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Risk factors for persistent enterococcal bacteraemia: a multicentre retrospective study

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ABSTRACT

Objectives: Conditions favouring persistent enterococcal bacteraemia (p-EB) have not been fully investigated yet. The aim of our study is to analyse risk factors for p-EB and its impact on mortality.

Methods: International two-centre retrospective study of all hospitalised adults with enterococcal bacteraemia managed with follow-up blood cultures (BCs) during the period 2011–2019. Exclusion criteria were: (1) death within 72 hours from index BCs and (2) polymicrobial bacteraemia. Primary endpoint was p-EB, defined as further isolation of the same species of *Enterococcus* spp. from BCs after at least 72 hours of appropriate antibiotic therapy. Multivariable logistic regression model was performed to assess risk factors for p-EB. The impact of p-EB on 30-day mortality was assessed by Kaplan-Meier survival curve and Cox regression multivariable model.

Results: During the study period, 244 enterococcal bacteraemia were diagnosed. P-EB were 13.5% (33/244). At multivariable analysis, factors independently associated with p-EB were hematologic malignancy (OR 4.60 [95% CI 1.32–16.00], $P = 0.01$), infective endocarditis (OR 7.99 [95% CI 2.20–28.9], $P = 0.002$), and use of daptomycin as initial treatment (OR 4.50 [95% CI 1.29–15.61], $P = 0.018$). Mortality rate was higher in the p-EB group (32% vs. 18%). Kaplan-Meier survival curve showed that patients with p-EB were less likely to survive at 30 days from index BCs (log-rank $P = 0.002$). Using a Cox regression model, independent predictors of 30-day mortality were hematologic malignancy (HR 2.30 [95% CI 1.02–4.11], $P = 0.043$), p-EB (HR 1.93 [95% CI 0.92–4.04], $P = 0.08$), and septic shock (HR 5.92 [95% CI 2.17–16.30], $P = 0.001$).

Conclusion: P-EB was diagnosed mainly in very fragile patients and in those receiving daptomycin as frontline therapy. P-EB may have an impact on mortality.

1. Introduction

Enterococci are leading causative agents of nosocomial infections, particularly bacteraemia. Fragile populations such as elderly, immunosuppressed patients or patients bearing indwelling devices have an increased risk of infection [1]. Major challenges of enterococcal bloodstream infections (BSI) encompass among others the management of enterococcal endocarditis, especially prosthetic endocarditis, as well as the duration of catheter-associated enterococcal bacteraemia (EB) and scant antibiotic alternatives to treat multidrug resistant EB [2].

Persistence of positive follow-up blood cultures (BCs) despite active antibiotic therapy is associated with complicated or deep-

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seated BSI and poor outcomes [3]. In studies performed in patients with *Staphylococcus aureus* bacteraemia or candidemia, the persistence of positive BCs is commonly associated with endocarditis or metastatic infections [3].

Although *Enterococcus* spp. represents the second cause of persistent bacteraemia after *S. aureus* [4], little is known about characteristics, risk factors, and impact on mortality of persistent enterococcal bacteraemia (p-EB) in hospitalised patients. The aim of our study is to analyse risk factors for p-EB and its impact on mortality.

2. Methods

2.1. Study setting and population

We performed a retrospective study in two European tertiary teaching hospitals, Policlinico di S. Orsola, Bologna, Italy (1450 beds) and Hospital Universitari Arnau de Vilanova, Lleida, Spain (500 beds) from January 2011 to December 2019. We enrolled all adult hospitalised patients with monomicrobial EB managed with follow-up blood cultures (FUBCs) (i.e., having FUBCs performed within 7 days from index BC [3]). Exclusion criteria were death within 72 hours from index BCs and polymicrobial BSI. Patients were followed up for one year after index BCs. Cases of EB were identified through prospectively collected databases. BCs processing is described in the Supplementary Materials. The study was approved by local institutional review board.

2.2. Data collection

Data were gathered from hospital medical records. We collected information about demographics, comorbidities, including Charlson comorbidity index [5], conditions of immunosuppression (absolute neutrophil count [ANC] <500 mmc, stem cell or solid organ transplantation, uncontrolled HIV infection [CD4+ <200 mmc] or ongoing corticosteroid therapy at a dosage higher than or equivalent to prednisone 16 mg/day for 15 days), presence of prosthesis or catheters, ward of admission. Data concerning the source of BSI was collected according to the Center for Disease Control and Prevention (CDC) definitions [6]. Because the study was designed before the development of SEPSIS-3 consensus definitions, severe sepsis was defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion; septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, according to the criteria proposed by the 2012 SSC guidelines [7]. Intensive care unit (ICU) admission, antibiotic susceptibility of enterococcal species isolated from blood, and antibiotic therapy were other major variables collected.

2.3. Definitions

Bacteraemia onset was considered the day of collection of first positive BCs for *Enterococcus* spp. The main endpoint was p-EB, which was defined as further isolation of the same species of *Enterococcus* spp. from BCs after at least 72 hours of appropriate antibiotic therapy.

Duration of bacteraemia was computed in days between index BC and the first negative BC.

Antibiotic treatment was considered appropriate if concordant with antimicrobial susceptibility test and in keeping with pharmacokinetic/pharmacodynamic drug properties according to current expert opinion [8].

2.4. Statistical analysis

Categorical variables were presented as absolute numbers and their relative frequencies. Continuous variables were presented as the mean and standard deviation if normally distributed or as the median and interquartile range (IQR) if non-normally distributed. Univariate and multivariate analysis were performed to assess relationship of study variables with p-EB and 30-day all-cause mortality as follows. First, categorical variables were compared using χ^2 or Fisher exact test for samples <5, and continuous variables were analysed using the Mann-Whitney *U* test. Then significant and clinically relevant covariates identified in univariate analysis were introduced into a multivariable logistic regression model to assess risk for p-EB using a *P* cut-off of 0.05. The impact of p-EB on 30-day mortality was assessed Kaplan-Meier survival curve and a Cox regression multivariable model.

3. Results

During the study period, 1028 cases of enterococcal bacteraemia were screened. Of these, 784 were excluded (237 polymicrobial infections, 32 patients expired within 72 hours from index BCs, and 515 were not managed with FUBCs). Thus, 244 monomicrobial enterococcal bacteraemia were included in the study. Males were 152 (62%), median age was 69 (IQR 57–79) years, and median Charlson comorbidity index was 6 (4–8). Overall, *Enterococcus faecalis* was the species mainly isolated (126, 52%). Other demographic and clinical variables of the study population are displayed in Table 1. The median (IQR) time between index BC and FUBC was 3 (2–4) days.

P-EB was identified in 33/244 (13.5%) patients. Age, comorbidities, and severity of infection were similar among patients with and without p-EB (Table 1). Patients with p-EB were significantly more affected by hematologic malignancies (9/33, 27% vs. 21/211, 10% $P = 0.005$) and heart valve disease (14/33, 45% vs. 28/211, 26% $P = 0.05$). They more often carried prosthetic heart valve (7/33, 21% vs. 20/211, 9.5%, $P = 0.46$) and vascular prosthesis (5/33, 15% vs. 15/211, 7%, $P = 0.12$). Endocarditis was generally diagnosed in the p-EB group (8/33, 24% vs. 19/211, 9%, $P = 0.009$). Therapeutic regimes were similar in the two groups, except for daptomycin, which was mainly administered for p-EB (10/33, 30.3% vs. 16/211, 7.6%, $P < 0.001$). Duration of bacteraemia was 7 days in median (IQR 4–11) in the p-EB group, whereas it was 4 days (IQR 2–5, $p < 0.001$) for non-persistent EB.

Factors independently associated with p-EB were hematologic malignancy (odds ratio [OR] 4.60 [95% confidence interval {CI} 1.32–16.00], $P = 0.01$), infective endocarditis (OR 7.99 [95% CI 2.20–28.9], $P = 0.002$), and use of daptomycin as initial treatment (OR 4.50 [95% CI 1.29–15.61], $P = 0.018$) (Table 2).

When compared, 30-day mortality rate was higher in the p-EB group (32% vs. 18%). Kaplan-Meier survival curve showed that patients with p-EB were less likely to survive at 30 days from index BCs (log-rank $P = 0.002$, Supplementary Fig. S1). Comparison of survivors vs. non-survivors after 30 days is summarised in Supplementary Table S1. Using a Cox regression multivariable, independent predictors of 30-day mortality were hematologic malignancy (HR 2.30 [95% CI 1.02–4.11], $P = 0.043$), p-EB (HR 1.93 [95% CI 0.92–4.04], $P = 0.08$), and septic shock (HR 5.92 [95% CI 2.17–16.30], $P = 0.001$) (Supplementary Table S2).

4. Discussion

In our study, p-EB was diagnosed in 13.5% of patients managed with FUBCs for enterococcal bacteraemia. Such a rate is slightly lower than that observed in previous studies, where p-EB was found in about 20% of EB managed with FUBCs [4,9].

Persistent bloodstream infections have been extensively investigated for species such as *S. aureus* and *Candida* spp., and they have been associated with deep-seated infections and death de-

Table 1
Comparison between patients with and without persistent enterococcal bacteraemia

	No persistent enterococcal bacteraemia (N=211)	Persistent enterococcal bacteraemia (N=33)	*P*
Demographics			
Male	132 (63%)	20 (61%)	0.8
Age, years, median (IQR)	69 (57–79)	70 (59–77)	0.70
Comorbidities			
Charlson comorbidity index, median (IQR)	6 (4–8)	5 (3–7)	0.19
Pitt's score [19], median (IQR)	1 (0–2)	1 (0–2)	
Myocardial infarction	20 (10%)	4 (12%)	0.63
Congestive heart failure	38 (18%)	7 (21%)	0.66
Peripheral vascular disease	32 (15%)	5 (15%)	0.99
Cerebrovascular accident or transient ischemic attack	25 (12%)	4 (12%)	0.96
Dementia	14 (7%)	1 (3%)	0.7
COPD	39 (19%)	8 (24%)	0.44
Connective tissue disease	11 (5%)	2 (6%)	0.69
Mild liver disease	10 (5%)	2 (6%)	0.67
Uncomplicated diabetes mellitus	22 (10%)	4 (12%)	0.76
Moderate to severe chronic kidney disease	51 (24%)	6 (18%)	0.45
Complicated diabetes mellitus	20 (10%)	3 (9%)	1
Localized solid tumour	51 (24%)	3 (9%)	0.52
Moderate to severe liver disease	34 (16%)	4 (12%)	0.79
Metastatic solid tumour	26 (12%)	0 (0%)	0.09
AIDS	1 (0.5%)	1 (3%)	0.25
Active hematologic malignancy	21 (10%)	9 (27%)	0.005
Solid organ transplant	16 (8%)	2 (6%)	0.76
Biologic drug therapy	14 (7%)	4 (12%)	0.28
Steroidal therapy	17 (8%)	4 (12%)	0.5
Heart valve disease	28 (26%)	14 (45%)	0.05
Prosthetic heart valve	20 (9.5%)	7 (21%)	0.46
Vascular prosthesis	15 (7%)	5 (15%)	0.12
Microbiology			
Enterococcus faecalis	114 (54%)	12 (36%)	0.59
Enterococcus faecium	89 (42%)	19 (58%)	0.09
Other enterococci	9 (4%)	2 (6%)	0.65
VRE	10 (5%)	0 (0%)	0.36
HLAR	69 (33%)	13 (39%)	0.45
Ampicillin resistance	87 (41%)	19 (58%)	0.08
Unit of admission			
Medical ward	121 (62%)	19 (65%)	0.72
Surgical ward	46 (25%)	5 (19%)	0.55
Hematologic ward	12 (7%)	7 (25%)	0.002
ICU	31 (17%)	2 (8%)	0.38
Nosocomial infection [20]	135 (64%)	19 (58%)	0.48
Healthcare-associated infection [20]	36 (17%)	4 (12%)	0.62
Community-acquired infection [20]	40 (19%)	10 (30%)	0.13
Severity			
Severe sepsis	29 (14%)	3 (9%)	0.59
Septic shock	5 (2%)	2 (6%)	0.24
Source of bacteraemia			
central venous catheter (CVC)	45 (21%)	8 (24%)	0.7
Surgical site infection	11 (5%)	0 (0%)	0.37
Skin and soft tissue	4 (2%)	1 (3%)	0.52
GI	66 (31%)	6 (18%)	0.12
UTI	32 (15%)	7 (21%)	0.38
Primary	57 (27%)	13 (39%)	0.14
Endocarditis	19 (9%)	8 (24%)	0.009
Antibiotic treatment			
Glycopeptides	77 (35%)	11 (33%)	0.84
Beta-lactams	91 (43%)	13 (39%)	0.71
Linezolid	14 (6%)	2 (6%)	0.99
Daptomycin	16 (7.6%)	10 (30.3%)	<0.001
Outcome			
Duration of EB, days, median (IQR)	4 (2–5)	7 (4–11)	<0.001
Time to FUBC, days, median (IQR)	2 (2–4)	3 (2–4)	0.79
Length of in-hospital stay, days, median (IQR)	31.5 (19–57)	45 (26–59)	0.45

COPD, chronic obstructive pulmonary disease; CVC central venous catheter , ; EB, enterococcal bacteraemia; GI, gastrointestinal; HLAR, high level minoglycoside Resistance; ICU, intensive care unit; IQR, interquartile range; UTI, urinary tract infection; VRE, vancomycin-resistant enterococci;

spite appropriate antimicrobial treatment [3]. Continuous EB (defined as a positive result in all of three BCs, or the majority if more than three BCs, with the first and last sample drawn at least 1 hour apart) was previously associated with diagnosis of endocarditis [10]. In this study we furtherly explored this fact, and we observed that consecutive positive BCs despite 72 hours of effective therapy remains significantly related to endocarditis.

Among the p-EB group, we identified about one-third (27%) of patients affected by an active hematologic malignancy. This aligns with previous reports finding association between p-EB and neutropenia [11,12]. Over the last decades, incidence of Enterococcus spp. has been increasing among causative agents of BSI in onco-hematologic patients mainly due to gastrointestinal translocation and large use of central vascular catheter for chemotherapy [13].

Table 2
Multivariable logistic regression model: Factors independently associated with persistent enterococcal bacteraemia

Covariate	OR	95% CI	*P* value
Age*	1.01	0.98–1.04	0.27
Sex, male	0.97	0.42–10.48	0.93
Active hematologic malignancy	4.77	1.72–13.20	0.003
Daptomycin as frontline therapy	3.58	1.31–9.81	0.013
Infective endocarditis	3.27	1.02–10.48	0.044
Community-acquired infection	1.75	0.63–4.80	0.27
Enterococcus faecium	1.75	0.71–4.31	0.22

CI, confidence interval; OR, odds ratio.
* Per year of increase. Hosmer and Lemeshow goodness-of-fit test, $P = 0.27$. Model discrimination: area under receiver operating characteristics (AUROC) 0.74.

Recent microbiome studies have found that chemotherapy-induced disruption of intestinal mucosa along with prolonged antibiotic courses were associated with loss of biodiversity, overgrowth of Enterococcus spp., and acquisition of resistance leading to higher risk of multidrug-resistant (MDR) bacteraemia and mortality [14–16].

Interestingly, use of daptomycin as frontline therapy was found to be strongly associated with p-EB. It is worth noting that most of our p-EB was sustained by ampicillin-resistant *E. faecium*. Daptomycin at a dosage of 6–8 mg/kg/day is considered an alternative option for uncomplicated non-vancomycin-resistant enterococcal (VRE) BSI, while higher dosages (10–12 mg/kg/day) are recommended for VRE [2]. However, cases of therapeutic failure of daptomycin with non-MDR enterococcal infections have been reported. Shukla et al. observed that in patients with *E. faecium* BSI, daptomycin MIC of 3–4 mcg/mL and immunosuppression were significantly related to microbiological failure even using high-dose daptomycin (≥8 mg/kg) [17]. For these reasons, a recent EUCAST position paper raises major concerns about the use of high-dose daptomycin for enterococcal BSI and endocarditis [18].

Persistent EB demonstrated to impact on mortality. Non-survival was also significantly related to other poor-outcome conditions such as hematologic malignancies and septic shock. If these data would be confirmed, implementation with FUBCs may be introduced in the common management of enterococcal BSI. In fact, in a pre-post, single-centre study the implementation of an intervention including infectious disease consultation, FUBCs, and echocardiography to all incident enterococcal BSI was associated with lower mortality [9].

This study was limited by retrospective design, which might have affected accuracy of data collection. Lack of VRE may impair the generalisability of our results to other settings. In conclusion, p-EB should be acknowledged as a serious complication affecting most vulnerable hospitalised patients. FUBCs should be considered for implementation of EB diagnostic work-up. Choice of antibiotic therapy for EB is crucial, and evidence of efficacy of anti-enterococcal drugs currently in use is urgently needed.

Declaration of Competing Interest

None to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2022.05.003.

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