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Linezolid vs glycopeptides in the treatment of glycopeptide-susceptible *Enterococcus faecium* bacteraemia: A propensity score matched comparative study

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ABSTRACT

Background: The incidence of ampicillin-resistant *Enterococcus faecium* bacteraemia is increasing. Vancomycin remains the first-line treatment in areas with a high prevalence of glycopeptide-susceptible isolates, but data comparing its clinical outcomes with other treatments are lacking. The objective of this study was to compare the effectiveness and safety of linezolid and glycopeptides for the treatment of glycopeptide-susceptible *E. faecium* bloodstream infection (GSEF-BSI).

Methods: This retrospective observational cohort study was conducted from January 2006 to May 2018 at the Hospital del Mar, Barcelona, Spain, and compared the clinical outcomes and safety of linezolid and glycopeptides in adult patients with GSEF-BSI. The main outcomes included clinical cure at the end of therapy, 30-day mortality, microbiological eradication and attributable length of stay (LOS). Propensity score matching was performed to reduce potential confounders among groups.

Results: In total, 105 patients with GSEF-BSI were included (linezolid, n=38; glycopeptides, n=67). After propensity score matched analysis, 56 (53.3%) patients, 28 in each cohort, entered the final analysis. No differences were observed in any of the main clinical outcomes among patients treated with linezolid or glycopeptides: clinical cure [16/28 (57.1%) vs 13/28 (46.4%), P=0.593], 30-day mortality [8/28 (28.6%) vs 12/28 (42.9%), P=0.403], microbiological eradication [22/28 (78.6%) vs 20/28 (71.4%), P=0.758] and median attributable LOS (18.0 vs 17.0 days, P=0.924). Adverse events were similar in both groups.

Conclusions: Linezolid and glycopeptides showed similar clinical effectiveness and safety in the treatment of GSEF-BSI. Linezolid could be an alternative to glycopeptides in the treatment of GSEF-BSI.

1. Introduction

Enterococci are commensals of the human gastrointestinal tract [1] that can cause serious infections such as bloodstream infections (BSI) and endocarditis [2,3]. Risk factors for enterococcal bacteraemia include immunosuppression, intensive care unit (ICU) stay, receipt of broad-spectrum antimicrobials, liver disease, and the use of urinary and intravascular catheters [1,4].

Enterococci have emerged as important nosocomial pathogens [2]. The prevalence of enterococcal nosocomial [2,5,6].

Up to the late 1980s, *Enterococcus faecalis* was predominant, but over the past three decades, *Enterococcus faecium* has become the main cause of enterococcal infections and today presents an annual increase in the rate of bacteraemia of 19% [7]. This is of concern given the higher related mortality [8,9].

Despite the increasing incidence of *E. faecium* BSI and its high mortality, the treatment of choice remains unknown. In addition

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to its inherent resistance to many antimicrobial agents, the worldwide dissemination of clonal complex 17 has increased resistance to ampicillin [8,10], which is >85% in the USA and Europe (87.5% in Spain) [11]. On the contrary, the prevalence of vancomycin-resistant isolates differs considerably between the USA (75–80%) [12] and Europe (0–46%, 2.1% in Spain) [3,11].

Most studies have focused on vancomycin-resistant *E. faecium* (VREF) isolates in the USA, mainly comparing linezolid and daptomycin with controversial results [6,13–15]. Unfortunately, differences in the prevalence of vancomycin resistance and intrinsic virulence among vancomycin-resistant and vancomycin-susceptible species [16,17] preclude the application of these data in areas with lower vancomycin resistance.

Vancomycin is the first-line treatment of glycopeptide-susceptible *E. faecium* (GSEF)-BSI [13] when the isolate is resistant to ampicillin due to its bactericidal activity, but specific clinical data on this scenario are missing. Despite its efficacy, its use has been related to some drawbacks, such as slow bactericidal activity and potential nephrotoxicity [18].

Linezolid is used for the treatment of infections caused by Gram-positive micro-organisms, including multi-drug-resistant strains. Linezolid may be a reasonable alternative to vancomycin for the treatment of enterococcal infections given its in-vitro activity [19], clinical efficacy in other types of infections [20] and different toxicity profile. Although its bacteriostatic activity, its efficacy has been shown in other BSI such as VREF-BSI [6,13–15] and meticillin-resistant *Staphylococcus aureus* bacteraemia [20].

Given the increasing incidence of *E. faecium* BSI and the lack of data concerning the treatment of choice, the aim of this study was to analyse the effectiveness and safety of linezolid and glycopeptides for the treatment of GSEF-BSI.

2. Materials and methods

2.1. Hospital setting and study design

This study was performed at Hospital del Mar, a 420-bed university tertiary care hospital located in Barcelona, Spain. It includes two adult ICUs (medical and surgical), an active programme for renal transplantation, and oncology and haematology wards. This study was reviewed and approved by the institutional ethics committee.

This retrospective observational cohort study was conducted from January 2006 to May 2018. All patients with GSEF-BSI were identified using computer-generated microbiological data, and trained study investigators reviewed inpatient medical records retrospectively.

2.2. Patients and variables

All adult patients (aged >18 years) with at least one positive blood culture for GSEF and treated with at least one dose of linezolid or glycopeptides (vancomycin or teicoplanin), including patients with endocarditis, were included in this study. Patients were excluded if they did not receive any treatment according to the responsible physician criteria or if they were treated with another anti-GSEF agent. Only the first episode was analysed in patients with more than one episode. No institutional protocol regarding the treatment of GSEF-BSI was present at any point during the study period. Teicoplanin and vancomycin were adjusted according to renal function, and linezolid and vancomycin plasmatic levels were adjusted when available by clinical pharmacists. For linezolid, both oral and intravenous therapies were considered appropriate. Patients were followed-up until 3 months after hospital discharge or death.

All data were gathered using a previously designed form that included epidemiological, clinical and microbiological data. Epidemiological data included age, sex, body mass index, hospitalization ward (medical or surgical), hospitalizations in the previous year, means of acquisition (community-acquired, healthcare-associated or nosocomial [21]), underlying diseases and their severity according to the Charlson Comorbidity Index score [22], immunosuppression, neutropenia, surgery or total parenteral nutrition in the previous 3 months, and presence of devices (vascular or urinary catheter, drainages). Clinical data included the source of bacteraemia, severity of illness and antimicrobial therapy. Severity of illness was assessed using the Pitt bacteraemia score [23], Sepsis-related Organ Failure Assessment [24], diagnosis of sepsis and septic shock according to the 2016 definitions [25], admission to the ICU (in these patients, the Acute Physiology And Chronic Health Evaluation II score was calculated [26]), and need for vasoactive drugs or mechanical ventilation on the day of the episode. The need for total renal replacement therapies was recorded on the day of the episode and during treatment. Regarding antimicrobial therapy, all antibiotic treatments received in the preceding 3 months, empirical therapy, definitive treatment, time to effective therapy, length of definitive treatment and antibiotic-related adverse events were recorded.

Outcomes analysed included clinical cure at the end of treatment (EOT) and at 14 days, need for salvage therapy, time to defervescence, microbiological eradication, relapse, superinfection and persistence of GSEF-BSI. Early (7-day), in-hospital and 30-day mortality; attributable and hospital length of stay (LOS); re-admission rates and treatment-related adverse events were also recorded.

2.3. Microbiology

Identification of *E. faecium* was performed using conventional methods [27]. The susceptibility of isolated *E. faecium* to antimicrobials (ampicillin, linezolid, teicoplanin and vancomycin) was included. The European Committee on Antimicrobial Susceptibility Testing clinical breakpoints were applied to characterize the isolate susceptibilities [28]. Polymicrobial bacteraemia and concomitant micro-organisms were also recorded. Polymicrobial bacteraemia was defined when at least one non *E. faecium* bacterial species was isolated from the same blood culture as the enterococci [29]. The full susceptibility test was performed by microdilution (MicroScan, Mahwah, NJ, USA). Minimum inhibitory concentrations of linezolid and vancomycin were confirmed by gradient diffusion (E-test, bioMérieux, Marcy l'Etoile, France).

2.4. Definitions

An episode of bacteraemia was defined according to the Centers for Disease Control and Prevention definition of BSI [30]. Immunosuppression was considered if the patient had received chemotherapy, radiotherapy or other immunosuppressive drugs including corticosteroids in the previous month. Neutropenia was defined as an absolute neutrophil count <500/μL [31]. To define the source of bacteraemia, microbiological and clinical criteria were used [30,32]. The source of bacteraemia was classified into two groups: low risk (urinary tract, vascular catheter and biliary tract) and high risk (all others) [33].

Empiric therapy was defined as therapy administered from 48 h before until culture was available, and was deemed appropriate if at least one of the antibiotics was active *in vitro* [33]. Time to effective therapy was recorded as the time in days until receiving an appropriate treatment.

Clinical cure was defined as the resolution of signs and symptoms of infection after treatment for GSEF was discontinued [13].

Treatment failure was considered when treatment was discontinued or changed before clinical cure was achieved because of persistence of infection, death or toxicity [13]. Microbiological eradication was considered when the last blood culture drawn after initiation of therapy was negative [13] or, if blood culture was not repeated, when clinical cure was achieved. Persistence of GSEF was defined as the isolation of GSEF in a blood culture after >72 h of adequate treatment, and relapse was defined as the isolation of a positive blood culture after documented clearance within 30 days of the index culture. Need for salvage therapy was defined as the change of antibiotic treatment due to persistence of infection or presence of adverse reactions. The attributable LOS was defined as the time from the index GSEF-positive blood culture until clinical cure was achieved. Re-admission to hospital was recorded up to 3 months after discharge. Adverse events were defined as the development of an adverse event proven or suspected to be related to the agent used after the initiation of therapy [13].

2.5. Statistical analysis

Baseline categorical variables were presented as percentages and were compared using χ^2 or Fisher's exact tests when appropriate. Continuous variables were described as median [interquartile range (IQR)] and were analysed by *t*-test or Mann-Whitney *U*-test.

Due to imbalances in the baseline characteristics of the treatment groups, propensity score matching was performed to reduce potential biases. This analysis was performed through logistic regression and using one-to-one nearest-neighbour matching without replacement, with treatment of GSEF-BSI as the dependent variable. Age, diagnosis of septic shock, source of bacteraemia (high or low risk), Pitt score and inappropriate empirical treatment were included as independent variables. The caliper was set to a width equal to 0.2 of the standard deviation of the logit of the propensity score [34]. $P<0.05$ was considered to indicate statistical significance in all analyses. Statistical analyses were performed using SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

One hundred and ninety-two patients with GSEF-positive blood cultures were identified over the study period, and 105 (52.1%) were analysed as they received either linezolid or glycopeptides. Patients who did not receive an active treatment (n=57) or who were treated with other anti-GSEF agents (n=30) were excluded.

Thirty-seven patients received linezolid and 68 received glycopeptides (nine teicoplanin and 59 vancomycin) as definitive therapy for GSEF-BSI based on the responsible physician criteria. After propensity score matching, 56 (53.3%) patients were included, with 28 in each treatment group (in the cohort treated with glycopeptides, five of 28 patients were treated with teicoplanin and the remaining 23 patients were treated with vancomycin). Two GSEF isolates in each group were ampicillin-susceptible but were treated either with linezolid or glycopeptides. No patient received combination therapy with beta-lactams or aminoglycosides for the treatment of GSEF-BSI.

Baseline epidemiological and clinical characteristics between treatment groups before and after propensity score analysis are shown in Table 1.

No significant differences were observed in the baseline demographic or clinical characteristics, apart from better renal function in the glycopeptide group, including creatinine (P=0.004) and Chronic Kidney Disease Epidemiology Collaboration (P=0.011). Although not significant, a trend towards a higher prevalence of previous surgery was noticed in the glycopeptide group (P=0.080). There were no differences concerning inappropriate empirical treatment in the linezolid and glycopeptide groups [16/28 (57.1%) vs 13/28 (46.4%), P=0.593]. Among those who received inappropriate empirical treatment, the number of days until appropriate treatment did not differ between treatment groups [3.0 (IQR 2.3–6.0) vs 2.0 (IQR 1.0–5.5) days, P=0.209].

The main source of infection was intra-abdominal infection with 28 (50.0%) patients, including biliary tract infection in 13 (23.2%) patients. Central-line-related BSI was diagnosed in nine (16.1%) patients, and the source of infection was unknown in six (10.7%) patients. No differences were present concerning the source of infection among cohorts.

The prevalence of polymicrobial bacteraemia was 41.7%, with no significant difference between the linezolid and glycopeptide groups [14/28 (50.0%) vs 9/28 (32.1%), P=0.277]. Concomitant isolated micro-organisms were Enterobacteriaceae in six (21.4%) patients in the linezolid group vs seven (25.0%) patients in the glycopeptide group (P=1.000); *Candida* spp. in one (3.6%) vs zero (0.0%) patients (P=1.000); coagulase-negative staphylococci in two (7.1%) vs two (7.1%) patients (P=1.000); and *E. faecalis* in three (10.7%) vs zero (0.0%) patients (P=0.236), respectively. All micro-organisms were treated appropriately according to susceptibility *in vitro*, antibiotic dosage and source control. Antibacterial susceptibilities for 55 isolates of *E. faecium* are shown in Table 2.

All patients received linezolid 600 mg every 12 h, whereas the median daily doses of teicoplanin and vancomycin were 400 (IQR 400–600) mg and 2000 (IQR 1200–2000) mg, respectively. All patients in the teicoplanin group received 6 mg/kg/12 h for three doses and then 6 mg/kg/24 h. Plasma levels were performed in five of 28 (17.9%) and 16 of 23 (69.6%) patients (P=0.005) in the linezolid and vancomycin groups, respectively. Length of treatment did not differ between the cohorts (data not shown).

Regarding the source control, among four patients with urinary tract GSEF-BSI, two patients had an indwelling catheter on the day of the episode; in both cases, this catheter was removed. Concerning line-related BSI, the catheter was removed in three of four patients in the linezolid group and four of five patients in the glycopeptide group (P=1.000). In intra-abdominal, biliary and wound infections, no differences in the performance of surgical treatment were noticed (P=1.000).

Overall, clinical cure at the EOT was 51.8% (n=29/56) and 30-day mortality was 35.7% (n=20/56). Both treatment groups showed similar clinical and microbiological efficacy, as shown in Table 3. There were no significant differences between the linezolid group and the glycopeptide group in clinical cure at the EOT [16/28 (57.1%) vs 13/28 (46.4%); odds ratio (OR) 1.54; 95% confidence interval (CI) 0.54–4.42; P=0.593] or clinical cure at 14 days [6/28 (21.4%) vs 6/28 (21.4%); OR 1.00; 95% CI 0.28–3.58; P=1.000]. Microbiological eradication was similar in the linezolid and glycopeptide groups ([22/28 (78.6%) vs 20/28 (71.4%); OR 0.68; 95% CI 0.20–2.38; P=0.758], as was 30-day mortality [8/28 (28.6%) vs 12/28 (42.9%); OR 1.88; 95% CI 0.62–5.70; P=0.403]. No difference in median attributable LOS was observed between cohorts [18.0 (IQR 14.0–26.0) days vs 17.0 (IQR 13.0–26.5) days; P=0.924].

The rate of adverse events compared by treatment group is shown in Table 4. No differences were found between different cohorts in terms of adverse events, attributable adverse events or need for discontinuation of treatment due to adverse events. Patients in the linezolid group presented more nausea and vomiting (4/26, 15.4% vs 0/27, 0.0%; OR 0.45; 95% CI 0.33–0.61; P=0.051), but no other differences were found. Neither serotoninergic toxicity nor red-man syndrome was diagnosed in any of the patients.

4. Discussion

To the best of the authors' knowledge, this is the first and the largest study to compare the effectiveness and safety of linezolid

Table 1
Baseline and clinical characteristics of patients treated with linezolid or glycopeptides for the treatment of glycopeptide-susceptible *Enterococcus faecium* bacteraemia.

	Whole cohort (*n*=105)		*P* value	Propensity score matched cohort (*n*=56)		*P* value
	Linezolid (*n*=37)	Glycopeptides (*n*=68)		Linezolid (*n*=28)	Glycopeptides (*n*=28)	
Demographics						
Age, years	71.4 (11.3)	67.0 (13.0)	0.105	72.0 (64.3–79.8)	71.0 (63.3–76.8)	0.403
Male gender	29 (78.4)	48 (70.6)	0.389	22 (78.6)	18 (64.3)	0.375
Hospitalization ward						
Medical	18 (48.6)	45 (66.2)	0.080	15 (53.6)	15 (53.6)	1.000
Surgical	19 (51.4)	23 (33.8)		13 (50.0)	13 (50.0)	
Previous length of stay, days	16.0 (22.2)	19.3 (17.1)	0.395	10.0 (0–24.8)	21.0 (2.0–39.0)	0.109
Previous length of stay in ICU, days	5.2 (9.6)	4.0 (8.8)	0.509	0.0 (0–7.8)	0.0 (0–9.0)	0.916
Community	4 (10.8)	4 (5.9)	0.363	3 (10.7)	2 (7.1)	1.000
Healthcare-associated	9 (24.3)	12 (17.6)	0.414	7 (25.0)	5 (17.9)	0.746
Nosocomial	24 (64.9)	52 (76.5)	0.204	18 (64.3)	21 (75.0)	0.562
Underlying diseases						
Charlson Comorbidity Index	1.2 (0.9)	1.3 (0.9)	0.705	2.0 (0.0–2.0)	1.0 (0.3–2.0)	0.544
Diabetes	14 (37.8)	23 (33.8)	0.681	9 (32.1)	12 (42.9)	0.582
Hypertension	31 (83.8)	38 (55.9)	0.004	23 (82.1)	19 (67.9)	0.355
Chronic obstructive pulmonary disease	6 (16.2)	13 (19.1)	0.712	5 (17.9)	6 (21.4)	1.000
Congestive heart failure	5 (13.5)	3 (4.4)	0.093	3 (10.7)	1 (3.6)	0.611
Solid tumour	9 (24.3)	24 (35.3)	0.247	7 (25.0)	7 (25.0)	1.000
Solid organ transplantation	2 (5.4)	2 (2.9)	0.529	2 (7.1)	0 (0.0)	0.491
Kidney	*2 (5.4)*	*2 (2.9)*	*0.529*	*2 (7.1)*	*0 (0.0)*	*0.491*
Immunosuppression	15 (40.5)	34 (50.0)	0.353	10 (35.7)	11 (39.3)	1.000
Use of immunosuppressive agents	*3 (8.1)*	*9 (13.2)*	*0.430*	*3 (10.7)*	*3 (10.7)*	*1.000*
Corticosteroids	*14 (37.8)*	*29 (42.6)*	*0.632*	*9 (32.1)*	*10 (35.7)*	*1.000*
Chemotherapy	*3 (8.1)*	*16 (23.5)*	*0.050*	*3 (10.7)*	*4 (14.3)*	*1.000*
Neutropenia	1 (2.7)	9 (13.2)	0.079	1 (3.6)	3 (10.7)	0.611
Chronic kidney disease	9 (24.3)	8 (11.8)	0.095	7 (25.0)	4 (14.3)	0.503
Liver cirrhosis	3 (8.1)	7 (6.7)	0.715	3 (10.7)	0 (0.0)	0.236
Previous surgery	9 (24.3)	22 (32.4)	0.389	5 (17.9)	12 (42.9)	0.080
Previous TPN	9 (24.3)	16 (23.5)	0.927	8 (28.6)	9 (32.1)	1.000
Source of bacteraemia						1.000
High risk	23 (62.2)	44 (64.7)	0.796	15 (53.6)	15 (53.6)	
Unknown	5 (13.5)	7 (10.3)		5 (17.9)	1 (3.6)	
Abdominal	14 (37.8)	27 (39.7)		6 (21.4)	9 (32.1)	
Respiratory	2 (5.4)	4 (5.9)		2 (7.1)	2 (7.1)	
Soft tissue	2 (5.4)	3 (4.4)		2 (7.1)	1 (3.6)	
Endocarditis	0 (0.0)	1 (1.5)		0 (0.0)	1 (7.1)	
Thrombophlebitis	1 (2.7)	3 (4.4)		0 (0.0)	1 (7.1)	
Low risk	14 (37.3)	24 (35.3)	0.796	13 (46.4)	13 (46.4)	1.000
Urinary tract	3 (8.1)	2 (2.9)		3 (10.7)	1 (3.6)	
Central line related	4 (10.8)	9 (13.2)		4 (14.3)	5 (17.9)	
Biliary	6 (16.2)	12 (17.6)		6 (21.4)	7 (25.0)	
Severity of illness						
ICU admission	12 (32.4)	11 (16.2)	0.054	7 (25.0)	7 (25.0)	1.000
APACHE II score, points	*18.4 (6.5)*	*22.7 (12.7)*	*0.491*	*22.5 (16.3–26.0)*	*15.0 (11.0–30.0)*	*0.714*
Septic shock	19 (51.4)	13 (19.1)	0.001	10 (35.7)	10 (35.7)	1.000
Vasoactive drugs	16 (43.2)	14 (20.6)	0.014	8 (28.6)	9 (32.1)	1.000
Mechanical ventilation	12 (32.4)	13 (19.1)	0.126	7 (25.0)	9 (32.1)	0.768
Need for renal replacement therapy	4 (10.8)	2 (3.0)	0.252	3 (10.7)	1 (3.6)	0.354
Pitt bacteraemia score, points	2.8 (2.1)	1.7 (1.7)	0.004	2.0 (1.0–3.0)	2.0 (0.3–4.0)	0.803
SOFA score, points	5.3 (3.4)	3.8 (3.2)	0.026	3.5 (2.3–5.8)	4.0 (1.0–7.0)	0.705
Leukocyte, $x10^3/\mu L$	16.4 (10.4)	12.6 (12.4)	0.117	13.1 (6.8–17.6)	13.3 (4.3–18.5)	0.909
Creatinine, mg/Dl	1.7 (1.2)	1.0 (0.9)	0.001	1.3 (0.9–1.9)	0.8 (0.6–1.0)	0.004
Glomerular filtration rate, CKD-EPI, mL/min/1.73 m^2	54.7 (31.3)	84.4 (30.3)	0.000	47.4 (29.5–85.2)	82.6 (65.0–101.7)	0.011
Haemoglobin, g/dL	10.3 (2.0)	10.0 (1.8)	0.488	10.2 (8.6–11.5)	9.9 (8.8–11.0)	0.870
Platelet count, $x10^4/\mu L$	245.2 (144.3)	221.2 (162.9)	0.465	238.5 (134.5–391.5)	212.5 (108.0–309.8)	0.422
Previous antimicrobial use						
Beta-lactam/beta-lactamase inhibitors	1 (2.7)	8 (11.8)	0.407	15 (53.6)	20 (71.4)	0.269
Cephalosporins	11 (29.7)	36 (52.9)	0.022	8 (28.6)	12 (42.9)	0.403
Carbapenems	20 (54.1)	35 (51.5)	0.800	15 (53.6)	16 (57.1)	1.000
Fluoroquinolones	11 (29.7)	29 (42.6)	0.193	10 (35.7)	11 (39.3)	1.000
Glycopeptides	2 (5.4)	12 (17.6)	0.078	2 (7.1)	5 (17.9)	0.422
Aminoglycosides	2 (5.4)	20 (29.4)	0.004	2 (7.1)	7 (25.0)	0.143
Daptomycin	2 (5.4)	1 (1.5)	0.248	2 (7.1)	1 (3.6)	1.000
Linezolid	7 (18.9)	8 (11.8)	0.317	5 (17.9)	4 (14.3)	1.000
Metronidazole	5 (13.5)	18 (26.5)	0.125	1 (3.6)	7 (25.0)	0.051
Colistin	4 (10.8)	2 (2.9)	0.097	4 (14.3)	1 (3.6)	0.352
Trimethoprim/sulfamethoxazole	6 (16.2)	6 (8.8)	0.255	6 (21.4)	3 (10.7)	0.469
Fluconazol	5 (13.5)	14 (20.6)	0.368	5 (17.9)	8 (28.6)	0.528
Echinocandins	2 (5.4)	10 (14.7)	0.091	2 (7.1)	5 (17.9)	0.422

ICU, intensive care unit; COPD, cardiopulmonary disease; TPN, total parenteral nutrition; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
Data are presented as mean (standard deviation) for the whole cohort and median (interquartile range) for the propensity score matched cohort, or as absolute number (percentage).

Table 2
Susceptibilities of 55 *Enterococcus faecium* isolates.

	Linezolid (*n*=27)	Glycopeptides (*n*=28)	*P* value
Ampicillin MIC, µg/mL			0.963
≤8	2 (7.4)	2 (7.1)	
>8	25 (92.6)	26 (92.9)	
Linezolid MIC, µg/mL			
≤2	25 (92.6)	19/19 (100)	0.504
2-4	1 (3.7)	0 (0.0)	1.000
>4	1 (3.7)	0 (0.0)	1.000
Vancomycin MIC, µg/mL			
≤1	16 (59.3)	21 (75.0)	0.259
1-2	11 (40.7)	7 (25.0)	0.259
Teicoplanin MIC, µg/mL			
≤1	27 (100)	27 (100)	1.000

MIC, minimum inhibitory concentration.
Data are presented as absolute number (percentage).

and glycopeptides in the treatment of GSEF-BSI. The results show that linezolid and glycopeptides have similar clinical cure rates, microbiological eradication, mortality and attributable LOS without significant differences in the rate of adverse events.

There is no literature comparing the clinical outcomes of linezolid and glycopeptides for the treatment of GSEF-BSI. In the in-vitro study performed by Miyazaki *et al.*, similar efficacy of linezolid and vancomycin was shown in a mice bacteraemia model, although the isolate was vancomycin-susceptible *E. faecalis* [19].

Several factors make it difficult to compare previous published data on GSEF-BSI. Firstly, information available on antibiotic treatment was not comparable since the antibiotics prescribed were not described or different antibiotics were used in addition to vancomycin, mainly beta-lactams with or without aminoglycosides [9,29,32]. Secondly, the effectiveness and safety of antimicrobials were not analysed in these studies as they assessed clinical characteristics, incidence and outcomes without comparison. Thirdly, contrary to the present study, beta-lactams could be used because sensitivity to ampicillin was preserved (40.0–70.0%); this did not occur in the present series (7.1%) [9,32,35,36]. Unfortunately, in other published articles with a similar ampicillin susceptibility rate (2.9–13.0%), clinical outcomes were not compared between different antibiotics [31,37–39].

All-cause 30-day mortality of GSEF-BSI series was 35.7% in this study, which is consistent with previous studies with a similar ampicillin susceptibility rate that showed mortality of 25.0–35.0% [29,31,37–39]. Interestingly, mortality rates were higher in the glycopeptide group (12/28, 42.9%) than in the linezolid group (8/28, 28.6%), although this difference was not statistically significant, perhaps due to the small sample size.

The mortality attributable to GSEF-BSI was not recorded as it was difficult to assess given the multiple comorbidities and the high prevalence of polymicrobial bacteraemia.

Clinical data regarding the treatment of bacteraemia in VREF-BSI show contradictory results. Daptomycin, a bactericidal lipopeptide, has been compared with linezolid. Two systematic reviews and meta-analyses that included 967 and 1188 patients concluded that mortality rates may be higher with daptomycin [13,15]. Nevertheless, another study performed by Britt *et al.* in 644 patients found that treatment with linezolid was associated with higher clinical failure and 30-day mortality [6]. However, it should be noted that most of these are retrospective studies, and there are numerous differences in terms of definitions, initial severity of illness and antibiotic dosages, especially for daptomycin. In fact, a change in the sensitivity cut-off for daptomycin is being considered for pharmacodynamic reasons [40].

Historically, the use of bactericidal antibiotics has always been preferred due to the belief that they can kill micro-organisms, while bacteriostatic agents only inhibit their growth. However, this fact has been questioned recently in a systematic review of 56 randomized clinical trials that compared the clinical efficacy of bacteriostatic vs bactericidal antibiotics in serious infections, including bacteraemia. In the global analysis, no differences were found in 49 studies, the bacteriostatic agent was superior in six studies, and the bactericidal agent was superior in one study; in the latter case, the differences could be explained due to possible underdosing of the bacteriostatic drug [41]. This fact may explain the similar effectiveness found in the present study as well as in other BSI.

As linezolid plasmatic levels were not performed until 2011, significant differences were observed in the performance of plasma levels of both antibiotics. The impact of this fact is uncertain, although it could have some influence in the rate of adverse events.

Linezolid could therefore be an alternative to vancomycin for the treatment of GSEF-BSI. In addition to being an effective choice in patients with renal impairment or allergy or intolerance to glycopeptides, the use of linezolid could lead to a faster switch from the intravenous to the oral route, which has been associated with a reduction in LOS and in intravenous-line-associated complications [42].

This study has several limitations. This was a non-randomized retrospective observational study, but through the propensity score matched analysis, the authors tried to reduce the potential bias

Table 3
Comparison of clinical outcomes of patients treated with linezolid or glycopeptides for glycopeptide-susceptible *Enterococcus faecium* bacteraemia.

	Linezolid (*n*=28)	Glycopeptides (*n*=28)	Odds ratio (95 % CI)	*P* value
Clinical data				
Cure at EOT	16 (57.1)	13 (46.4)	1.54 (0.54–4.42)	0.593
Cure at 14 days	6 (21.4)	6 (21.4)	1.00 (0.28–3.58)	1.000
Need for salvage therapy	8 (28.6)	7 (25.0)	0.83 (0.25–2.73)	1.000
Time to defervescence, days	0 (0.0–1.0)	0 (0.0–2.0)	–	0.285
Microbiological data				
Eradication	22 (78.6)	20 (71.4)	0.68 (0.20–2.38)	0.758
Relapse	2 (7.1)	1 (3.6)	0.48 (0.04–5.64)	1.000
Superinfection	18 (64.3)	13 (46.4)	0.48 (0.17–1.41)	0.282
Persistent bacteraemia	0 (0.0)	2 (7.1)	0.48 (0.37–6.4)	0.491
Mortality				
7-day	1 (3.6)	6 (21.4)	7.36 (0.80–65.8)	0.101
30-day	8 (28.6)	12 (42.9)	1.88 (0.62–5.70)	0.403
In-hospital	13 (46.4)	14 (50.0)	1.15 (0.40–3.29)	1.000
Attributable LOS, days	18.0 (14.0–26.0)	17.0 (13.0–26.5)	–	0.924
Hospital LOS, days	42.5 (26.0–74.5)	38.5 (23.5–63.8)	–	0.385
Readmission	6 (21.4)	4 (14.3)	0.611 (0.15–2.46)	0.729

EOT, end of treatment; LOS, length of stay.
Data are presented as median (interquartile range) or as absolute number (percentage).

Table 4
Adverse events by antibiotic treatment for glycopeptide-susceptible *Enterococcus faecium* bacteraemia.

Outcome	Linezolid (n=28)	Glycopeptides (n=28)	Odds ratio (95 % CI)	P value
Any adverse event	14/26 (53.8)	16/27 (59.3)	1.25 (0.42–3.70)	0.785
Attributable adverse event	13/26 (50.0)	12/27 (44.4)	0.80 (0.27–2.36)	0.786
Discontinuation of treatment	3/26 (11.5)	5/27 (18.5)	1.74 (0.37–8.18)	0.704
Nausea and vomiting	4/26 (15.4)	0/27 (0.0)	0.45 (0.33–0.61)	0.051
Diarrhoea	3/26 (11.5)	2/27 (7.4)	0.61 (0.09–4.01)	0.669
Nephrotoxicity	3/25 (12.0)	5/27 (18.5)	1.67	0.705
No toxicity	22/25 (88.0)	22/27 (81.5)	(0.35–	0.215
R	1/25 (4.0)	4/27 (14.8)	7.84)	
F	2/25 (8.0)	0/27 (0.0)		
L	0/25 (0.0)	1/27 (3.7)		
Thrombocytopenia	12/25 (48.0)	7/26 (26.9)	0.40 (0.12–1.29)	0.153
Final platelet count <100,000/mm^3	10/25 (40.0)	7/26 (26.9)	0.55 (0.17–1.80)	0.382
Anaemia	1/25 (4.0)	5/26 (19.2)	5.71 (0.62–52.90)	0.191
Final lactic acidosis (>2.2 mmol/L)	2/3 (66.7)	1/5 (20.0)	0.13 (0.01–3.23)	0.464

R, Risk; F, Failure; L, Loss.
Data are presented as absolute number (percentage).
Renal toxicity was assessed through RIFLE criteria.
Thrombocytopenia was defined as a decrease in platelet count to <75% of baseline.
Anaemia was defined as a decrease ≥2 g/dL in haemoglobin concentration from baseline.

and achieve an analysis with similar cohorts. Given the difficulty of obtaining monomicrobial bacteraemia caused by *E. faecium*, a global analysis with both polymicrobial and monomicrobial bacteraemia was undertaken. Although this fact could have affected the outcomes, no differences were observed between the groups in the prevalence of polymicrobial bacteraemia or the different isolated micro-organisms. In addition, all concomitant micro-organisms were treated appropriately in terms of spectrum, dosage and source control. Although the initial analysis included 105 patients, the attempt to adjust the possible confounding factors as much as possible resulted in a small final sample. Nevertheless, this study used 12 years of data from the study institution and, to the authors' knowledge, is the first study to compare the clinical outcomes of both antibiotics in the treatment of GSEF-BSI.

5. Conclusion

Treatment with either linezolid or glycopeptides presented similar clinical outcomes in terms of clinical cure, mortality and microbiological eradication for the treatment of GSEF-BSI with a similar safety profile. Linezolid treatment seems to be an appropriate alternative to vancomycin for the treatment of GSEF-BSI.

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