International Journal of Antimicrobial Agents 53 (2019) 761–766

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

β-lactam antibiotics vs. vancomycin for the early treatment of enterococcal bacteraemia: A retrospective cohort study

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ARTICLE INFO

Article history:
Received 23 November 2018
Accepted 27 March 2019

Editor: Stefania Stefani

Keywords:
Enterococcus
Bacteraemia
Ampicillin
Vancomycin
Beta-lactams

ABSTRACT

Background: The efficacy of vancomycin compared with ampicillin for enterococcal infections is unknown. This study aimed to compare their efficacy among patients with enterococcal bacteraemia.

Methods: Retrospective cohort study including adults aged >16 years with enterococcal bacteraemia, treated with β-lactam antibiotics active against *Enterococcus* spp. or vancomycin. Treatment classification was based on the first antibiotic used for >4 days in the 7 days after blood culture collection. Subgroup analyses for patients with penicillin-susceptible enterococcal bacteraemia and patients with monomicrobial penicillin-susceptible enterococcal bacteraemia were performed. The dependent variable was 30-day all-cause mortality. The propensity score (PS) for vancomycin treatment was calculated. Univariate and multi-variate analyses adjusted for PS were performed.

Results: In total, 516 patients with enterococcal bacteraemia were included. Mortality was similar for patients treated with β-lactams (123/315, 39%) and vancomycin (82/201, 40.8%). Independent factors significantly associated with mortality included healthcare-associated or hospital-acquired infection, age, female sex, Charlson Comorbidity Index, dialysis, SOFA score and low albumin. After adjustment for these factors and PS, the odds ratio (OR) for death in patients treated with vancomycin was 0.95 [95% confidence interval (CI) 0.56–1.59]. Results were similar among patients with penicillin-susceptible enterococcal bacteraemia and patients with monomicrobial penicillin-susceptible enterococcal bacteraemia (n=237, adjusted OR 0.59, 95% CI 0.25–1.43).

Conclusion: No difference in mortality was observed following treatment with a β-lactam or vancomycin among patients with enterococcal bacteraemia. Vancomycin is not recommended for the treatment of penicillin-susceptible enterococcal infections; however, when needed, it is not inferior to β-lactams and the addition of a β-lactam is not necessary.

1. Introduction

Enterococci are a common cause of community and hospital-acquired bloodstream infections, accounting for approximately 6% and 10% of these infections, respectively [1,2]. Mortality rates for enterococcal bacteraemia range from 20% for ampicillin-susceptible strains [3] to 32% for vancomycin-resistant strains [4], partially attributed to severe comorbid conditions.

β-lactam antibiotics and glycopeptides constitute the backbone of therapy for enterococcal infections, despite intrinsic partial resistance of enterococci to both antibiotic classes. Tolerance to penicillins is mediated by production of class B penicillin-binding protein 5 (PBP5) which has a low affinity to penicillins. Even in the presence of β-lactam antibiotics, which saturate most enterococcal PBP, PBP5 is still active and can synthesize peptidoglycan [5]. Glycopeptides, the action of which is mediated by binding to D-Ala-D-Ala termini, are not affected by PBP5. Tolerance to vancomycin has been described in vancomycin-susceptible strains of *Enterococcus faecalis* and *Enterococcus faecium* [6,7], although the mechanism by which the tolerance is mediated is not well understood. The main hypothesis is that free radicals of O^{2-} released in the presence of vancomycin treatment are being detoxified, leaving the bacteria tolerant. Some mutations in superoxide dismutase enzyme prevent this detoxification, leading to bacterial death [8].

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https://doi.org/10.1016/j.ijantimicag.2019.03.023
0924-8579/

Few studies have assessed the comparative efficacy of β-lactam antibiotics and glycopeptides in the treatment of enterococci [9–11]. It is well known that glycopeptide treatment, in comparison with β-lactam treatment, has an adverse effect on outcomes in patients with meticillin-susceptible *Staphylococcus aureus* bacteraemia [12]. It is less clear whether the same occurs in enterococcal bacteraemia. In-vitro studies evaluating anti-enterococcal activity of penicillins (mostly ampicillin and piperacillin) and vancomycin reported better results in terms of time-kill curves for penicillins [13–17]. In general, vancomycin had slower kill kinetics than ampicillin [17], and for most concentrations above the minimal inhibitory concentration (MIC) did not achieve 99.9% killing of strains, rendering it bacteriostatic [13,15,16].

This study aimed to compare the outcomes of patients with enterococcal bacteraemia treated with β-lactam antibiotics with patients receiving vancomycin-based therapy. The study hypothesis was that treatment with β-lactam antibiotics would lead to improved patient outcomes compared with treatment with vancomycin.

2. Methods

A retrospective cohort study was conducted at Rambam Health Care Campus, a primary and tertiary hospital located in Haifa, Israel, between 2010 and 2016. The hospital serves as a referral centre to a population of approximately 2.2 million, with 840 adult beds and an average of 47 615 admissions per year during the study period. The hospital has cardiac surgery and neurosurgery departments, a large bone marrow transplantation unit, and tertiary level burns and trauma care.

Patients were identified by a report of all enterococcal bacteraemias from the microbiology database. All adults aged >16 years with clinically significant enterococcal bacteraemia were included; this was defined as growth of *Enterococcus* spp. in at least one blood culture bottle accompanied by systemic inflammatory response syndrome [18], or growth from two separate sets of blood cultures. Patients that were not treated with a covering β-lactam or vancomycin (the only glycopeptide used in the study centre) and vancomycin-resistant *Enterococcus* spp. were excluded. Inclusion was not restricted by antibiotic dosing or vancomycin drug levels. In patients with multiple episodes of enterococcal bacteraemia, only the first episode was included. Both penicillin-susceptible and -resistant *Enterococcus* spp. and polymicrobial bacteraemias were included. Subgroup analyses of patients with penicillin-susceptible enterococcal bacteraemia and patients with monomicrobial, penicillin-susceptible, enterococcal bacteraemia were performed.

The dependent variable was all-cause 30-day mortality. The exposure variable was treatment with β-lactam antibiotics vs. treatment with vancomycin. The β-lactam group included antibiotics active against penicillin-susceptible *Enterococcus* spp., including penicillin, ampicillin, penicillin–β-lactamase combinations and imipenem. Treatment assignment was based on the main antibiotic used, defined as the first antibiotic used for ≥4 days in the 7 days after blood culture collection. Patients receiving β-lactam–vancomycin combination therapy were included in the β-lactam antibiotics group in the primary analysis (assuming superiority of β-lactams). A sensitivity analysis was conducted assessing only penicillin or ampicillin in the β-lactam group, and excluding patients treated with β-lactam–vancomycin combinations.

Gentamicin combination therapy was defined when combined with the β-lactam or vancomycin for at least 2 days in the first week. Confounders and other risk factors for mortality included demographic data, place of acquisition (community-acquired, nursing home, other healthcare-associated or hospital-acquired using previous definitions [19]), comorbidities (using the Charlson Comorbidity Index [20]), risk factors for enterococcal bacteraemia and for endocarditis (e.g. urinary catheter, recent abdominal surgery, prosthetic heart valve, pacemaker), clinical presentation, source of bacteraemia, empirical and definitive antimicrobial therapy, and microbiological data. Clinical data were collected manually from the patients' electronic files. Post-discharge mortality data were updated from the national Ministry of Health Registry.

Blood culture bottles were incubated using BACTEC FX (Becton Dickinson, Franklin Lakes, NJ, USA). Gram-positive cocci were grown on 5% blood and CHROMagar orientation plates (Hy Laboratories, Rehovot, Israel) at 37°C for 18–24 h. Isolates were identified using VITEK 2 (bioMérieux, Marcy l'Etoile, France) up to 2015, and matrix assisted laser desorption ionization-time of flight mass spectrometry (bioMérieux) thereafter. Antibiotic susceptibility testing was determined using VITEK 2 with interpretation based on Clinical Laboratory Standards Institute breakpoints.

Patients treated with β-lactams were compared with patients treated with vancomycin, and patients who died were compared with those remaining alive at 30 days. Categorical variables were compared using Chi-squared test. Continuous variables were compared using a *t*-test or non-parametric tests by variable distribution. The propensity score (PS) for vancomycin treatment was calculated based on comparison between treatment groups. Significant variables associated with mortality were assessed for clinical and statistical correlation. Uncorrelated variables were entered into a multi-variable logistic regression analysis to identify independent risk factors for mortality, including the defined exposure variable and the PS for vancomycin treatment. Data analysis was performed using SPSS Version 23 (IBM Corp., Armonk, NY, USA). The study was approved by the local ethics committee with a waiver of informed consent given the non-interventional study design.

3. Results

In total, 678 adults with enterococcal bacteraemia, hospitalized in Rambam Health Care Campus between 2010 and 2016, were identified. Of these, 516 patients met the inclusion criteria for the primary analysis based on their main treatment. In secondary analyses, 401 patients with penicillin-susceptible enterococcal bacteraemia and 237 patients with monomicrobial penicillin-susceptible bacteraemia were included (Fig. 1).

The mean age of patients was 68.4 (standard deviation 16.1) years, and 222 (43%) were female. Most infections (436/516, 84.4%) were healthcare-associated or hospital-acquired. The most common diagnoses were urinary tract infections (36%), abdominal infections (25%) and central catheter-associated infections (12%). Additional epidemiologic data are shown in Table 1. *E. faecalis* bacteraemia occurred in 399 patients, of which 371 were penicillin-susceptible and 28 were penicillin-resistant. *E. faecium* bacteraemia occurred in 103 patients, of which 22 were penicillin-susceptible and 81 were penicillin-resistant. Polymicrobial growth was observed in 37.5% (194/516) of patients. Immunodeficiency, malignancy, diabetes, time from admission to bacteraemia, *E. faecium*, a non-urinary source of bacteraemia, and having a central line catheter were associated with vancomycin treatment. Community acquisition of infection was associated with β-lactam antibiotic treatment (given by definition to penicillin-susceptible *Enterococcus* spp.). These variables were used to derive the PS (Supplementary Table 1). The overall 30-day mortality was 39.7% (205/516).

3.1. Primary analysis, all patients

Among all 516 patients with enterococcal bacteraemia, mortality was significantly associated with older age, female sex, impaired functional capacity, increased Charlson Comorbidity Index, healthcare or hospital acquisition of infection, presence

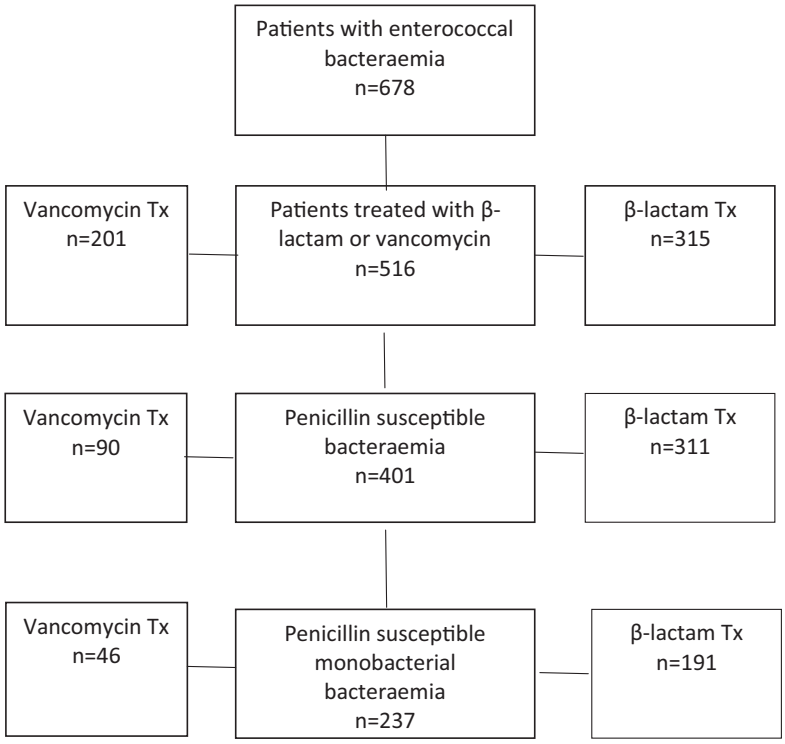

Fig. 1. Patient flow chart.

of a urinary catheter or a nasogastric tube, mechanical ventilation, creatinine values, higher SOFA score, elevated leukocyte count and lower albumin level at bacteraemia presentation, and gastrointestinal source of bacteraemia (Table 1). Conversely, chronic dialysis was associated with survival, as were the presence of a mechanical heart valve, endocarditis, urinary source of bacteraemia and gentamicin combination therapy. Mortality rates were similar in patients infected with *E. faecalis* and *E. faecium*, and penicillin-sensitive vs. penicillin-resistant strains. Counterintuitively, mortality rates were higher for patients treated with appropriate empirical therapy. Mortality did not differ significantly between patients treated with β-lactam antibiotics and patients with vancomycin as the main treatment (P=0.692).

Endocarditis and gentamicin combination therapy were highly correlated; as such, only the latter was used in the regression analysis. Age, female sex, higher Charlson Comorbidity Index, patients without dialysis, healthcare or hospital acquisition of infection, higher SOFA score and lower albumin level remained significantly associated with increased mortality in the PS-adjusted logistic regression analysis (Table 2). The choice of treatment (β-lactam antibiotics vs. vancomycin) was not associated with mortality [adjusted odds ratio (OR) for mortality with vancomycin 0.95, 95% confidence interval (CI) 0.56–1.59, P=0.83].

Among patients in the β-lactam group, 150/315 (47.6%) were treated with ampicillin or penicillin as their main treatment, 103 (32.7%) with piperacillin-tazobactam, 36 (11.4%) with amoxicillin-clavulanate or ampicillin-sulbactam, and 26 (8.3%) with imipenem. Concomitant vancomycin was administered to 12 (3.8%) patients. Restricting the analysis to patients treated with ampicillin or penicillin (excluding other β-lactams and combined treatment) compared with vancomycin resulted in a similarly non-significant adjusted OR for mortality with vancomycin (OR 1.21, 95% CI 0.62–2.36).

3.2. Secondary analyses

3.2.1. Penicillin-susceptible bacteraemia

In the subgroup of 401 patients with penicillin-susceptible bacteraemia, 30-day mortality was 38.9% (121/311) for patients treated with a β-lactam and 36.7% (33/90) for patients treated with vancomycin (P=0.71). Risk factors for mortality are shown in Supplementary Table 2. In a PS-adjusted multi-variate analysis, community acquisition and independent functional capacity were associated with survival, whereas SOFA score and low albumin level were associated with mortality. Similar to the main analysis, there was no association between treatment with vancomycin or a β-lactam and mortality (adjusted OR 0.71, 95% CI 0.39–1.28) (see Supplementary Table 3).

3.2.2. Penicillin-susceptible monobacterial bacteraemia

In the subgroup of 237 patients with penicillin-susceptible monobacterial enterococcal bacteraemia, 30-day mortality was 37% (71/191) for patients treated with a β-lactam and 28% (13/46) for patients treated with vancomycin (P=0.25). Risk factors for mortality are shown in Supplementary Table 4. In the PS-adjusted logistic regression model, Charlson Comorbidity Index, SOFA score and low albumin level remained independently associated with mortality. Again, there was no association between treatment with vancomycin or a β-lactam and mortality (adjusted OR 0.59, 95% CI 0.25–1.43) (Table 3).

4. Discussion

In this cohort of patients with enterococcal bacteraemia, many of whom had significant comorbid conditions and hospital-acquired infections, mortality was not associated with the choice of antibiotic class, namely β-lactams (for penicillin-susceptible *Enterococcus* spp.) vs. vancomycin. The analysis was robust to

Table 1
Factors associated with mortality among all patients with enterococcal bacteraemia: univariate analysis

Variable	Alive n=311	Dead n=205	P-value
Demographics			
Sex, female	119 (38.3)	103 (50.2)	0.007
Age, years; mean (SD)	66 (16)	73 (15)	<0.001
Acquisition, community	64 (20.6)	16 (7.8)	<0.001
Background conditions			
Independent functional capacity	174 (56.1)	80 (39)	<0.001
Diabetes	125 (40.2)	97 (47.3)	0.110
Active malignancy	95 (30.5)	74 (36.1)	0.189
Heart failure	62 (19.9)	50 (24.4)	0.230
Dementia	60 (19.3)	51 (24.9)	0.131
Chronic kidney disease	74 (23.9)	51 (24.9)	0.794
Dialysis	26 (8.4)	8 (3.9)	0.046
Immune deficiency	77 (24.8)	52 (25.4)	0.876
Liver disease	23 (7.4)	12 (5.9)	0.496
Chronic lung disease	43 (13.9)	32 (15.7)	0.568
Charlson Comorbidity Index; median (range)	5 (0–16)	6 (0–20)	<0.001
Devices			
Urine catheter	140 (45)	127 (62)	<0.001
Mechanical heart valve	36 (11.6)	8 (3.9)	0.002
Central venous catheter	112 (36)	78 (38)	0.639
Recent operation	50 (16.1)	37 (18)	0.558
Nasogastric tube	83 (26.7)	94 (45.9)	<0.001
Mechanical ventilation	55 (17.7)	67 (32.7)	<0.001
Source of infection			
Urinary	121 (38.9)	67 (32.7)	0.005
Gastrointestinal	66 (21.2)	67 (32.7)	
Skin/soft tissue	27 (8.7)	22 (10.7)	
Central line	41 (13.2)	23 (11.2)	
IE/primary bacteraemia	35 (11.3)	9 (4.4)	
Febrile neutropenia	13 (4.2)	6 (2.9)	
Other, unknown	8 (2.6)	11 (5.4)	
Documented endocarditis	22 (7.1)	3 (1.5)	0.004
Infection presentation and characteristics			
Temperature, °C, mean (SD)	38.09 (0.98)	37.97 (1.31)	0.224
Systolic BP, mmHg; mean (SD)	118 (30.9)	110 (28.7)	0.004
Acute confusion	87 (28.1)	98 (48.3)	<0.001
Acute kidney injury	91 (29.5)	111 (55)	<0.001
Mechanical ventilation	30 (9.6)	60 (29.4)	<0.001
SOFA score; median (range)	4 (0–17)	7 (0–20)	<0.001
Leukocytes (X $10^3/\mu$L); median (range)	11.175 (0–122.7)	12.500 (0.03–242.0)	0.016
Albumin (g/dL); mean (SD)	2.31 (0.63)	1.81 (0.53)	0.006
Creatinine (mg/dL); median (range)	1.13 (0.23–12.1)	1.5 (0.1–9.6)	0.001
Time to bacteraemia, days; median (range)	6 (1–115)	8 (1–127)	0.117
Enterococcus spp.			
E. faecalis	240 (77.2)	159 (77.6)	0.678
E. faecium	61 (19.6)	42 (20.5)	
Other	10 (3.2)	4 (2)	
Penicillin resistance	64 (20.6)	51 (24.9)	0.251
Polymicrobial	108 (34.7)	86 (42)	0.097
Antibiotic treatment			
Appropriate empirical 24 h	92 (29.6)	87 (42.4)	0.003
Main treatment			
β-lactam	192 (61.7)	123 (60%)	0.692
Vancomycin	119 (38.3)	82 (40%)	
Gentamicin combination therapy	24 (7.7%)	2 (1%)	<0.001

IE, infective endocarditis; BP, blood pressure; SD, standard deviation.

sensitivity analyses, including restriction of the β-lactam examined to ampicillin or penicillin, analysing only penicillin-susceptible enterococcal bacteraemia, and analysis of monomicrobial bacteraemias susceptible to penicillin. This observation stands in contrast to what is known regarding β-lactams compared with vancomycin in *Staphylococcus aureus* infections.

Three retrospective studies comparing the clinical outcomes of patients treated with β-lactams or vancomycin reported conflicting results. A study conducted in Australia concluded that glycopeptide treatment of enterococcal bacteraemia is associated with higher mortality compared with β-lactam antibiotics [9]. The investigators analysed 172 bacteraemic episodes susceptible to β-lactams and glycopeptides, 115 of which were monomicrobial. The 30-day mortality was 15.1% overall, and vancomycin was significantly associated with mortality (adjusted OR 2.46, 95% CI 1.01–6.02). A study conducted in North Carolina, USA included 186 patients with ampicillin-susceptible monobacterial enterococcal bacteraemia, 21% of whom were diagnosed with endocarditis, and found no difference in 30-day mortality for patients treated with β-lactams and vancomycin (7.1% and 6.7%, respectively, P=0.92) [10]. An analysis from Spain investigated 153 episodes of *E. faecalis* bacteraemia and found no association between glycopeptide treatment and mortality [11]. Including the present study, the majority of observational studies (3/4) report no difference between β-lactams and vancomycin in the treatment of patients with enterococcal bacteraemia.

Table 2
Factors associated with mortality among all patients with enterococcal bacteraemia: multi-variate analysis

Variable	OR (95% CI)	*P*-value
Community acquired	0.49 (0.24–0.99)	0.05
Female sex	1.58 (1.03–2.42)	0.04
Age (years)	1.04 (1.02–1.05)	<0.001
Charlson Comorbidity Index	1.09 (1.01–1.19)	0.03
Dialysis	0.32 (0.12–0.85)	0.02
Albumin levels (g/dL)	0.41 (0.28–0.62)	<0.001
SOFA score	1.23 (1.15–1.32)	<0.001
Systolic blood pressure (mmHg)	0.99 (0.98–1.01)	0.39
Leukocyte count (X $10^3/\mu$L)	1 (0.98–1.02)	0.88
Propensity score for vancomycin treatment	2.07 (0.7–6.14)	0.17
Treatment with vancomycin, compared with β-lactam antibiotics	0.95 (0.56–1.59)	0.83
Gentamicin combination therapy	0.34 (0.07–1.59)	0.169
Regression performance		
Hosmer–Lemeshow test		0.09
Area under the ROC curve	0.82 (0.78–0.86)	

OR, odds ratio; CI, confidence interval; ROC, receiver operating characteristic.

Table 3
Factors associated with mortality among patients with penicillin-susceptible, monomicrobial enterococcal bacteraemia: multi-variate analysis

Variable	OR (95% CI)	P-value
Community acquired	0.44 (0.15–1.31)	0.14
Time to bacteraemia (days)	1 (0.98–1.02)	0.83
Charlson Comorbidity Index	1.11 (1.002 –1.23)	0.05
SOFA score	1.27 (1.12–1.43)	<0.001
Systolic blood pressure	1 (0.99–1.01)	0.56
Albumin (g/dL)	0.35 (0.19–0.66)	0.001
Propensity score for vancomycin treatment	0.47 (0.01–35.8)	0.735
Treatment with vancomycin, compared with β-lactam antibiotics	0.59 (0.25–1.43)	0.24
Gentamicin combination therapy	0.2 (0.02–1.73)	0.14
Regression performance		
Hosmer–Lemeshow test		0.48
Area under the ROC curve	0.82 (0.77–0.88)	

OR, odds ratio; CI, confidence interval; ROC, receiver operating characteristic.

The contribution of *Enterococcus* spp. infections to ultimate patient outcome has long been debated [21]. Compared with previous studies, the patients in the present study had more comorbid conditions, as reflected in a median Charlson Comorbidity Index of 6 and a higher rate of nosocomial infections (84% of patients). With increasing baseline morbidity, the choice of therapy might be less significant. However, clinically significant enterococcal bacteraemia was defined strictly. Patients that never received covering antibiotics for the enterococcal bacteraemia were excluded from the current analysis; the mortality among these patients (51/83, 61.4%) was significantly higher than that among patients who received covering therapy (205/516, 39.7%). The analysis restricted to monomicrobial enterococcal bacteraemia was intended to delineate the group of patients where therapy selection would be most expected to alter outcomes. Further focusing on monomicrobial penicillin-susceptible bacteraemia also removed non-measured baseline differences that may exist between therapy groups associated with resistance.

Enterococci, being inherently tolerant to many classes of antibiotics, present a therapeutic challenge to clinicians, as most bactericidal antibiotics have only a bacteriostatic effect. There is no consensus nor guidelines on the optimal antibacterial treatment for various serious enterococcal infections, including bacteraemia. The results of this study suggest that vancomycin is an acceptable therapeutic alternative for patients who cannot be treated with β-lactam antibiotics (e.g. penicillin allergy). While not encouraging vancomycin treatment for penicillin-susceptible enterococcal bacteraemia, the knowledge that vancomycin is not inferior to β-lactams simplifies the treatment of patients with polymicrobial infections involving *Enterococcus* spp. when administration of two β-lactams is not advisable. It allows confidence in treating polymicrobial infections caused by ampicillin-susceptible *Enterococcus* spp. and meticillin-susceptible *S. aureus* infection with oxacillin and vancomycin (when administration of ampicillin and oxacillin is not reasonable), or with vancomycin alone for combined infection with meticillin-resistant *S. aureus*. In addition, vancomycin is a more convenient choice for patients with enterococcal infection who are on haemodialysis, as it can be administered on an outpatient basis.

This study is limited by its retrospective single-centre design. As in all studies assessing treatment comparisons observationally, exposure to the treatment arm is imperfect despite protocol definitions due to varying treatment durations and combined treatments [22]. Vancomycin trough levels were not assessed systematically and were not considered in this analysis. However, the lack of vancomycin monitoring and dose adjustment leads most commonly to suboptimal vancomycin levels (median vancomycin level 11.3 μg/mL, interquartile range 6.5–17.8, for the first vancomycin level obtained clinically in the study cohort); this would bias results, if at all, in favour of β-lactams [23]. The propensity to use either β-lactam antibiotics or vancomycin might create a bias in treatment selection. Although a PS was included in this study to overcome such bias, the existence of other, hidden factors which may have influenced the choice of treatment is a possibility. Appropriateness of empirical therapy was confounded with enterococcal susceptibility to β-lactams and nosocomial infections; as this was not the focus of this study, the crude association observed between covering empirical antibiotics and mortality was not analysed further. Lower mortality rates for patients with enterococcal bacteraemia on dialysis can probably be explained by a relatively

high proportion of catheter-related bacteraemia. Lower mortality among patients with endocarditis might be related to the fact that only patients who survived for long enough to have persistent bacteraemia were investigated for endocarditis.

In summary, contrary to in-vitro predictions, this study found no clinical advantage for the use of β-lactams over vancomycin in the treatment of enterococcal bacteraemia. It is suggested that patients with a contraindication to a β-lactam, or another indication for vancomycin, can be safely treated with this agent.

Acknowledgements

The authors wish to thank Hillel Mendelson for his assistance.

Funding

None.

Competing interests

None declared.

Ethical approval

This study was approved by the local ethics committee with a waiver of informed consent given the non-interventional study design. Data were collected anonymously.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.03.023.

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