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Risk factors for treatment failure in patients receiving β-lactam/β-lactamase inhibitor combinations for Enterobacteriaceae bloodstream infection: A retrospective, single-centre, cohort study

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ABSTRACT

The aim of this study was to investigate risk factors for treatment failure in patients receiving in vitro-active therapy with β-lactam/β-lactamase inhibitor (BL/BLI) for Enterobacteriaceae bloodstream infection (E-BSI). This was a retrospective, single-centre study of patients diagnosed with E-BSI at an Italian centre over a 4-year period. Exclusion criteria were age <18 years, clinical data unavailable, polymicrobial BSI, failure to receive in vitro-active therapy and death within 72 h from drawing the index blood culture. Patients who received BL/BLI as appropriate empirical and/or definitive therapy for ≥50% of the total treatment duration were selected. The primary endpoint was all-cause 30-day mortality. The secondary endpoint was 90-day relapse. Of 1319 eligible patients, 835 were selected. A total of 714 received BL/BLI as appropriate empirical therapy, of whom 522 remained on BL/BLI as definitive therapy and 192 shifted to another antibiotic for <50% of the treatment duration; 121 received BL/BLI as definitive therapy only. Non-susceptibility to extended-spectrum cephalosporins (NS-ESCs) was detected in 207 episodes (24.8%). All-cause 30-day mortality was 6.8%. In multivariate analysis adjusted for NS-ESC, independent predictors of mortality were Charlson comorbidity index, septic shock, *Proteus* spp. and CVC-related BSI, whilst urinary source was a protective factor. The 90-day relapse rate was 4.2%. Immunosuppression was the main independent predictor for relapse. BL/BLI was the most common antibiotic administered to patients with E-BSI in this cohort. Among patients appropriately treated with BL/BLI, failure rates were low and were primarily associated with underlying diseases, clinical severity at BSI onset and infection source.

1. Introduction

The emergence of resistance to carbapenems among Enterobacteriaceae has increased the clinical need to use carbapenem-sparing regimens whenever feasible [1]. However, the high prevalence of non-susceptibility to extended-spectrum cephalosporins (NS-ESCs) among Enterobacteriaceae in some geographical areas often limits the use of carbapenem alternatives [2]. A number of studies have assessed the efficacy of carbapenem-sparing regimens for treating infections due to NS-ESC Enterobacteriaceae [3,4]. Most of them have compared the efficacy of β-lactam/β-lactamase inhibitor (BL/BLI) combinations with that of carbapenems in patients with NS-ESC Enterobacteriaceae bloodstream infection (E-BSI), with conflicting results [5–8].

In clinical practice, the use of BL/BLI combinations goes far beyond the need of carbapenem-sparing regimens for NS-ESC infections owing to their characteristics such as good antimicrobial spectrum, bactericidal activity, very good tolerability and low propensity to select for further resistance and/or *Clostridium difficile* infection [9–12]. With this premise, knowledge of risk factors for failure in patients treated with BL/BLI for E-BSI could be helpful to identify those conditions in which an alternative regimen should be considered.

The aim of this study was to investigate risk factors for treatment failure in patients receiving in vitro-active therapy with a BL/BLI combination for E-BSI. The hypothesis was that NS-ESC was an independent predictor of an unfavourable outcome.

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2. Methods

2.1. Study design and setting

A retrospective cohort study of patients hospitalised at S. Orsola-Malpighi Hospital, a 1450-bed tertiary-care university hospital in Bologna in the region of Emilia-Romagna (Northern Italy), from 1 January 2013 to 31 December 2016 was performed.

Patients were identified through the database of the Laboratory of Microbiology. Clinical charts and hospital records were reviewed to gather study variables using a case report form for up to 90 days after the index blood culture (BC). The accuracy of data was systematically checked by an investigator before being introduced into a database.

During the study period, performance of index and follow-up BCs was at the discretion of the attending physician and was not dictated by a study protocol.

2.2. Participants

Inclusion criteria were all adult (≥18 years) patients diagnosed with E-BSI, defined as one or more positive BC obtained from a patient suspected of having infection. Patients were considered only once at the time of first episode (index BC).

Exclusion criteria included: (i) polymicrobial BSI, defined as growth of more than one micro-organism, excluding potential contaminants (i.e. coagulase-negative staphylococci, *Corynebacterium* spp., *Propionibacterium* spp.); (ii) death within 72 h from drawing the index BC; (iii) failure to receive at least one agent with in vitro activity against the isolate from the index BC to the completion of antibiotic therapy; and (iv) clinical data unavailable.

For this analysis, patients who received a BL/BLI combination as appropriate empirical and/or definitive treatment for ≥50% of the total duration of therapy were selected.

Empirical therapy was defined as antibiotics administered before the susceptibility report was available. It was considered appropriate when at least one in vitro-active drug (according with the susceptibility pattern of the isolate) was administered within 24 h after drawing the BC. Delayed or no active antibiotic administration within this period was considered as inappropriate empirical therapy. Definitive antibiotic therapy was defined as antibiotic treatment administered according to susceptibility results.

In accordance with local guidelines, administered dosages were piperacillin/tazobactam (TZP) 18 g/day by continuous infusion following a loading dose of 9 g, amoxicillin/clavulanic acid (AMC) 2.2 g every 8 h or ampicillin/sulbactam (SAM) 3 g every 6 h, with adjustment for renal dysfunction.

2.3. Variables and definitions

The primary outcome was 30-day mortality, defined as all-cause mortality within 30 days after the index BC [13]. The secondary outcome was relapse, defined as repeat isolation of the same Enterobacteriaceae from BCs within 90 days after the index episode in patients with documented clinical cure and completion of the antibiotic course for the initial episode [14]. Clinical cure, defined as the resolution of all signs and symptoms of infection according to vital signs, evolution of the Sequential Organ Failure Assessment (SOFA) score and laboratory data, was assessed at Day 7 after the index BC and at the end of therapy (EOT). To reduce the risk of bias, a senior investigator who was not aware of the therapeutic management of patients reviewed the variables defining the outcome.

Predictor variables included age and sex. Underlying diseases were assessed according to the Charlson comorbidity index [15]. Immunosuppression included neutropenia (absolute neutrophil count $<500/mm^3$), solid-organ transplantation, hematopoietic stem cell transplantation, corticosteroid therapy at a dosage higher than or equivalent to prednisone 16 mg/day for ≥15 days and uncontrolled human immunodeficiency virus (HIV) infection (<200 $CD4^+$ cells/mm^3). BSI was classified according to the site of acquisition into nosocomial, healthcare-associated or community-acquired using Friedman's criteria [16]. Clinical severity at infection onset was assessed according to SOFA score and septic shock criteria [17]. BSI sources were established according to US Centres for Disease Control and Prevention (CDC) criteria [18]. In the absence of a recognised source, BSI was considered as primary. BSI was defined as complicated when the infection source was not fully removable. Regarding microbiological variables, the species of causative agent, the susceptibility to ESCs and carbapenems according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards, and the minimum inhibitory concentration (MIC) for TZP were collected. Combination therapy was defined as a regimen including more than one in vitro-active drug. Duration of antibiotic treatment was defined as the number of consecutive days during which the patient received an appropriate antibiotic regimen. Source control was defined as the removal of the infection source within 7 days of index BC, including the performance of non-surgical or surgical procedures to treat an obstructive focus or abscess at any site including, among others, the urinary tract, biliary tract and surgical site, and the removal of any device deemed as the source of BSI. Infectious diseases (ID) consultation was defined as a bedside patient evaluation with a written report performed by an ID specialist within 7 days of the index BC.

2.4. Microbiology

BCs were incubated using a BD BACTEC™ FX Automated Blood Culture System (Becton Dickinson, Franklin Lakes, NJ). All positive BCs were processed using a MALDI Biotyper matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) system (Bruker Daltonik GmbH, Bremen, Germany) for rapid and reliable species identification of micro-organisms. Antimicrobial susceptibility testing of strains was performed using a VITEK®2 automated system (bioMérieux, Marcy-l'Étoile, France). Enterobacteriaceae MICs were interpreted using EUCAST clinical breakpoints for all tested antibiotics.

2.5. Statistical analysis

For the descriptive 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.

Categorical variables were compared using χ^2 or Fisher exact test when appropriate, and continuous variables were compared using the Mann–Whitney *U*-test.

Risk factors for all-cause 30-day mortality were analysed using a Cox regression model; patients were considered from the day of index BC to death or 30 days; and all variables with a *P*-value of ≤0.1 in the univariate analysis were entered into the multivariate model that was adjusted for NS-ESC and central venous catheter (CVC) removal. Survival analysis in the subgroups of patients with urinary and non-urinary sources, according to susceptibility and NS-ESC, was also done by Kaplan–Meier curves and Cox analysis adjusted for SOFA score.

Risk factors for relapse were analysed both using Cox regression and Fine & Gray competing risk analysis. This method accounts for the competing risk of death before relapse and was adjusted for significant covariates associated with relapse in the Cox regression

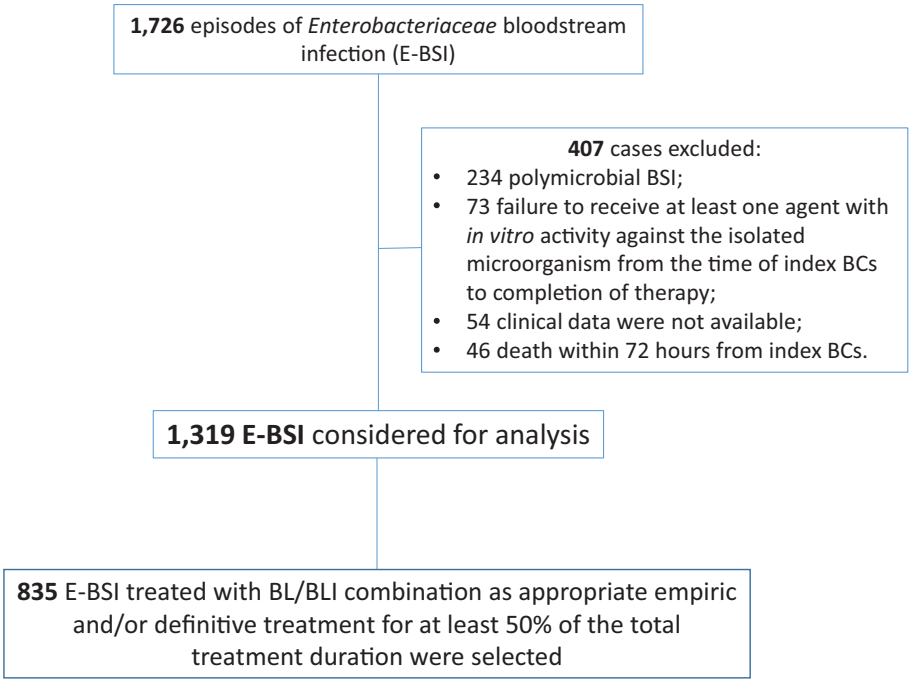

Fig. 1. Study flow chart. BC, blood culture; BL/BLI, β-lactam/β-lactamase inhibitor.

analysis. Adjusted estimates of the cumulative incidence of relapse were calculated from the time of index BC to relapse, death or 90 days, whichever occurred first.

Statistical analysis was performed using IBM SPSS Statistics v.21.0 (IBM Corp., Armonk, NY) and STATA 13 (StataCorp LP, College Station, TX).

2.6. Ethical issues

This study was approved by the Ethics Committee of S. Orsola-Malpighi Hospital, and waiving of informed consent was given due to the retrospective, non-interventional study design. Data were collected anonymously.

3. Results

During the study period, 1726 patients were diagnosed with E-BSI. Among the screened patients, 407 met the exclusion criteria, thus 1319 patients remained in the study cohort (Fig. 1). The distribution of micro-organisms was as follows: *Escherichia coli,* $n = 891$ (67.6%); *Klebsiella pneumoniae,* $n = 295$ (22.4%); *Enterobacter* spp., $n = 78$ (5.9%); and *Proteus* spp., $n = 55$ (4.2%). Of the 1319 isolates, 352 (26.7%) were NS-ESC, 283 (21.5%) were resistant to TZP (median MIC = 4 mg/L, IQR 4–16 mg/L) and 105 (8.0%) were resistant to carbapenems. Susceptibility patterns varied between micro-organisms (Supplementary Table S1).

The most common empirical antibiotic regimens were BL/BLI [monotherapy ($n = 723$; 54.8%) or combination ($n = 125$; 9.5%)], carbapenem [monotherapy ($n = 115$; 8.7%); combination ($n = 63$; 4.8%)] and ESC [monotherapy ($n = 114$; 8.6%); combination ($n = 22$; 1.7%)]. The most common definitive regimens were BL/BLI [monotherapy ($n = 544$; 41.2%); combination ($n = 100$; 7.6%)], carbapenem [monotherapy ($n = 155$; 11.8%); combination (142; 10.8%)] and ESC [monotherapy ($n = 134$; 10.2%; combination ($n = 19$; 1.4%)].

In total, 835 patients were selected according to the study criteria. Of these 835 patients, 714 received BL/BLI as appropriate empirical therapy, of whom 522 remained on BL/BLI as definitive therapy and 192 shifted to another antibiotic but for <50% of the treatment duration; 121 patients received BL/BLI as definitive therapy only. BL/BLI consisted of TZP, SAM and AMC in 75.2%, 17.4% and 7.4% of cases, respectively. Overall, 138 patients (16.5%) received combination therapy.

The general characteristics of selected patients are shown in Table 1. NS-ESC rates among *E. coli, K. pneumoniae, Enterobacter* spp. and *Proteus* spp. were 25.5%, 20%, 12.2% and 42.2%, respectively.

The all-cause 30-day mortality rate in the selected population was 6.8% (57/835). A comparison of survivors and non-survivors is shown in Table 1. Significant differences were found for Charlson comorbidity index, SOFA score at BSI onset, septic shock, urinary tract as BSI source, *E. coli* and *Proteus* spp., and clinical cure at Day 7 and at EOT. In the multivariate analysis adjusted for NS-ESC, the independent predictors of all-cause 30-day mortality were Charlson comorbidity index, septic shock, *Proteus* spp. and CVC-related BSI, whilst urinary tract source was associated with significantly lower mortality (Table 2). In the subgroup of patients with non-urinary source, 30-day survival was not significantly different among patients with susceptible and NS-ESC strains both by Kaplan–Meier and Cox regression analysis adjusted for SOFA score (Supplementary Fig. S1).

The 90-day relapse rate was 4.2% (35/835). A comparison of patients with and without relapse is shown in Table 3. Significant differences were found for age, immunosuppression, neutropenia and solid-organ transplantation, whilst there was a trend between higher TZP MIC and relapse. In the multivariate analysis adjusted for SOFA score, NS-ESC and source control, the only independent predictor of relapse was immunosuppression (Table 4). Competing risk analysis showed that along with immunosuppression, higher SOFA score was also a risk for relapse (Table 4; Fig. 2).

4. Discussion

In this study, BL/BLI combination was the most common antibiotic regimen used in patients with E-BSI both for empirical and definitive therapy. The all-cause 30-day mortality rate was low (6.8%) in patients receiving appropriate empirical or definitive

Table 1
Patients treated with β-lactam/β-lactamase inhibitor combinations for Enterobacteriaceae bloodstream infection (BSI): comparison of those with and without all-cause 30-day mortality

Characteristic	*n* (%)[a]			*P*-value
	Total (*N* = 835)	Survivors (*N* = 778)	Non-survivors (*N* = 57)	
Demographics				
Age (years) [median (IQR)]	74 (62–83)	74 (61–83)	76 (66–84)	0.12
Male sex	446 (53.4)	414 (53.2)	32 (56.1)	0.68
Underlying diseases				
Congestive heart failure	116 (13.9)	111 (14.3)	5 (8.8)	0.32
Chronic kidney disease	159 (19.0)	148 (19.0)	11 (19.3)	1.0
COPD	126 (15.1)	115 (14.8)	11 (19.3)	0.44
ESLD	68 (8.1)	63 (8.1)	5 (8.8)	0.80
Immunosuppression	164 (19.6)	150 (19.3)	14 (24.6)	0.60
Neutropenia	46 (5.5)	42 (5.4)	4 (7.0)	0.76
SOT	53 (6.3)	50 (6.4)	3 (5.3)	1
Corticosteroids[b]	41 (4.9)	36 (4.6)	5 (8.8)	0.19
HSCT	16 (1.9)	14 (1.8)	2 (3.5)	0.29
Uncontrolled HIV[c]	8 (1.0)	8 (1.0)	0 (0)	1
Charlson comorbidity index [median (IQR)]	6 (5–8)	6 (5–8)	7 (5–9)	0.008
Site of BSI acquisition				0.18
Community-acquired	309 (37.1)	294 (37.9)	15 (26.3)	
Healthcare-associated	156 (18.8)	145 (18.7)	11 (19.3)	
Hospital-acquired	370 (44.3)	339 (43.6)	31 (54.4)	
Ward				0.21
Medical	704 (84.3)	660 (84.8)	44 (77.2)	
Surgical	93 (11.1)	85 (10.9)	8 (14.0)	
ICU	38 (4.6)	33 (4.2)	5 (8.8)	
Clinical severity at BSI onset				
SOFA score [median (IQR)]	3 (1–5)	3 (1–5)	5 (3–7)	<0.001
Septic shock	82 (9.8)	60 (7.7)	22 (38.6)	<0.001
BSI source				
Urinary tract	377 (45.1)	362 (46.5)	15 (26.3)	0.003
Primary	147 (17.6)	140 (18.0)	7 (12.3)	0.29
Biliary tract	126 (15.1)	116 (14.9)	10 (17.5)	0.70
Intra-abdominal	88 (10.5)	77 (9.9)	11 (19.3)	0.40
Lower respiratory tract	43 (5.1)	38 (4.9)	5 (8.8)	0.20
CVC-related BSI	26 (3.1)	21 (2.7)	5 (8.8)	0.02
Skin and soft tissue	9 (1.1)	8 (1.0)	1 (1.8)	1.00
Complicated BSI	213 (25.5)	192 (24.7)	21 (36.8)	0.06
Microbiological data				
Escherichia coli	611 (73.2)	578 (74.3)	33 (57.9)	0.009
Klebsiella pneumoniae	130 (15.6)	121 (15.6)	9 (15.8)	1
Enterobacter spp.	49 (5.9)	45 (5.8)	4 (7.0)	0.57
Proteus spp.	45 (5.4)	34 (4.4)	11 (19.3)	<0.001
NS-ESC	207 (24.8)	190 (24.4)	17 (29.8)	0.42
TZP MIC [median (IQR)]	4 (4–4)	4 (4–4)	4 (4–5)	0.28
Therapeutic management				
ID consultation	286 (34.3)	258 (33.2)	28 (49.1)	0.02
Combination therapy	138 (16.5)	130 (16.7)	8 (14.0)	0.71
Source control	100 (12.0)	95 (12.2)	5 (8.8)	0.53
CVC removal	52 (6.2)	46 (5.9)	6 (10.5)	0.25
Urinary catheter removal	112 (13.4)	103 (13.2)	9 (15.8)	0.68
Outcome				
Clinical cure at Day 7	654 (78.3)	642 (82.5)	12 (21.1)	<0.001
Clinical cure at EOT	661 (79.2)	653 (83.9)	8 (14.0)	<0.001

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ESLD, end-stage liver disease; SOT, solid-organ transplantation; HSCT, hematopoietic stem cell transplantation; HIV, human immunodeficiency virus; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; CVC, central venous catheter; NS-ESC, non-susceptibility to extended-spectrum cephalosporins; TZP, piperacillin/tazobactam; MIC, minimum inhibitory concentration; ID, infectious diseases; EOT, end of therapy.

[a] Data are *n* (%) unless otherwise stated.

[b] Corticosteroid therapy at a dosage higher than or equivalent to prednisone 16 mg/day for ≥15 days.

[c] $CD4^+$ cell count <200 cells/mm^3.

therapy with BL/BLI. Higher Charlson comorbidity index, septic shock, infection source and *Proteus* spp. were independently associated with outcome. No association between NS-ESC and increased 30-day mortality or higher 90-day relapse rate could be found. In the multivariate analysis, the only predictor of relapse was immunosuppression, mainly in patients with higher SOFA score at BSI onset.

The debate surrounding the use of BL/BLI versus carbapenems for NS-ESC E-BSI has been addressed mostly by observational studies, with conflicting results [19]. Some studies have suggested that BL/BLI may be effective for the treatment of NS-ESC E-BSI in patients with lower-inoculum infections and lower piperacillin MICs [5,20]. However, the recently published MERINO study, the first randomised controlled multinational trial comparing TZP with meropenem for the definitive treatment of ceftriaxone-non-susceptible, TZP-susceptible *E. coli* and *Klebsiella* spp. BSIs concluded that definitive treatment with TZP compared with meropenem did not result in a non-inferior 30-day mortality [8]. As expected, in the current study no association between NS-ESC and worse outcome was found, also in the subgroup of

Table 2
Multivariate analysis of risk factors for all-cause 30-day mortality in patients treated with β-lactam/β-lactamase inhibitor combinations for Enterobacteriaceae bloodstream infection (BSI)

	HR (95% CI)	*P*-value
Charlson comorbidity index	1.17 (1.07–1.28)	0.001
Septic shock	6.62 (3.76–11.65)	<0.001
Proteus spp.	5.56 (2.54–12.16)	<0.001
CVC-related BSI	3.92 (1.50–10.22)	0.005
Urinary tract	0.24 (0.12–0.50)	<0.001

HR, hazard ratio; CI, confidence interval; CVC, central venous catheter.
Variables introduced into the model were: Charlson comorbidity index; Sequential Organ Failure Assessment (SOFA) score; septic shock; *Escherichia coli; Proteus* spp.; non-susceptibility to extended-spectrum cephalosporins (NS-ESCs); piperacillin/tazobactam minimum inhibitory concentration; urinary tract source; CVC-related BSI; complicated BSI; CVC removal; and infectious diseases consultation.

patients with non-urinary source. However, these findings could have been biased by the single-centre, retrospective design and the low rate of NS-ESC isolates, limiting statistical power. On the other hand, we would remark that in the current cohort, in contrast to the MERINO trial, BL/BLI was always administered at the highest allowed dosage, according to renal function, and by extended or continuous infusion, thus overriding any bias related to different and/or suboptimal drug exposure.

The impact of TZP MIC on the risk of 30-day mortality and 90-day relapse was further analysed. According to Delgado-Valverde et al. who performed a prospective observational study of 275 patients with E-BSI treated with TZP examining the effect of MIC on 30-day mortality, piperacillin MICs were not associated with a higher mortality rate (relative risk = 1.06, 95% confidence interval 0.34–3.27; $P = 1$) [21]. In addition, in the current study, although patients with higher TZP MIC experienced a higher 90-day relapse rate, this association was not confirmed in the multivariate analysis.

Studies comparing *E. coli* and *K. pneumoniae* NS-ESC BSIs have shown different epidemiological profiles between the two groups as well as higher mortality rates associated with *K. pneumoniae* [22,23]. We failed to observe this association; however, we have to remark that more than one-half of *K. pneumoniae* BSIs occurring in our hospital during the study period were caused by BL/BLI-resistant strains (Supplementary Table S1) and thus were not included. Otherwise, it was observed that isolation of *Proteus* spp. was an independent predictor of mortality. The NS-ESC rate was highest in *Proteus* spp. (42.2%), but mortality rates were similar between susceptible and NS-ESC strains (data not shown). In a retrospective observational study of 11 extended-spectrum β-lactamase (ESBL)-producing *Proteus mirabilis* BSIs, only 1/4 BSIs (25%) treated with BL/BLI responded to therapy [24]. On the other hand, 5/5 BSIs due to non-ESBL-producing isolates responded to BL/BLI therapy ($P = 0.02$). All BSIs treated with a carbapenem responded to therapy, regardless of the presence or absence of ESBL production [24]. Tsai et al. conducted a multicentre retrospective study comparing TZP with carbapenems and with other antibiotics for the treatment of ESBL-producing *P. mirabilis* BSI [25]. In-hospital mortality (30.8% vs. 19.1%; $P = 0.68$) and 30-day mortality (23.1% vs. 14.3%; $P = 0.65$) were not significantly different between patients treated with TZP ($n = 13$) and carbapenems ($n = 21$), respectively. Decreased 30-day mortality rates (0% vs. 60%; $P = 0.045$) were observed in patients receiving TZP with lower MICs (0.5/4 mg/L; $n = 7$) compared with those with higher MICs ($n = 5$) [25]. The urinary tract was the most common source of *Proteus* spp. BSI (75.6%) in the current cohort.

Bacteraemia resulting from CVC-related infection was another independent predictor of mortality in this study, confirming the suboptimal performance of BL/BLI in the treatment of high-inoculum infections such as intravascular infections [19]. Of note, CVC source was an independent risk factor for recurrence in a retrospective case–control study of NS-ESC *E. coli* or *K. pneumoniae* BSI [26].

This study has some limitations. The retrospective design could have hampered a comprehensive collection of data, however data integrity and accuracy were guaranteed by systematic revision of collected data by two senior investigators. The single-centre design may limit the generalisability of the results, as local epidemiology and local prescription practices could have influenced the results

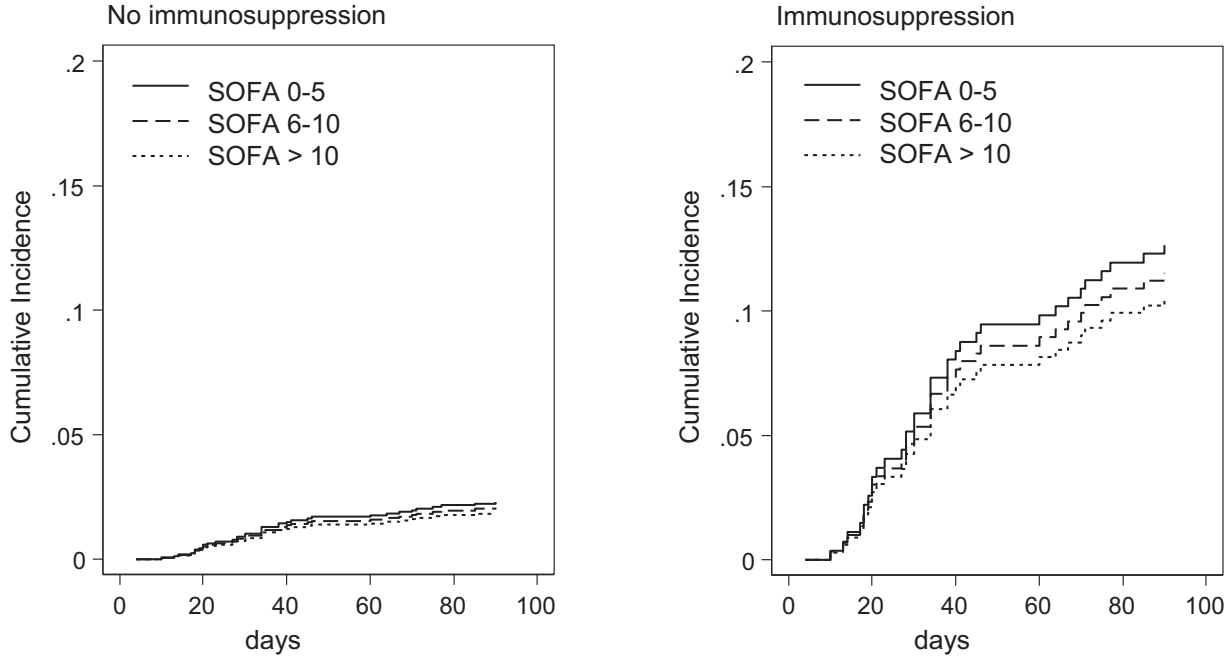

Fig. 2. Competing risk analysis for relapse according to Sequential Organ Failure Assessment (SOFA) score in immunosuppressed and non-immunosuppressed patients treated with β-lactam/β-lactamase inhibitor for Enterobacteriaceae bloodstream infection.

Table 3
Patients treated with β-lactam/β-lactamase inhibitor combinations for Enterobacteriaceae bloodstream infection (BSI): comparison of those with and without 90-day relapse

Characteristic	*n* (%)[a]		*P*-value
	Relapse ($N=35$)	Non-relapse ($N=800$)	
Demographics			
Age (years) [median (IQR)]	64 (53–79)	74 (62–83)	0.01
Male sex	18 (51.4)	428 (53.5)	0.86
Underlying diseases			
Congestive heart failure	3 (8.6)	113 (14.1)	0.46
Chronic kidney disease	6 (17.1)	153 (19.1)	0.83
COPD	2 (5.7)	124 (15.5)	0.14
ESLD	4 (11.4)	64 (8.0)	0.52
Immunosuppression	26 (74.3)	138 (17.3)	<0.001
Neutropenia	10 (28.6)	36 (4.5)	<0.001
SOT	9 (25.7)	44 (5.5)	<0.001
Corticosteroids[b]	5 (14.3)	36 (4.5)	0.24
HSCT	2 (5.7)	14 (1.8)	0.14
Uncontrolled HIV[c]	0 (0)	8 (1.0)	1
Charlson comorbidity index [median (IQR)]	6 (4–8)	6 (5–8)	0.26
Site of BSI acquisition			0.04
Community-acquired	9 (25.7)	300 (37.5)	
Healthcare-associated	3 (8.6)	153 (19.1)	
Hospital-acquired	23 (65.7)	347 (43.4)	
Ward			0.18
Medical	26 (74.3)	678 (84.8)	
Surgical	7 (20.0)	86 (10.8)	
ICU	2 (5.7)	36 (4.5)	
Clinical severity at BSI onset			
SOFA score [median (IQR)]	4 (2–5)	3 (1–5)	0.27
Septic shock	4 (11.4)	78 (9.8)	0.76
BSI source			
Urinary tract	10 (28.6)	367 (45.9)	0.55
Primary	12 (34.3)	135 (16.9)	0.13
Biliary tract	6 (17.1)	120 (15.0)	0.80
Intra-abdominal	4 (11.4)	84 (10.5)	0.78
Lower respiratory tract	1 (2.9)	42 (5.3)	1
CVC	1 (2.9)	25 (3.1)	1
Skin and soft tissue	0 (0)	9 (1.1)	1
Complicated BSI	8 (22.9)	205 (25.6)	0.84
Microbiological data			
Escherichia coli	29 (82.9)	582 (72.8)	0.24
Klebsiella pneumoniae	5 (14.3)	125 (15.6)	1
Enterobacter spp.	0 (0)	49 (6.1)	0.25
Proteus spp.	1 (2.9)	44 (5.5)	1
NS-ESC	12 (34.3)	195 (24.4)	0.22
TZP MIC [median (IQR)]	4 (4–8)	4 (4–4)	0.06
Therapeutic management			
ID consultation	12 (34.3)	274 (34.3)	1
Combination therapy	8 (22.9)	130 (16.3)	0.34
Source control	2 (5.7)	98 (12.3)	0.42
CVC removal	2 (5.7)	50 (6.3)	1
Urinary catheter removal	5 (14.3)	107 (13.4)	0.8
Days of therapy [median (IQR)]	9 (7–12)	10 (8–15)	0.10
Outcome			
Clinical cure at Day 7	29 (82.9)	625 (78.1)	0.54
Clinical cure at EOT	33 (94.3)	628 (78.5)	0.2
All-cause 90-day mortality	6 (17.1)	73 (9.1)	0.13

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ESLD, end-stage liver disease; SOT, solid-organ transplantation; HSCT, hematopoietic stem cell transplantation; HIV, human immunodeficiency virus; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; CVC, central venous catheter; NS-ESC, non-susceptibility to extended-spectrum cephalosporins; TZP, piperacillin/tazobactam; MIC, minimum inhibitory concentration; ID, infectious diseases; EOT, end of therapy.
[b] Corticosteroid therapy at a dosage higher than or equivalent to prednisone 16 mg/day for ≥15 days.
[c] $CD4^+$ cell count <200 cells/mm^3.

as discussed above. The majority of patients in this cohort had *E. coli* BSI, which is usually associated with a better outcome than other Enterobacteriaceae [19]. However, the distribution of microorganisms in this study reflects what occurs in clinical practice. Although infections with *E. coli* are generally less severe than those caused by *K. pneumoniae*, they are significantly more common with a huge impact on antibiotic use and patient outcome. Indeed, in a recent report regarding attributable deaths and disability-adjusted life-years due to infections with antibiotic-resistant bacteria in Europe, NS-ESC *E. coli* accounted for most attributable deaths [27]. We did not perform ESBL confirmatory testing in accordance with Clinical and Laboratory Standards Institute (CLSI) guidance. Cefotaxime-non-susceptibility was used as a proxy for ESBL presence; however, whilst it is true that ESBL-producers are likely to have a cefotaxime MIC in the non-susceptible range, not all Enterobacteriaceae with such a condition are ESBL-producers [28]. Finally, we could not assess whether there was an association between the type of ESBL (CTX-M versus non-CTX-M) and poor

Table 4
Multivariate analysis of risk factors for 90-day relapse in patients treated with β-lactam/β-lactamase inhibitor combinations for Enterobacteriaceae bloodstream infection (BSI)

	HR (95% CI)	*P*-value	SHR (95% CI)	*P*-value
Immunosuppression	5.80 (2.97–11.34)	<0.001	5.29 (2.70–10.36)	<0.001
SOFA			1.07 (1.03–1.11)	<0.001

HR, hazard ratio; CI, confidence interval; SHR, subdistribution hazard ratio; SOFA, Sequential Organ Failure Assessment.
The variables introduced into the model were: age; immunosuppression; site of BSI acquisition; SOFA score; non-susceptibility to extended-spectrum cephalosporins (NS-ESCs); piperacillin/tazobactam minimum inhibitory concentration; source control; and days of therapy.

outcome. However, in a recent study including ESBL-producing *E. coli* and *K. pneumoniae* BSIs, no differences in clinical characteristics or mortality between CTX-M and non-CTX-M ESBLs were detected [22].

To conclude, according to the current results, when active in vitro the use of BL/BLI for E-BSI is effective, mainly in episodes secondary to urinary infection. It should be avoided in more critically ill patients, in those with CVC-related BSI and upon isolation of *Proteus* spp.

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Competing interests

None declared.

Ethical approval

This study was approved by the Ethics Committee of S. Orsola-Malpighi Hospital (Bologna, Italy) [79/2017/O/OssN], and waiving of informed consent was given due to the retrospective, non-interventional study design. Data were collected anonymously.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.01.005.

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