapy with linezolid or daptomycin was associated with increased treatment failure. Treatment with an anti-enterococcal β-lactam agent was also associated with increased microbiological failure and recurrent infection. Other factors associated with treatment failure in multivariate analysis were abdominal/biliary source of infection and polymicrobial bacteraemia. Overall, treatment with linezolid or daptomycin for non-*faecium*, non-*faecalis* VRE BSI appeared to result in improved clinical outcomes; however, no difference in mortality was observed. These results should be further replicated

in a prospective investigation; however, this is likely not feasible given the low overall incidence of these infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- 30-day mortality was 10.4% among *vanC*-type vancomycin-resistant enterococcal bloodstream infections (VRE BSIs).
- Composite treatment failure was 39.6% among *vanC*-type VRE BSIs.
- Treatment with anti-VRE agents lowered treatment failure in *vanC*-type VRE BSIs.

Table 1

Patient characteristics by treatment outcome for non-*faecium*, non-*faecalis* vancomycin-resistant enterococcal bloodstream infections (VRE BSIs)

Characteristic	Treatment success (*n* = 29)[a]	Treatment failure (*n* = 19)[a]	*P*-value[b]
Age (years) [median (IQR)]	65 (57–78)	70 (59–78)	0.506
Male sex	29 (100)	18 (94.7)	0.396
β-Lactam treatment	13 (44.8)	15 (78.9)	0.019
Enterococcus gallinarum BSI	18 (62.1)	11 (57.9)	0.772
Enterococcus casseliflavus BSI	11 (37.9)	8 (42.1)	0.772
Polymicrobial bacteraemia[c]	3 (10.3)	7 (36.8)	0.036
Infection source			
Line	12 (41.4)	7 (36.8)	0.753
Genitourinary	2 (6.9)	1 (5.3)	1.000
Abdominal/biliary	3 (10.3)	11 (57.9)	0.001
Undocumented	12 (41.4)	0 (0.0)	0.001
Facility complexity level[d]			
1a	22 (75.9)	16 (84.2)	0.486
1b	3 (10.3)	0 (0.0)	0.267
1c	3 (10.3)	2 (10.5)	1.000
2	1 (3.4)	1 (5.3)	1.000
ICU admission	13 (44.8)	8 (42.1)	0.853
Charlson co-morbidity index [median (IQR)]	4 (3–5)	3 (3–4)	0.940
Past myocardial infarction	0 (0.0)	1 (5.3)	1.000
Congestive heart failure	1 (3.4)	0 (0.0)	1.000
Peripheral vascular disease	1 (3.4)	0 (0.0)	1.000
Cerebrovascular disease	1 (3.4)	1 (5.3)	1.000
Dementia	2 (6.9)	1 (5.3)	1.000
Mild liver disease	0 (0.0)	2 (10.5)	0.152
Diabetes, uncomplicated	4 (13.8)	1 (5.3)	0.635
Diabetes, with end-organ damage	1 (3.4)	0 (0.0)	1.000
Hemiplegia	1 (3.4)	0 (0.0)	1.000
Moderate or severe renal disease	2 (6.9)	0 (0.0)	0.512
Any malignancy	2 (6.9)	0 (0.0)	0.512
Peptic ulcer disease	4 (13.8)	2 (10.5)	1.000
Neutropenia	6 (20.7)	3 (15.8)	1.000
APACHE II score [median (IQR)]	6 (3–9)	5 (3–6)	0.525

IQR, interquartile range; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation.

[a] Data are *n* (%) unless otherwise stated.

[b] Categorical variables were compared by χ^2 or Fisher's exact test, and continuous variables were compared by Mann–Whitney *U*-test.

[c] ±72 h of index VRE blood culture.

[d] Facility complexity designation at the time of index non-*faecium*, non-*faecalis* VRE blood culture. Facility complexity levels are determined based on patient population, complexity of clinical services and education/research, with level 1a designated as the most complex.

Table 2

Patient characteristics by treatment classification for non-*faecium*, non-*faecalis* vancomycin-resistant enterococcal bloodstream infections (VRE BSIs)

Characteristic	β-Lactam treatment (*n* = 28)[a]	Anti-VRE treatment (*n* = 20)[a]	*P*-value[b]
Age (years) [median (IQR)]	67 (59–77)	65 (57–78)	0.818
Male sex	27 (96.4)	20 (100)	1.000
Enterococcus gallinarum BSI	16 (57.1)	13 (65.0)	0.583
Enterococcus casseliflavus BSI	12 (42.9)	7 (35.0)	0.583
Polymicrobial bacteraemia[c]	5 (17.9)	5 (25.0)	0.721
Infection source			
Line	6 (21.4)	13 (65.0)	0.003
Genitourinary	3 (10.7)	0 (0.0)	0.255
Abdominal/biliary	13 (46.4)	1 (5.0)	0.003
Undocumented	6 (21.4)	6 (30.0)	0.520
Facility complexity level[d]			
1a	23 (82.1)	15 (75.0)	0.721
1b	2 (7.1)	1 (5.0)	1.000
1c	3 (10.7)	2 (10.0)	1.000
2	0 (0.0)	2 (10.0)	0.168
ICU admission	9 (32.1)	12 (60.0)	0.055
Charlson co-morbidity index [median (IQR)]	4 (3–5)	4 (3–5)	0.708
Past myocardial infarction	1 (3.6)	0 (0.0)	1.000
Congestive heart failure	1 (3.6)	0 (0.0)	1.000
Peripheral vascular disease	0 (0.0)	1 (5.0)	0.417
Cerebrovascular disease	1 (3.6)	1 (5.0)	1.000
Dementia	1 (3.6)	2 (10.0)	0.563
Mild liver disease	2 (7.1)	0 (0.0)	0.504
Diabetes, uncomplicated	5 (17.9)	0 (0.0)	0.046
Diabetes, with end-organ damage	1 (3.6)	0 (0.0)	1.000
Hemiplegia	1 (3.6)	0 (0.0)	1.000
Moderate or severe renal disease	1 (3.6)	1 (5.0)	1.000
Any malignancy	2 (7.1)	0 (0.0)	0.504
Peptic ulcer disease	2 (7.1)	4 (20.0)	0.218
Neutropenia	3 (10.7)	6 (30.0)	0.137
APACHE II score [median (IQR)]	6 (3–7)	6 (3–6)	0.757

IQR, interquartile range; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation.

[a] Data are *n* (%) unless otherwise stated.

[b] Categorical variables were compared by χ^2 or Fisher's exact test, and continuous variables were compared by Mann–Whitney *U*-test.

[c] ±72 h of index VRE blood culture.

[d] Facility complexity designation at the time of index non-*faecium*, non-*faecalis* VRE blood culture. Facility complexity levels are determined based on patient population, complexity of clinical services and education/research, with level 1a designated as the most complex.

Table 3

Clinical outcomes by treatment classification for non-*faecium*, non-*faecalis* vancomycin-resistant enterococcal bloodstream infections (VRE BSIs)

Outcome	RR (95% CI)	*P*-value
Treatment failure	2.62 (1.03–6.65)	0.019
30-day all-cause mortality	1.51 (0.50–4.54)	0.380
Microbiological failure [a]	1.76 (1.18–2.62)	0.030
30-day VRE BSI recurrence	1.95 (1.45–2.63)	0.032
Hospital mortality	1.20 (0.57–2.51)	0.600

RR, risk ratio; CI, confidence interval.

Reference group: β-lactam treatment.

[a]Percentages among those with at least one follow-up blood culture drawn during treatment period.