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Short Communication

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 multivariable 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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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*

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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 univariable 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 towards 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