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Original article

Monotherapy vs. combination therapy for *Enterococcus faecalis* bacteraemia: a target trial emulation

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ABSTRACT

Objectives: Optimal treatment for *Enterococcus faecalis* bloodstream infection (EF-BSI) remains a topic of debate. We aim to evaluate the effectiveness of combination therapy compared with monotherapy in patients with EF-BSI and no endocarditis.
Methods: This was a target trial emulation based on a prospective, multicentre, international dataset collected in 24 international centres from January 2019 to December 2024. We included all adult patients with monomicrobial EF-BSI with negative echocardiography within 7 days from BSI onset. Exclusion criteria were diagnosis of endocarditis, not receiving or completed the therapy at randomization. Primary endpoint was clinical failure defined as a composite of death, relapse of EF-BSI, and diagnosis of endocarditis, at 90 days.
Results: Overall, 373 patients were eligible for inclusion, 267 of whom (71%) received monotherapy, mainly ampicillin (174 of 267, 65%); most prescribed combination regimens were ampicillin with either ceftriaxone or gentamicin (80 of 106, 75%). The composite clinical failure was met by 114 of 373 (31%) patients. The outcomes among patients who received monotherapy or combination treatment were 75 of 267 (28%) versus 39 of 106 (36%); p 0.185, leading to an overall risk difference in favour of monotherapy of 2% (95% CI, −10% to 15%). Sepsis or septic shock at the time of presentation was the only independent variables associated with clinical failure, after performing a weighted univariable and multivariable Cox regression model (adjusted hazard ratio, 0.85; 95% CI, 0.52−1.39).
Conclusions: With the limitation of our sample size and observational design, we were not able to observe a better outcome associated with combination treatment for EF-BSI. If confirmed, these results would promote therapeutic simplification according to antimicrobial stewardship principles.
Michele Bartoletti, Clin Microbiol Infect 2026;32:983

Introduction

Enterococcus faecalis is a major pathogen in bloodstream infections (BSIs), and the incidence of infections caused by *E. faecalis* has increased in recent decades, potentially due to the global aging of the population. Common sources of *E. faecalis* BSI (EF-BSI) include urinary tract and intra-abdominal infections [1–3]. Furthermore, *E. faecalis* is a prominent cause of infective endocarditis (IE), especially in elderly patients including those with transcatheter aortic valve implantation [4].

Mortality for EF-BSI ranges from 11% to 26% [2,5–7]. Key factors contributing to short-term mortality include the number of comorbidities, baseline conditions and the promptness of appropriate antibiotic treatment administration [2].

Although combination treatment is considered the standard of care for *E. faecalis*–associated IE, the optimal treatment for EF-BSI without endocarditis remains a topic of debate [8]. Aminopenicillins (ampicillin or amoxicillin) are commonly considered the drug of choice. However, because of its bacteriostatic activity against most *E. faecalis* strains, many experts recommend combination therapy with an aminoglycoside or ceftriaxone in life-threatening infections to exploit their synergistic effect [9–12]. The Infectious Diseases Society of America's 2009 guidelines on catheter-related BSI highlighted the need for further investigation into combination therapy for enterococcal catheter-related BSI [13]. This uncertainty in management was evident in two recent European surveys among infectious disease specialists, where only 37–57% recommended combination treatment for EF-BSI [14,15].

The aim of this study is to evaluate the effectiveness of combination therapy compared with monotherapy in patients with monomicrobial EF-BSI and no endocarditis.

Methods

Study design

This prospective, multicentre, international, study was conducted in 24 centres in 5 different countries (Italy, Spain, Switzerland, Romania, and Brazil) from January 2019 to December 2024. Design of the emulated trial is depicted in Table S1, whereas in Table S2, the Target 2025 checklist is reported.

Study population

\Adult (aged ≥18 years) patients with clinically significant monomicrobial BSI and at least one negative transthoracic echocardiography within day 7 from BSI onset were included. Exclusion criteria were diagnosis of IE at the time of echocardiography (time zero of emulated randomization, see next paragraph), mortality within 72 hours from index blood cultures, receipt of inappropriate therapy before time of inclusion, defined as no *in vitro* active drug (monotherapy of ceftriaxone, gentamicin or streptomycin without a penicillin were considered inactive). Follow-up blood cultures were not mandatory per protocol but were performed according to the standard of care of the study site. Patients' follow-up was set at day 90 after blood cultures collection and was assessed with medical records or telephone call. The study was approved by Committee of Ethics of Emilia Centrale (CE-AVEC protocol. 293/2019/Oss/AOUBo) and thereafter in any single participating centre.

Treatment arms

The emulated randomization occurred when the echocardiography was performed and resulted negative (time zero); patients

were included in the combination arm in case of treatment with at least two *in vitro* active drugs (ampicillin, amoxicillin, ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin, piperacillin-tazobactam, vancomycin, teicoplanin, daptomycin, linezolid, ceftobiprole, or intravenous fosfomycin) or one *in vitro* active penicillin plus a synergistic drug (ceftriaxone, gentamicin, or streptomycin) as targeted treatment. Patients receiving one *in vitro* active drug were included in the monotherapy arm. Regimen choice and treatment duration was not dictated by study protocol.

Treatment allocation

We implemented a cloning–censoring–weighting approach [16]. Each patient was duplicated into both treatment arms (monotherapy vs. combination). A clone was censored if its treatment deviated from the assigned arm. The grace period was the interval from blood culture collection to negative echocardiography. If an event occurred before censoring, it was attributed to both clones.

Endpoints

The primary endpoint was clinical failure defined as death, relapse of EF-BSI and diagnosis of endocarditis at day 90.

Secondary endpoints were: (i) worsening of sequential organ failure assessment (SOFA) score during treatment; (ii) persistence of fever at day 7 of treatment; (iii) relapse of EF-BSI within 90 days; (iv) diagnosis of IE within 90 days; (v) all-cause 90-day mortality.

Variables collected and definitions

Variables were collected through clinical charts and hospital electronic records. De-identified data were collected and managed using REDCap electronic data capture tool. Comorbidities were identified using the Charlson Comorbidity Index [17]. Immunocompromised host were defined by neutropenia ($<500/mm^3$); hematopoietic stem cell or solid organ transplantation; receipt of steroids (at a dose of 0.3 mg/kg/day of prednisone equivalent or higher for more than 3 weeks); or treatment with other recognized T-cell immunosuppressive agents such as calcineurin inhibitors, tumour necrosis factor-α blockers, specific monoclonal antibodies, or nucleoside analogues within the past 90 days. The presence of cardiac devices, including prosthetic valves and implantable cardiac electronic devices, was also collected as well as BSI epidemiological classification, according to the Friedman criteria [18]. We also collected SOFA [19], Number of positive blood cultures, Origin of infection unknown, Valve disease, Auscultation of a murmur (NOVA) [20] and Duration of symptoms $\geq$7 days, Embolic phenomena Number of positive blood cultures, Origin of infection unknown Valve disease and Auscultation of a murmur (DENOVA) [21,22] scores at the time of blood culture collection, and information regarding the source of infection and any source control procedures employed. Persistent bacteraemia was defined as positive blood cultures for *E. faecalis* at 72 hours after the index EF-BSI in patients despite receiving active treatment. Endocarditis diagnosis was made using 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria [23] that consider *E. faecalis* a typical pathogen for endocarditis. All patients enrolled before the publication of these novel criteria were retrospectively reclassified.

Statistical analysis

Descriptive statistics were produced for clinical characteristics and outcomes of patients. Continuous variables were presented as median with interquartile range (IQR) (quartile 1 to quartile 3), whereas count and percentage were used for categorical variables. Categorical variables underwent comparison via the χ^2 test or Fisher's exact test, as appropriate. The Wilcoxon rank sum test was employed for continuous variables.

To simulate a randomization, a clone–censoring–weighting approach was emulated: specifically, because the allocation to treatment after the grace period (time from diagnosis of infection and performance of echocardiography to targeted treatment) is not random, inverse probability of censoring weight is necessary to restore between-group comparability. The probability of remaining uncensored on each day during the grace period was estimated using a multivariate Cox model fitted in each arm, and weights were equal to the inverse of this probability. Variable selection included variables that were considered associated both with exposure or outcome and outcome only. The final model is presented in Table S3. Specifically, in the model, sepsis/septic shock and initial empirical therapy (monotherapy, combo or, no active drugs) were treated as time-varying covariates during the grace period. The model was checked for missing variables that were absent. Finally, standardized differences were examined to assess balance using a threshold of 10% to indicate clinically meaningful imbalance requiring a further adjustment in outcome analyses (Table S4) [17].

A treatment effect regression was made to determine the 'per-protocol' impact of monotherapy versus combination therapy on risk of composite clinical failure; results were expressed as risk difference and 95% CI, obtained through a nonparametric bootstrap with 1000 replicates.

Weighted Kaplan–Maier and Cox regression models were used to estimate predictors of composite clinical failure, after covariates adjustment.

The independent impact of variables on the primary endpoint (composite clinical success) was assessed through both unadjusted and multivariate-adjusted hazard ratios (HRs) using Cox proportional hazards regression. To improve precision and account for residual imbalance, weighted Cox proportional hazards models were fitted to estimate HRs for the primary outcome. Covariates included in the outcome model were selected *a priori* based on clinical relevance and prior evidence, rather than statistical significance alone. This approach constitutes a doubly robust estimation strategy, providing consistent effect estimates if either the censoring model or the outcome model is correctly specified. Adjusted HRs and their 95% CIs were determined for each variable. The model was replicated to ensure different comparisons: 'any monotherapy' versus 'any combination therapy' (model A); 'monotherapy with a β-lactam' versus 'other therapies' (model B); and comparison between β-lactam monotherapy and combination of penicillin plus ceftriaxone or an aminoglycoside (model C).

In order to confirm the generalizability of results, the treatment effect regression was made also on specific subgroups of patients, including type of ward of admission, presence of endovascular devices, severity of infection, DENOVA score and primary site of infection.

A sensitivity analysis was also performed after censoring patients shifting from monotherapy to combination after randomization (or vice versa).

In all cases, a p value < 0.05 was considered statistically significant. Statistical analysis was performed using STATA 'Standard Edition', version 19.5 (StataCorp, College Station, TX, USA).

Sample size

Assuming that 80% of E-BSI treated with combination therapy did not experience clinical failure according to literature, a

noninferiority margin of 14% (equivalent to a success rate of 70%) was considered acceptable. Hence, a total sample size of 228 patients (at least 114 per arm) was calculated with an alpha error of 0.05 and a β error of 0.8 (equivalent to a power of 80%).

Results

Clinical characteristics of the study population

During the study period, 620 patients with monomicrobial EF-BSI were enrolled, of whom 373 (60%) were eligible for final study inclusion. We excluded 133 patients with IE, 79 patients who not received an echocardiography within 7 days from EF-BSI onset and 35 patients with incomplete data or lost to follow-up (Fig. S1). A detailed contribution of each centre is depicted in Table S5.

A total of 373 patients were included at the time of echocardiography, which occurred after a median of 3 (2–4) days from EF-BSI onset: 131 of 373 (35%) were female, with a median age of 73 years (IQR, 62–81 years), and a median Charlson Comorbidity Index of 6 points (IQR, 4–8 years) (Table 1).

When the two groups were compared, some significant differences emerged. Patients treated with combination therapy were more likely to have prosthetic valves (34 of 106 [32%] vs. 34 of 267 [13%], p < 0.001), and primary BSI (35 of 106 [33%] vs. 49 of 267 [18%] p 0.002). Moreover, the median DENOVA score was higher in the combination therapy group (1 [0–3] vs. 1 [0–2], p < 0.001).

After cloning, artificial censoring and inverse probability of censoring weighting a total of 267 patients (71%) received monotherapy, whereas the remaining 106 (29%) being treated with combination therapy. After this adjustment, the difference between the two groups was comparable (Table S3). All prescribed regimens are detailed in Table S6. The most common regimen in the monotherapy group was β-lactam monotherapy (249 of 373, 67%), mainly ampicillin, whereas the most prescribed combination regimens were ampicillin with either ceftriaxone or gentamicin. A comparison of patients receiving combination and monotherapy is shown in Table 1.

Table 1
Clinical characteristics of patients treated with monotherapy or combination therapy

Characteristic	Any monotherapy (*n* = 267)	Any combination therapy (*n* = 106)	p
Age (y), median (IQR)	73 (61–81)	75 (64–82)	0.292
Female sex, *n* (%)	96 (36)	35 (33)	0.592
Charlson comorbidity index, median (IQR)	5 (4–8)	6 (4–7)	0.434
Comorbidities, *n* (%)			
Myocardial infarction	54 (20)	34 (32)	**0.015**
Congestive heart failure	68 (25)	35 (33)	0.141
Cerebrovascular disease	30 (11)	18 (17)	0.135
Dementia	23 (9)	13 (12)	0.282
Chronic obstructive pulmonary disease	42 (16)	21 (20)	0.343
Diabetes without organ damage	53 (20)	21 (20)	0.993
Diabetes with organ impairment	34 (13)	16 (15)	0.546
Moderate or severe CKD	64 (24)	21 (20)	0.388
Moderate or severe liver failure	20 (7)	6 (6)	0.531
Any neoplastic disease	57 (21)	23 (22)	0.941
Immunosuppressive diseases, *n* (%)			
Neutropenia (>7 d)	7 (3)	3 (3)	0.910
Corticosteroid chronic therapy	25 (9)	6 (6)	0.243
Solid organ transplant	9 (3)	4 (4)	0.848
Other	13 (5)	10 (9)	0.098
Presence of any valvular prothesis, *n* (%)	34 (13)	34 (32)	**<0.001**
Presence of any vascular prothesis, *n* (%)	12 (5)	10 (10)	0.052
DENOVA score, median (IQR)	1 (0––2)	1 (0––3)	**0.001**
DENOVA >3, *n* (%)	42 (16)	27 (25)	**0.029**
DENOVA parameters, *n* (%)			
Duration of symptoms >7 d	23 (9)	19 (18)	**0.010**
Embolization	8 (3)	10 (9)	**0.009**
At least 2 positive blood cultures	80 (30)	37 (35)	0.353
Unknown origin of bacteraemia	63 (24)	37 (35)	**0.026**
Any valvulopathy	62 (23)	39 (37)	**0.008**
Heart murmur at auscultation	50 (19)	24 (23)	0.392
Ward of hospitalization, *n* (%)			
Emergency department	24 (9)	9 (8)	0.879
Internal medicine	161 (60)	72 (68)	0.170
Surgical unit	64 (24)	17 (16)	0.094
ICU	28 (10)	10 (9)	0.762
Severity of disease: sepsis-3 definition, *n* (%)			
No sepsis	160 (60)	65 (61)	0.804
Sepsis or septic shock	107 (40)	41 (39)	
Site of infection,[a] *n* (%)			
Primary BSI	49 (18)	35 (33)	**0.002**
Urinary tract	108 (40)	33 (31)	0.094
Intra-abdominal	31 (12)	11 (10)	0.734
CVC-related	45 (17)	9 (8)	**0.038**
Appropriate empirical antibiotic therapy, *n* (%)	134 (50)	47 (44)	0.308
Duration of therapy (d), median (IQR)	9 (6––14)	11 (7––16)	**0.004**

Boldface means statistically significant (p < 0.05); IQR is quartile 1 to quartile 3.
BSI, bloodstream infection; CKD, chronic kidney disease; ICU, intensive care unit; IQR, interquartile range; CVC, Central Venous Catheter; DENOVA, Duration of symptoms ≥7 days, Embolic phenomena Number of positive blood cultures, Origin of infection unknown Valve disease and Auscultation of a murmur.
[a] Not mutually exclusive.

Primary endpoint analysis

The composite clinical failure was met by 114 (31%) patients. No difference was observed among patients who received monotherapy or combination treatment in primary endpoint (75 of 267 [28%] vs. 39 of 106 [36%]) and secondary endpoints (Table 2).

The overall risk difference on composite clinical failure of receiving monotherapy versus combination therapy was 2% (95% CI, −10% to 15%) (model A). Similar results were obtained for Model B (risk difference, 5%; 95% CI, −7% to 17%) and model C (risk difference, 1%, 95% CI, −14% to 13%).

Fig. 1 show weighted Kaplan–Meier curves of probability of composite clinical failure at day 90 according to monotherapy vs. combination (model B and model C are shown in Figs S2 and S3). In all cases no statistical differences among the groups were found.

By performing a univariable and multivariable Cox regression model (Table 3), severity of infection at presentation (according to Sepsis-3 definition) was the only independent predictor of composite clinical failure of EF-BSI in all models. Conversely, monotherapy or combination therapy was not significantly associated with the outcome. The Cox model was also adjusted for different centres of enrolment, but no significant differences were noticed in the primary outcome (data not shown).

Secondary outcome analysis

Monotherapy was not associated with worsening SOFA during treatment, persistent fever at day 7, 90-day relapse of EF-BSI, 90-day incidence of endocarditis or 90-day all-cause mortality (Table 2).

Subpopulation exploratory and sensitivity analysis

The impact of monotherapy on probability of composite clinical success (Fig. 2) was tested on several subgroups: also in this case, no significant impact of monotherapy was noticed (see Figs S4 and S5 for models B and C).

A sensitivity analysis was performed after censoring patients who switched from one arm to another during the treatment. Specifically, 12 patients were identified, 9 of whom shifted from combination to monotherapy after a median of 5 (4–6) days from randomization. Results of the analysis did not change after removing these patients (data not shown).

Discussion

In this target trial emulation, we found that there was no significant difference in the primary composite outcome of clinical failure between patients treated with monotherapy and those treated with combination therapy for EF-BSI after excluding patients with IE. This was consistent even after adjusting for potential confounding factors using Cox-regression models. Similarly, subgroup analyses did not reveal any significant impact of monotherapy on the probability of composite clinical success in any specific subgroup of patients. Additionally, the worsening of SOFA score, persistent fever, relapse of EF-BSI, diagnosis of endocarditis during the follow-up and all-cause mortality were not significantly influenced by whether patients received monotherapy or combination therapy.

Not surprisingly, the presence of sepsis or septic shock at the time of presentation was the only independent variables associated with the composite clinical failure in patients with EF-BSI.

The baseline hypothesis is that combination therapy may outperform monotherapy because enterococci's low Penicillin Binding Protein (PBP) affinity reduces β-lactam bactericidal activity, risking treatment failure in high-burden bacteraemia such as IE [2]. However, the efficacy of the combination treatment in patients with EF-BSI was poorly evaluated in clinical studies [24]. In a retrospective study of EF-BSI in children, the adjunctive of aminoglycoside to ampicillin was associated with an increase of acute kidney injury without a clear benefit in term of mortality, relapse of bacteraemia and subsequent development of endocarditis [25].

The results of this study, if further confirmed, can be considered another example of 'less is more' theory and an opportunity to further reduce antibiotic pressure to hospitalized patients. This could be of particular importance in the setting of patients developing EF-BSI, typically elderly patients with multiple comorbidities in whom the risk of antibiotic adverse events, secondary infections or *Clostridioides difficile* colitis could be even higher than usual [26].

This study has several strengths: at first it includes a quite wide population of patients from different teaching hospitals: this increases the generalizability of results. Second, the analysis was performed both including any monotherapy, or more specifically, β-lactams: this improves the clinical applicability of results to different settings. Third, despite this being an observational study, the large sample size permitted performing several subgroup analysis and propensity score adjusted models. Finally, this work analysed many endpoints that are clinically meaningful, including clinical cure, mortality, EF-BSI recurrence, incidence of persistent bacteraemia and onset of IE.

Nevertheless, our study has several important limitations. Despite all statistical adjustment to simulate a target trial on this topic, including the use of clone–censoring–weighting, potential selection bias based on unmeasured confounding could still be present, hampering results. In addition, to limit indication bias, all patients underwent echocardiography and IE was excluded, and results were unchanged in subgroup analyses by prosthetic valve

Table 2
Primary and secondary outcome analysis

Outcome	Model A			Model B			Model C		
	Any combination therapy (n = 106)	Any monotherapy (n = 267)	p	Any mono/combination therapy (n = 124)	Monotherapy with β-lactams (n = 249)	p	Beta-lactam plus AG or CTX (n = 80)	Monotherapy with β-lactams (n = 249)	p
Composite – clinical failure, n (%)	39 (36)	75 (28)	0.185	42 (34)	72 (28)	0.328	26 (33)	72 (29)	0.542
Worsening of SOFAduring treatment, n (%)	10 (9)	24 (9)	0.992	12 (10)	22 (9)	0.790	6 (8)	22 (9)	0.710
Febrile at day 7, n (%)	7 (7)	9 (3)	0.201	6 (59	10 (4)	0.712	2 (3)	10 (4)	0.529
90-d relapse of BSI, n (%)	29 (27)	54 (20)	0.291	9 (7)	12 (6)	0.336	6 (8)	12 (5)	0.359
Diagnosis of endocarditis, n (%)	7 (7)	14 (5)	0.691	6 (5)	3 (1)	0.055	4 (5)	3 (1)	0.055
90-d all-cause mortality, n (%)	29 (27)	54 (20)	0.319	31 (25)	52 (21)	0.328	19 (24)	52 (21)	0.653

AG, aminoglycoside; BSI, bloodstream infection; CTX, ceftriaxone; SOFA, sequential organ failure assessment.

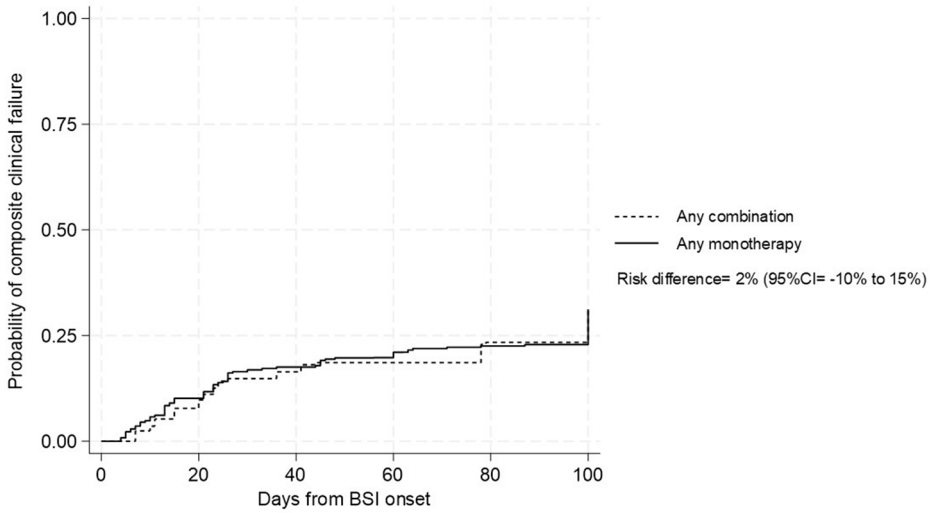

Fig. 1. Kaplan–Meier curves for incidence of composite clinical success in patients receiving combination vs. monotherapy for *Enterococcus faecalis* bloodstream infection (BSI). Any monotherapy as variable of interest; log rank p 0.351.

Table 3
Cox regression model for predictor of composite clinical failure

Characteristic	Univariable analysis			Multivariable analysis (model A)			Multivariable analysis (model B)			Multivariable analysis (model C)		
	HR	95% CI	p	aHR	95% CI	p	aHR	95% CI	p	aHR	95% CI	p
Age (per 1 y increase)	1.01	0.99–1.02	0.226	\			\			\		
Female sex	1.29	0.83–2.00	0.251	\			\			\		
Charlson comorbidity index (per 1 point increase)	1.05	0.99–1.13	0.089	1.03	0.95–1.11	0.382	1.03	0.96–1.12	0.331	1.04	0.96–1.13	0.306
Ward of hospitalization												
Emergency department	0.28	0.11–0.74	**0.011**	0.25	0.10–0.65	**0.005**	0.26	0.10–0.68	**0.006**	0.18	0.05–0.60	**0.005**
Internal medicine	1.69	1.05–2.72	**0.030**	0.80	0.45–1.42	0.451	0.81	0.45–1.46	0.502	0.69	0.36–1.31	0.261
Surgical unit	0.39	0.19–0.78	**0.008**	0.33	0.14–0.79	**0.013**	0.34	0.14–0.80	**0.014**	0.29	0.11–0.75	**0.011**
ICU	1.26	0.66–2.37	0.475	\			\					
Presence of any valvular/ endovascular prosthesis	0.75	0.44–1.27	0.293	0.76	0.37–1.56	0.461	0.74	0.35–1.52	0.416	0.91	0.38–2.15	0.839
DENOVA score ≥3	0.89	0.53–1.51	0.687	0.99	0.48–2.06	0.998	0.98	0.48–2.00	0.971	0.97	0.41–2.28	0.951
Severity of disease: sepsis-3 definition												
No sepsis	1			1			1			1		
Sepsis or septic shock	1.83	1.19–2.81	**0.006**	1.57	1.01–2.45	**0.045**	1.58	1.01–2.46	**0.043**	1.53	0.94–2.49	0.081
Site of infection												
Primary BSI	0.85	0.50–1.49	0.566	\			\			\		
Urinary tract	0.98	0.62–1.54	0.945	\			\			\		
Intra-abdominal	0.93	0.43–2.00	0.867	\			\			\		
CVC-related	0.95	0.49–1.84	0.901	\			\			\		
Adequate empirical antibiotic therapy	0.97	0.62–1.50	0.894	\			\					
Any monotherapy	0.93	0.59–1.45	0.762	0.85	0.52–1.39	0.541	\			\		
Monotherapy with β-lactams	0.85	0.55–1.31	0.467	\			0.76	0.47–1.23	0.274	\		
β-lactams plus CTX/AG versus monotherapy with β-lactams	1.01	0.60–1.68	0.962	\			\			0.97	0.55–1.71	0.924

Model A: multivariable analysis with 'any monotherapy' as variable of interest. Model B: multivariable analysis with 'β-lactam monotherapy' as variable of interest. Model C: multivariable analysis with 'β-lactam monotherapy vs. monotherapy plus CTX/AG'; as variable of interest. Boldface means statistically significant ($p < 0.05$). \ defines not included in the model.
AG, aminoglycoside; aHR, adjusted hazard ratio; BSI, bloodstream infection; CTX, ceftriaxone; HR, hazard ratio; ICU, intensive care unit; CVC, Central Venous Catheter; DENOVA, Duration of symptoms ≥7 days, Embolic phenomena Number of positive blood cultures, Origin of infection unknown Valve disease and Auscultation of a murmur.

status and DENOVA score. Finally, the requirement for echocardiography, interruption of the enrolment during the recent SARS-CoV-2 pandemic and specific follow-up have led to non-consecutive screening/enrolment at most centres.

In conclusion, this study shows that monotherapy may be similar to combination therapy in patients with EF-BSI without IE in terms of clinical response, mortality and relapse. To answer this definitively, we would design a randomized, controlled non-inferiority trial enrolling all patients with *E. faecalis* bacteraemia, excluding those with IE diagnosed within 72 hours, using the same composite clinical-failure endpoint we have chosen. Assuming our observed event rates (control [combination] = 0.36 vs.

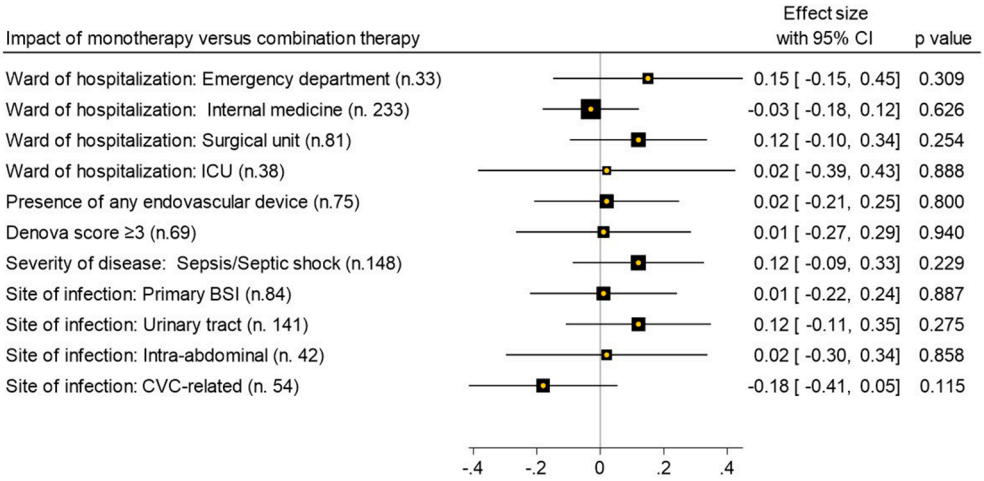

Fig. 2. Treatment effect regression model on subgroups of interest. Any monotherapy as variable of interest. BSI, bloodstream infection; ICU, intensive care unit; CVC, Central Venous Catheter.

experimental [monotherapy] = 0.28), a noninferiority margin of 10%, power 80%, and one-sided $\alpha = 0.05$, the required total sample size is 540 patients.

Transparency declaration

Potential conflict of interest

The authors declare that they have no conflicts of interest.

Credit authorship contribution statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2026.03.018.

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