



Clinical and microbiological characteristics of bloodstream infections caused by *Enterococcus* spp. within internal medicine wards: a two-year single-centre experience

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Abstract

Enterococcal bloodstream infections (E-BSI) constitute the second cause of Gram-positive bacterial BSI in Europe with a high rate of in-hospital mortality. Furthermore, E-BSI treatment is still challenging because of intrinsic and acquired antibiotic resistances. We conducted a retrospective, 2-year, observational, single-centre study to evaluate clinical outcome and risk factors for E-BSI mortality in internal medicine wards. 201 patients with E-BSI were included in the analysis. Infection rate was 2.4/1000 days of hospital admission. Most E-BSI were hospital acquired (78.1%). The median age was 68 years. Charlson Comorbidity Index, adjusted for age, was 5 (range 4–6). Patients with E-BSI frequently had at least one invasive device, predominantly a central venous (73%) or a bladder catheter (61.7%). *Enterococcus faecium* accounted for 47.94% of E-BSI (resistance rate to ampicillin or vancomycin was 22.2 and 23.3%, respectively) and *Enterococcus faecalis* for 52.08% (resistance rate to ampicillin or vancomycin was 3.1 and 2.2%, respectively). Among all E-BSI, 25% of patients received appropriate therapy. In total, 59% of E-BSI underwent echocardiography. At the multivariate analysis, resistance to vancomycin (OR 2.09, $p=0.025$), sepsis (OR 2.57, $p=0.003$) and septic shock (OR 3.82, $p=0.004$) was a predictor of mortality. No difference in 28-day survival was observed between appropriate or inappropriate treatment, except for endocarditis. However, E-BSI sources in clinical practices are not always properly investigated, including the rule-out of intracardiac vegetations. We did not demonstrate a difference in mortality for inappropriate therapy in the absence of endocarditis in comorbid patients with a long history of medicalization.

Keywords Enterococci · Bloodstream infections · *faecalis* · *faecium* · Internal medicine wards

Introduction

Enterococcus faecalis and *Enterococcus faecium* have become increasingly common causes of healthcare-associated infections (HAIs) in the United States (US) and Europe [1–3]. Six-year surveillance on Gram-positive organisms causing bacteraemia in US and European hospitals reported that 10.6% and 9.4% of bloodstream infections (BSI) were due to *E. faecalis* and *E. faecium*, which constitute, respectively, the second and the third pathogen in terms of frequency after *Staphylococcus aureus* [4].

The incidence of enterococci as the causative agent of BSI (E-BSI) continues to be also elevated during the COVID-19 pandemic, probably because of a more extensive empirical use of corticosteroids and cephalosporins which have variable in vivo activity against *Enterococcus* spp. [5]. In COVID-19 subjects, *E. faecalis* and *E. faecium* represented

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18% and 9% of all BSI, according to a recent retrospective study by Giacobbe et al. [5].

Moreover, it is well established that E-BSI retained high in-hospital mortality estimated between 30 to 50% [6–10] and it has been identified as an independent predictor of increased 30-day mortality in elderly patients [11].

Furthermore, enterococci also play an increasingly important role in infective endocarditis, being the third leading causative agent in high-income countries and more frequently occurring in aged patients with high complexity of comorbidities [12].

Antibiotic combination is usually needed to achieve bactericidal activity in enterococcal-related endocarditis, although the possibility of combining antibiotics has become more challenging due to the increasing rate of acquired antimicrobial resistance among enterococci [13, 14]. Antibiotics' timing and selection represent another critical issue, since two meta-analyses showed that inappropriate and delayed therapy in clinical practice is associated with more unfavourable outcomes and higher mortality [13, 14].

This retrospective study aimed to evaluate the clinical outcome and risk factors for mortality of patients with E-BSI admitted to internal medicine wards (IMW) in a large teaching hospital in northwest Italy over 2 years.

Methods

This retrospective study was conducted in IMWs, in a 1200-bed academic hospital with a primary and secondary referral (City of Health and Sciences, Molinette, Turin, Italy).

All adults with positive blood culture for *E. faecalis* or *E. faecium* between 1st January 2015 and 31st December 2016 were enrolled in the study, and the demographic, clinical and microbiological data were collected.

BSI were defined as community acquired (CA-BSI), hospital acquired (HA-BSI) or healthcare associated (HCA-BSI), according to the time and setting of the onset of infection. HA-BSI was defined as a first positive blood culture ≥ 48 h after hospital admission or within 48 h of discharge from the hospital. HCA-BSI was defined as a first positive blood culture obtained < 48 h of admission in patients with recent and/or frequent exposure to healthcare settings and procedures. Community-acquired infections are those with a first positive culture obtained < 48 h of admission that do not fulfil criteria for the healthcare-associated classification.

The Sequential Organ Failure Assessment (SOFA) score and quick-SOFA (q-SOFA) were used to assess the severity of the disease [15], and the Charlson Comorbidity Index [16], a weighted index of 17 coexisting medical conditions, was used as the measure of the risk of mortality of each comorbidity in this population.

According to Sepsis-2 guideline [17], sepsis was defined as the presence of at least two systemic inflammatory response syndrome (SIRS) criteria. Severe sepsis was defined accordingly as Sepsis-2, and sepsis was defined according to Sepsis-3 guideline [15].

Antibiotic therapy was defined as appropriate if all the following criteria were present: the administration of an active antibiotic against *Enterococcus* spp., the administration of an active combination therapy (at least two drugs simultaneously, except daptomycin) in infective endocarditis and a duration of at least 15 days of an active antibiotic treatment [18–21]. Antimicrobials considered active in monotherapy or in combination therapy against *Enterococcus* spp. were penicillin G, ampicillin, ampicillin/sulbactam, amoxicillin, amoxicillin/clavulanate, piperacillin/tazobactam, imipenem, vancomycin, teicoplanin, daptomycin, ceftriaxone, gentamicin, tigecycline and linezolid.

In case of death or discharge within 15 days from the beginning of antibiotic therapy, the therapy was considered appropriate if criteria 1 and 2 were satisfied. Moreover, the 21-day mortality was investigated.

The Vitek MS MALDI-TOF mass spectrometry (bioMérieux, Craponne, France) was routinely used for identifying *Enterococcus* spp. BSI, whereas the Vitek 2 automated system (bioMérieux, Craponne, France) was routinely used for susceptibility testing. The results of the susceptibility tests were interpreted according to the criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (breakpoint tables for interpretation of minimum inhibitory concentrations [MIC] and zone diameters, version 10.0, 2020; <http://www.eucast.org>). For daptomycin, isolates were considered susceptible in the case of MIC 4 mg/L. Specifically, daptomycin was used at high dose, in combination therapy, in *Enterococcus* spp. strains reporting MIC < 4 mg/L.

The need for informed consent was waived due to the study's retrospective nature, which the medical direction of the hospital approved (PROT.N.0115709). Data were collected according to the Italian laws on privacy.

At the time of blood cultures, demographic and clinical characteristics were summarized using absolute and percentage frequencies (qualitative variables) or using the mean and standard deviation or percentile (quantitative variables). Categorical variables were tested in the Chi-square test. Numeric variables were tested by Student's *t* test or Wilcoxon test. Overall survival was defined as the time between the first blood sample culture and hospital death. The equivalence of survival curves was tested through the log-rank test. A Cox proportional-hazards model was used for multivariate analysis. Statistical analysis was made using STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

Results

Two hundred and eighteen episodes of E-BSI were included in the study. Due to incomplete medical records, the analysis was performed on 201 patients. The infection rate was 2.4/1000 days of hospital admission. Most E-BSIs were nosocomial related (78.1% HA-BSI, 12.4% HCA and 8.9% CA).

As shown in Table 1, E-BSI occurred mainly in female (61.7%), with a median age of 68.

98.5% of all patients had comorbidities, and the median Charlson Comorbidity Index, adjusted for age, was five (range between four and six). Cancer was the most common comorbidity ($N=67$, 33.3%), followed by diabetes ($N=52$, 25.9%) and chronic obstructive pulmonary disease (COPD) ($N=51$; 25.4%). Approximately 117 patients (58.5%) were hospitalized during the previous 3 months (67.8% in a medical ward, 12.9% in a surgical ward and 21.4% in an intensive care unit).

Patients with E-BSI frequently had invasive devices, mainly a central venous catheter (CVC) (73%) or a urinary catheter (61.7%) (Table 1).

21% of patients were on immunosuppressive therapy other than chronic corticosteroid treatment (12.4%) or had undergone solid organ or hematopoietic stem cell transplant (9.4% and 1.5%, respectively).

Among all E-BSI cases, in 47.9%, *E. faecium* was responsible, whereas *E. faecalis* was isolated in 52.1%. *E. faecalis* was resistant to ampicillin ($N=7$; 3.1%) or vancomycin-resistant enterococci (VRE) $N=5$; 2.2%. On the other hand, *E. faecium* were ampicillin resistant in 22.2% and VRE strains were 23.3% ($N=39$).

Regarding the source of infection, abdominal infections were the most frequent (21.2%), followed by pulmonary infections (18.0%) and urinary tract infections (16.0%), according to clinical presentation and radiological features. Infective endocarditis was diagnosed in 5.5%, but overall only 58.6% of patients did not undergo echocardiography.

Following Sepsis-2 criteria, sepsis occurred in 41.7% of participants and septic shock in 8.0%. Data on severe sepsis have not been analysed for lack of complete data.

According to Sepsis-3 criteria, 15.9% of participants developed sepsis, and 5.4% developed septic shock.

Fifty-two patients (25.8%) received appropriate therapy. The most frequent antibiotic used was vancomycin (17.8%), followed by piperacillin/tazobactam (15.9%) alone or in combination (Table 2).

Risk factors for mortality

According to the univariate analysis (Table 3), mortality was associated with resistance to vancomycin ($p=0.042$, 95% CI [1.02, 3.31]), sepsis ($p=0.003$, 95% CI [1.36, 4.58]) and septic shock ($p=0.007$, 95% CI [1.39, 8.05]). SIRS presentation, instead, was linked to lower mortality ($p=0.047$, 95% CI [1.39, 8.05]). The multivariate analysis (Table 4) confirmed resistance to vancomycin (OR 2.09, 95% CI [1.10, 3.99], $p=0.025$), sepsis (OR 2.57, 95% CI [1.37, 4.82], $p=0.003$) and septic shock (OR 3.82, 95% CI [1.53, 9.55], $p=0.004$) as risk factors for death and sepsis, according to Sepsis-2 criteria as a protective factor (OR 0.50, 95% CI [0.26, 0.99], $p=0.047$).

Survival

No difference was found between the group that received appropriate therapy and the group that did not receive appropriate therapy, except for endocarditis, which was more frequent in the first group ($p=0.003$).

During hospitalization, 53 people (26%) died. Their median survival time was 65 days after the first blood draw. The other 75.4% lived at least 21 days, as shown by the Kaplan-Meier curve. After 28 days of follow-up, the survivorship curve showed no difference between the patients who received appropriate treatment and the patients who did not (Fig. 1).

Discussion

Enterococci are Gram-positive pathogens frequently involved in BSI related to high in-hospital mortality, especially in high comorbid, frail patients [6, 7]. There is a high burden of widespread, difficult-to-treat multi-drug-resistant *E. faecium*, and *E. faecalis* is increasingly resistant to first-line antibiotic choices [7, 8]. While evidence suggests that combination therapy can decrease mortality in patients with enterococcal infective endocarditis, there is no strong evidence on the best therapy for patients with an E-BSI without endocarditis [13, 14].

We retrospectively reported epidemiological, microbiological and clinical features of the population with E-BSI in a single-centre, 2-year observational study. In our study, almost 80% of E-BSIs were hospital acquired, whereas, in similar studies, the incidence was about 40% [7, 22]. Nonetheless, the healthcare-associated incidence of E-BSI was much lower in our study than that in recent literature (about 10% vs 45%) [22]. Moreover, as previously described [7, 8, 22], we observed that BSI frequently occur in the elderly with several comorbidities. Among comorbidities, solid tumour, cardiovascular diseases and diabetes were the three

Table 1 Descriptive analysis of demographic, clinical and microbiological data sorted according to the appropriateness of treatment in bloodstream infections due to *Enterococcus* spp.

	Appropriate treatment (N=149)		Inappropriate treatment (N=52)		Total (N=201)		p-value
	No.	%	No.	%	No.	%	
Sex							0.333
Female	89	59.73	35	67.31	124	61.69	
Male	60	40.27	17	32.69	77	38.31	
Age—average (SD)	69.95	12.65	68.65	13.90	68.02	12.96	0.537 ^a
Comorbidities (at least 1)	171	99.30	57	96.61	198	98.51	0.153
Diabetes	37	24.83	15	28.85	52	25.87	0.569
Liver disease	21	14.09	5	9.62	26	12.94	0.407
Cancer	45	30.2	22	42.31	67	33.33	0.111
AIDS	0	0	0	0	0	0	
Kidney disease	26	17.45	13	25	39	19.4	0.236
Hearth failure	26	17.45	11	21.15	37	18.41	0.553
Myocardial infraction	31	20.81	11	21.15	42	20.9	0.958
COPD	38	25.5	13	25	51	25.37	0.943
Peripheral vascular disease	22	14.77	7	13.46	29	14.43	0.818
Stroke	22	14.77	5	9.62	27	13.43	0.348
Hemiplegia	10	6.71	3	5.77	13	6.47	0.812
Dementia	11	7.38	7	13.46	18	8.96	0.186
Rheumatologic disease	4	2.68	0	0	4	1.99	0.233
Peptic ulcer	6	4.03	0	0	6	2.99	0.142
Charlson Index—median (interquartile range)	5	(4–5)	6	(5–6)	5	(4–6)	0.111 ^b
Risk factors for infection							
Hospitalization (last 3 months) ^c	83	56.08	34	65.38	117	58.5	0.241
Antibiotic therapy (last 6 months) ^d	74	50.34	26	50.98	100	50.51	0.937
Surgical procedure (last 6 months)	57	38.26	17	32.69	74	36.82	0.474
Abdominal surgical drain (last 6 months) ^e	25	17.01	9	17.31	34	17.09	0.960
Abdominal trauma	2	1.34	0	0	2	1	0.401
Use of steroids	19	12.75	6	11.54	25	12.44	0.819
Solid organ transplant	16	10.74	3	5.77	19	9.45	0.292
Stem cell transplant	2	1.34	1	1.92	3	1.49	0.766
Ileocolostomy	6	4.03	3	5.77	9	4.48	0.601
Percutaneous endoscopic gastrostomy ^f	8	5.41	3	5.77	11	5.50	0.921
Parenteral nutrition	43	28.86	14	26.92	57	28.36	0.790
Enteral nutrition	31	20.81	11	21.15	42	20.90	0.958
Immunosuppressive therapy ^g	31	20.95	11	21.15	42	21.00	0.975
Mechanical ventilation							0.265
No	104	71.23	36	70.59	140	71.07	
Endotracheal	34	23.29	9	17.65	43	21.83	
Non-invasive	8	5.48	6	11.76	14	7.11	
Intravenous catheter	94	63.09	30	57.69	124	61.69	0.491
Central line catheter ^h	109	73.65	37	71.15	146	73	0.727
Source of infection							
Urinary tract infection ⁱ	28	18.92	4	7.69	32	16.00	0.057
Pulmonary infection ^j	27	18.24	9	17.31	36	18.00	0.880
Bile duct infection ^k	18	12.16	5	9.62	23	11.50	0.620
Intraabdominal infection ^l	5	3.38	4	7.84	9	4.52	0.186
Gastroenteritis ^m	1	0.68	2	3.85	3	1.50	0.106
Surgical site infection ⁿ	4	2.7	1	1.92	5	2.50	0.757
Diabetic foot ^o	3	2.03	0	0	3	1.50	0.301
Cellulitis ^p	1	0.68	0	0	1	0.50	0.551
Infected decubitus ^q	8	5.48	5	9.8	13	6.60	0.284
Echocardiography							0.003
Not executed	91	61.9	25	49.02	116	58.59	
Negative	52	35.37	18	35.29	70	35.35	
Positive for endocarditis	3	2.04	8	15.69	11	5.56	
Diagnosis of endocarditis with negative echocardiography	1	0.68	0	0	1	0.51	
Type of acquisition							0.942
Community acquired	13	8.72	5	9.62	18	8.96	
Healthcare associated	18	12.08	7	13.46	25	12.44	

Table 1 (continued)

	Appropriate treatment (N=149)		Inappropriate treatment (N=52)		Total (N=201)		p-value
	No.	%	No.	%	No.	%	
Nosocomial acquired	118	79.19	40	76.92	158	78.61	
Clinical presentation							
Sepsis-3 criteria							0.292
No	116	77.85	42	80.77	158	78.61	
Shock	9	6.04	2	3.85	11	5.47	
Sepsis	24	16.11	8	15.38	32	15.92	
Sepsis-2 criteria							0.318
No	75	51.02	25	48.08	100	50.25	
Shock	14	9.52	2	3.85	16	8.04	
Sepsis	58	39.46	25	48.08	83	41.71	
Severe sepsis	NA	NA	NA	NA	NA	NA	
Microbiological data							
Polymicrobial	45	30.2	14	26.92	59	29.35	0.655
<i>Enterococcus faecium</i> ^f	64	45.07	29	55.77	93	47.94	0.186
Ampicillin resistant ^g	61	41.78	27	51.92	88	44.44	0.206
Gentamicin resistant ^h	62	42.47	28	53.85	90	45.45	0.157
Vancomycin resistant ⁱ	23	15.97	14	27.45	37	18.97	0.072

^aT test p value

^bWilcoxon test p value

^cN = 200

^dN = 198

^eN = 199

^fN = 200

^gN = 200

^hN = 200

ⁱN = 200

^jN = 200

^kN = 200

^lN = 199

^mN = 200

ⁿN = 200

^oN = 200

^pN = 199

^qN = 197

^rN = 198

^sN = 199

^tN = 198

^uN = 195

most frequent underlying diseases. Interestingly in this series, COPD (25.3%) was reported at a higher rate than previous studies [7, 9]. This data might be explained, according to literature, by a frequent need for hospitalization, chronic corticosteroid treatment, and airways and gut bacterial colonization in people with COPD accounting for a higher risk of E-BSI. Inghammar et al. [23] described a 2.5-fold increase in bacteraemia in the COPD population in Sweden, and among pathogens involved, E-BSI was more frequent than in the control group [HR 1.9, 95% CI (1.3, 2.6)]. In previous works, COPD patients, notably in the ICU, reported

frequent VRE colonization and higher related BSI rates [24, 25]. Moreover, a high comorbidity burden such as the one in our population with a median Charlson Comorbidity Index (CCI) of 5 must be taken into account in prognostic considerations given that in E-BSI a Charlson Comorbidity Index (CCI) higher than four has been independently associated with 30-day mortality [26].

Iatrogenic immunosuppression is a common risk for enterococcal-related infections, with up to 33% of these patients being admitted to receiving immunosuppressive therapy other than chronic corticosteroids, and 9.4% being

Table 2 Antibiotic molecules used in monotherapy or in combination during empirical or targeted therapy in bloodstream infections due to *Enterococcus* spp.

Antibiotic	N (%)
Vancomycin	106 (17.8)
Piperacillin/tazobactam	95 (15.9)
Linezolid	53 (8.9)
Ceftriaxone	30(5.0)
Gentamicin	25(4.2)
Tigecycline	25(4.2)
Daptomycin	24(4.0)
Ampicillin	22(3.7)
Ampicillin/sulbactam	17(2.8)
Teicoplanin	12 (2.0)
Amoxicillin/clavulanate	11 (1.9)
Imipenem	8 (1.3)

Table 3 Univariate analysis of risk factors for 21-day mortality associated with *Enterococcus* spp. bacteraemia

	HR	CI	p
Appropriated therapy	1.25	[0.70, 2.23]	0.452
Sex	0.98	[0.56, 1.73]	0.956
Age	1	[0.98, 1.02]	0.976
Charlson Index	1.1	[0.99, 1.22]	0.084
Solid organ transplant	0.9	[0.36, 2.26]	0.819
Use of steroids	1.53	[0.77, 3.04]	0.228
Polymicrobial	0.6	[0.32, 1.13]	0.113
<i>E. faecium</i> vs. <i>E. faecalis</i>	1.14	[0.66, 1.95]	0.638
Ampicillin-resistant strains	1.23	[0.72, 2.11]	0.454
Gentamicin-resistant strains	1.55	[0.90, 2.68]	0.114
Vancomycin-resistant strains	1.84	[1.02, 3.31]	0.042
Medical ward	1	[1.00, 1.00]	–
Surgical ward	1.18	[0.52, 2.71]	0.694
Intensive care unit	1.62	[0.89, 2.96]	0.115
Previous stay in intensive care unit	0.98	[0.39, 2.46]	0.968
Shock (sepsis 3)	3.34	[1.39, 8.05]	0.007
Sepsis (sepsis 3)	2.29	[1.36, 4.58]	0.003
Shock (sepsis 2)	1.91	[0.91, 4.02]	0.087
Severe sepsis	–	–	–
Sepsis (sepsis 2)	0.49	[0.25, 0.97]	0.047

admitted to receiving procedures resulting in more aggressive immune-suppression such as solid organ transplant. Besides, in COVID-19 subjects, the acute use of anti-inflammatory agents has been recently identified as an independent predictor of the development of E-BSI [4].

In our cohort, up to 54.7% of participants received enteral or parenteral nutrition during hospitalization. Enteral feeding has reported previously contrasting findings as a protective

[23] or risk factor [7] for enterococcal infection, whereas parenteral nutrition is a well-known factor associated with catheter-related BSI in patients with central venous catheters (CVC) used to administer parenteral nutrition [28–30]. It is relevant to consider that the relative majority, almost one third, of our population received parenteral nutrition. Also, almost 80% of patients had a CVC. The primary source of infections was intraabdominal, including peritonitis, gastroenteritis and biliary tract infections, as stated in several studies [7–9, 24–27].

We also described a surprisingly high proportion of infection supposed to originate from the respiratory tract. Several authors have suggested a correlation between enterococcal pneumonia and enteral feeding, based on a higher risk of oropharynx colonization and the use of broad-spectrum antibiotics [28–30]. In this study, the number of BSI with pulmonary sources (18%) was the highest reported, to our knowledge, with more than 50% of the total population reporting an antibiotic treatment in the previous 6 months and more than 20% having been submitted previously to IMW admission to invasive mechanical ventilation.

Enterococcus spp. is commonly known as a healthcare-associated pathogen, according to the literature [22–31]. The in-hospital incidence combined with the advanced age of those infected, the high rate of medication and the high rate of comorbidities suggest that the infection typically occurs in frail patients.

E. faecalis was the most typical species isolated in this work. Furthermore, the prevalence of *E. faecium* was almost 50%, appearing higher among patients in our study than reported in other studies [8–11]. An estimated 3.1% of strains of *E. faecalis* and 22.2% of strains of *E. faecium* were resistant to ampicillin; moreover, resistance to gentamicin was found in 16.2% and 47.3% of strains, respectively.

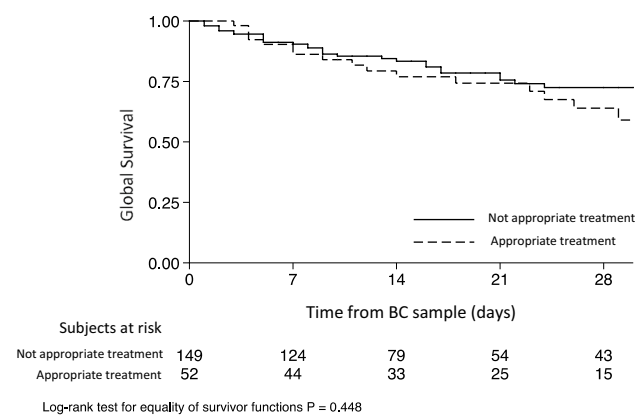
The susceptibility reported for ampicillin is far from that reported in Asian literature [10], which reported susceptibility against 100% of *E. faecalis* isolates and from 3.8% up to 10.8% of *E. faecium* isolates. On the contrary, studies from Denmark and Canada reported susceptibility to ampicillin in 12.3% and 30% of *E. faecium*, respectively, and in 1.3% and 0.4% of *E. faecalis*, respectively [8, 9].

Nonetheless, ampicillin-resistant *E. faecium* was not reported frequently in previous studies and outside Europe [2, 4, 8–11]. This data did not likely represent Italy's basic epidemiology [3, 5, 7, 11]; therefore, more recent homogeneous studies are warranted.

Our study reported VRE in 2.2% of *E. faecalis* strains and 23.3% of *E. faecium* strains. The National Healthcare Safety Network in the US reported a higher rate, with 6.9% and 80% of vancomycin-resistant *faecalis* and *faecium*, respectively [2]. Among Danish and Canadian studies [8, 9], VRE data in *E. faecalis* were 1.5% and 1%, respectively. These studies also reported lower rates of *E. faecium* VRE than us,

Table 4 Multivariate analysis of risk factors for 21-day mortality-associated with *Enterococcus* spp. bacteraemia

	Model 1			Model 2			Model 3		
	HR	CI	<i>p</i>	HR	CI	<i>p</i>	HR	CI	<i>p</i>
Appropriate therapy	1.44	[0.79, 2.63]	0.23	1.39	[0.76, 2.53]	0.289	1.16	[0.64, 2.08]	0.628
Sex	1.11	[0.61, 2.04]	0.727	1.12	[0.61, 2.06]	0.715	1.09	[0.60, 1.99]	0.773
Age	0.99	[0.96, 1.01]	0.319	0.98	[0.96, 1.01]	0.219	0.99	[0.97, 1.02]	0.576
Charlson Index	1.12	[0.98, 1.27]	0.087	1.14	[1.00, 1.30]	0.045	1.13	[1.00, 1.28]	0.056
Solid organ transplant	0.6	[0.23, 1.57]	0.298	0.65	[0.24, 1.74]	0.395	0.95	[0.34, 2.60]	0.913
Use of steroids	1.28	[0.57, 2.84]	0.548	1.44	[0.67, 3.09]	0.35	1.54	[0.71, 3.30]	0.272
Polymicrobial									
<i>E. faecium</i> vs. <i>E. faecalis</i>	0.94	[0.52, 1.70]	0.843	1.03	[0.58, 1.83]	0.922	0.84	[0.46, 1.55]	0.582
Shock (sepsis 3)	3.82	[1.53, 9.55]	0.004						
Sepsis (sepsis 3)	2.57	[1.37, 4.82]	0.003						
Shock (sepsis 2)				2.41	[1.11, 5.25]	0.027			
Sepsis (sepsis 2)				0.50	[0.26, 0.99]	0.047			
Severe sepsis									
Vancomycin-resistant strains							2.09	[1.10, 3.99]	0.025
<i>N</i> patients	201			199			201		
<i>N</i> deaths	53			53			53		

**Fig. 1** Survival at 28 days from time from blood culture sample

at 1.3% and 7% in each group [8, 9]. Antibiotic resistance for ampicillin and vancomycin in our study was higher for both *E. faecalis* and *E. faecium* than that reported in northern European and Canadian literature; however, it was far from the high rates in the US, notably for VRE strains [2, 4, 8, 9].

Although 59% of patients in our study did not undergo echocardiography, the prevalence of endocarditis is in line with the literature where *Enterococcus* spp. is well known to be one of the most frequent causes of endocarditis [12]. Many infectious disease consultations discuss the importance of defining the source of infection, initiating appropriate antimicrobial therapy, managing treatment duration and de-escalation of the therapy once culture isolates are obtained [32, 33].

However, the management of BSI does not always occur after an infection specialist advises it [32, 33]. We demonstrated in enterococcal endocarditis a significant difference in survival when appropriate treatment is administered. Unfortunately, we did not adjust for inappropriate therapy as a confounding factor for survival. Appropriate case management driven by infectious diseases consults includes repeated cultures to assess clearance and ultrasonography to rule out endocarditis in E-BSI [32, 33]. These approaches might also have a role in mortality as previously shown [8–11].

The second aim of this study was to determine if combination therapy decreases mortality in patients with E-BSI. Only one out of four patients received appropriate therapy because clinicians stopped the therapy early; they decided only to use one drug or choose a drug not active against *Enterococcus* spp. To define the role of combination therapy, we identified differences between the number of patients who received appropriate therapy and those who received inappropriate therapy. Each variable was associated with choosing one of the two therapeutic regimens, except for diagnosed endocarditis which was more frequent in the group that received appropriate therapy. This finding can be explained considering that the length of treatment for endocarditis, antimicrobial choice and combinations could rely on many studies and guidelines [18–21].

At the univariate and multivariate analysis, we confirmed some risk factors for mortality previously described in the literature, such as resistance to vancomycin, sepsis and septic shock [13, 14]. On the contrary, appropriate antibiotic therapy was not associated with lower mortality in our casuistic analysis. This finding is likely since the enrolled

patients who received appropriate therapy could still have a poor outcome due to their multiple comorbidities. Therefore, the high medicalization and frailty of these patients may be confounding factors. Furthermore, we found that sepsis seems to be protective for mortality: this result could be due to the fact that Sepsis-2 criteria excluded more critically ill patients. Unfortunately, we are not able to control the confounding factor of the use of combination therapy in patients with sepsis.

A survival of 28 days in 69.94% of patients seems to be higher than in other studies, in which a 21-day mortality was estimated in 21.4–24.8% of participants [13, 14]. However, it is necessary to consider that extensive literature has valued a 30-day survival rate showing a range of mortality from 21% up to 34% to be higher for *E. faecium* bacteraemia [13, 14].

There are several limitations to this study. First, this is a single-centre study that may not accurately reflect the general demographics of Italy. Second, the recurrence of BSI, surveillance blood culture and performance of surgical source control, especially in intraabdominal infections, were other missing data. Moreover, recently EUCAST has warned about the use of daptomycin in the treatment of *Enterococcus* spp. with daptomycin MIC of 4 mg/L, despite that the warning was published after the study design and after our data collection.

Our retrospective study demonstrates that many E-BSI sources in clinical practices within IMWs are not always adequately investigated, and the adequate rule-out of intracardiac vegetations lacks in E-BSI. Despite these elements, inappropriate therapy did not decrease survival in this population. We reported a higher rate of *E. faecium* than other studies. While the rate of ampicillin resistance was lower than expected, the VRE rate was higher than that of Asian and northern European countries [4, 6, 10]. This resistance pattern is consistent with the local epidemiology and the nosocomial acquisition of the infection for the large majority of our cohort. It reflects the microbiological counterpart of the features of the elderly comorbid population with a lengthy history of medicalization and recent previous antibiotic exposure that often populates the internist wards.

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Availability of data and material Available on affordable request.

Code availability Not applicable.

Declarations

Conflict of interest All authors have no conflicts of interest to declare.

Human and animal rights statement Data acquisition and analysis was performed in compliance with protocols approved by the Ethical

Committee of all the participant centers (Città della Salute e della Scienza, Turin, Piedmont, Ethics Committee; Ethical approval number 0031285). The study was conducted according to the guidelines of the Declaration of Helsinki.

Informed consent For this type of study, formal consent is not required.

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