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Major article

β-lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli*: A post-hoc analysis of prospective cohorts

Short title: Inhibitors in bacteremia by ESBL-*E. coli*

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40-word summary

In a post-hoc analysis of prospective cohorts, carbapenems were not superior to in vitro active β-lactam/β-lactam inhibitor combinations (amoxicillin/clavulanic acid or piperacillin/tazobactam) in the treatment of bacteremia caused by ESBL-producing *Escherichia coli*, mostly from urinary or biliary infections.

ABSTRACT

Background. Extended-spectrum ß-lactamase-producing *Escherichia coli* (ESBL-EC) is an important cause of invasive infections. Alternatives to carbapenems— considered the drugs of choice—are needed because of the emergence of carbapenemase-producing enterobacteria. The efficacy of ß-lactam/ß-lactam inhibitors (BLBLI) in such infections is controversial.

Methods. A post-hoc analysis of patients with bloodstream infections (BSI) due to ESBL-EC from 6 previously published prospective cohorts was performed. Mortality and length of hospital stay of patients treated with an active BLBLI (amoxicillin-clavulanic acid [AMC] and piperacillin-tazobactam [PTZ]) or carbapenem was compared in two cohorts: the empirical therapy cohort (ETC) and the definitive therapy cohort (DTC). Confounding was controlled by multivariate analysis; for patients in the ETC, a propensity score for receiving carbapenem was also used.

Results. The ETC included 103 patients (BLBLI: 72; carbapenem: 31), and the DTC 174 (BLBLI: 54, carbapenem: 120). Mortality rates at day 30 for those treated with BLBLI vs carbapenems were 9.7% vs 19.4% for the ETC, and 9.3% vs 16.7% for the DTC, respectively ($p > 0.2$, log rank test). After adjusting for confounders, no association was found between either empirical therapy with BLBLI (adjusted HR= 1.14; 95% CI: 0.29-4.40; p=0.84) or definitive therapy (adjusted HR=0.76; 95% CI: 0.28-2.07; p=0.5) and increased mortality. Furthermore, BLBLI therapy, with respect to carbapenem, was not found to influence length of hospital stay.

Conclusions. These results suggest that AMC and PTZ are suitable alternatives to carbapenems for treating patients with BSI due to ESBL-EC if active in vitro, and would be particularly useful as definitive therapy.

INTRODUCTION

In recent years, the spread of extended-spectrum β-lactamases (ESBL), particularly CTX-M enzymes, in Enterobacteriaceae has become a serious public health problem worldwide. In fact, ESBL-producing *Escherichia coli* (ESBL-EC) are now a frequent cause of infection in the community and in healthcare centers [1-3]. Carbapenems, which are not affected by ESBLs, are considered the drugs of choice for treating severe infections caused by ESBL producers because, according to some observational studies, the prognosis for patients treated with carbapenems is better in comparison with other drugs, mainly cephalosporins and fluoroquinolones [1-3]. In this context, clinicians are increasingly forced to consider the use of carbapenems as empiric or definitive therapy in moderate or severe community-onset and nosocomial infections whenever an ESBL-producing organism is suspected or demonstrated. This may be leading to an increase in the consumption of carbapenems, which is particularly worrisome in a scenario where carbapenemase-producing organisms are also spreading [4,5]. Thus, alternatives to carbapenems for the treatment of ESBL-producers are urgently needed.

ESBLs are inhibited by β-lactamase inhibitors [1-3]. While hyperproduction of β-lactamases or additional resistance mechanisms may hamper the activity of these compounds, β-lactam/β-lactam inhibitor combinations (BLBLI) such as amoxicillin-clavulanuate (AMC) or piperacillin-tazobactam (PTZ) remain active against a considerable proportion of ESBL-producing enterobacteria, particularly *E. coli,* in many areas [6-10]. However, the efficacy of BLBLI for treating serious infections caused by ESBL-producing enterobacteria is controversial; while some authors do not recommend their use [1], others consider them a useful alternative [11]. PTZ is administered

intravenously while AMC may be administered orally or intravenously, although the intravenous formulation is only available in some countries (including Spain but not the US). This study was conducted in order to compare the outcomes of patients with bloodstream infections (BSI) caused by ESBL-EC who had been treated with intravenous BLBLI or carbapenems.

METHODS

Study design and patients

This analysis was reported according to the STROBE recommendations [12]. We performed a post-hoc analysis of individual patients with BSI due to ESBL-EC; these patients had been included in 6 previously published studies carried out in Spain which investigated the epidemiology and clinical impact of ESBL-EC [9,13-17]. The studies used similar methodologies, as follows: all were prospective cohort studies made up of all consecutive patients with infections caused by ESBL-producing *E. coli* during each study period in all the participating centers, all used similar questionnaires and definitions for the variables collected, and all were coordinated by our group. No patient was included in more than one cohort. The features of the studies are shown in table 1.

Patients from these studies were eligible for the present analysis if they fulfilled all of the following criteria: (a) age >17 years; (b) clinically significant monomicrobial bacteremia was demonstrated via isolation of ESBL-EC alone in blood cultures, along with criteria for sepsis [18]; and (c) therapy with a BLBLI or a carbapenem had been administered for at least 48 hours. Two non-mutually exclusive cohorts were constructed and analysed separately: (i) The *empirical therapy cohort* (ETC) included

patients who received empirical therapy with BLBLI or carbapenem in monotherapy, whose first dose was administered during the first 24 hours after the blood culture had been drawn and the isolate was susceptible to the empirical antimicrobial administered, and (ii) the *definitive therapy cohort* (DTC), which included patients receiving definitive monotherapy with an active BLBLI or carbapenem, administered for at least 50% of the total duration of antimicrobial therapy (figure 1). Data from the databases of the previous studies was used and, when necessary, patients' charts were reviewed. Patients were followed for 30 days. The study was approved by the Ethics Committee of the Hospital Universitario Virgen Macarena, Seville.

The microbiological studies carried out have been published previously [9,13-17]. In brief, ESBL production and antimicrobial susceptibility were studied according to CLSI recommendations [19,20]; ESBLs were characterised by PCR and sequencing.

Variables and definitions

Data collected from all patients included age, gender, nosocomial or community-onset-acquisition, type and severity of underlying conditions using the Charlson comorbidity index [21], type of hospital service, source of BSI according to clinical and microbiological data, severity of disease the day before BSI was diagnosed according to Pitt score [22], severity of systemic inflammatory response syndrome at BSI presentation [18], antimicrobial therapy, mortality, and length of stay after BSI.

Antimicrobial therapy administered before susceptibility results were available was considered empirical; therapy administered afterwards was considered definitive. Therapy with BLBLI or carbapenem was considered as monotherapy if no other drug with activity against gram-negative organisms—including penicillins, cephalosporins, monobactams, fluoroquinolones, aminoglycosides, trimethoprim-sulphamathoxazole,

fosfomycin or colistin—was co-administered (irrespective of isolate susceptibility). The main outcome variable was mortality; length of hospital stay after BSI was also evaluated.

Statistical analysis

Separate analyses were performed on the 2 cohorts. Mortality rates of patients treated with BLBLI or carbapenems were compared using Kaplan-Meier curves and log rank test. Also, mortalities at days 7, 14 and 30 were compared using chi squared test in order to detect possible trends of very early, early or late mortality. To control for confounding, multivariate analysis was performed by Cox regression, using time until death as the dependent variable, and therapy with BLBLI or carbapenem as the explanatory variable of interest. Potential confounders and interactions were added using a forward method. In the ETC, a propensity score for receiving carbapenem as empirical therapy was added to the model. The propensity score —the probability of receiving carbapenem as empirical therapy— was calculated using a non parsimonious multivariate logistic regression model, in which the outcome variable was use of carbapenem as empirical therapy. The validity of the model was assessed by estimating goodness-of-fit to the data with the Hosmer-Lemeshow test, and its discrimination ability with the area under the receiver operating characteristic (ROC) curve. The software used for the analysis was SPSS v15.0.

RESULTS

The 6 cohort studies included 740 episodes of infection caused by ESBL-EC, of which 287 were cases of bacteremia; 192 were considered eligible for the present study

according to the criteria specified above: 103 patients were included in the ETC and 174 in the DTC; 85 patients were included in both cohorts (table 1, figure 1).

Empirical therapy cohort (ETC)

Of the 103 patients included in the ETC, 72 received empirical therapy with a BLBLI (37 AMC, 35 PTZ), and 31 with a carbapenem (22 imipenem [IMP], 8 meropenem [MER], and 1 ertapenem [ERT]). The characteristics of patients by treatment type are shown in table 2. The most frequent ESBLs produced by the isolates were CTX-M-14 in 50 cases (48.5%), and CTX-M-15 or SHV-12 in 19 (18.4%), respectively, with similar distributions for those treated with BLBLI or carbapenems. As regards dosage regimen, >90% of patients in each group received the following intravenous doses (or adjusted equivalent in the case of renal failure): PTZ, 4.500 mg every 6 hours; AMC, 1.200 g every 8 hours; IMP, 500 mg every 6 hours; MER, 1 g every 8 hours, and ERT, 1 g every 24 hours. Mortality rates among patients treated with BLBLI or carbapenem were: 2.8% vs 9.7% (day 7); 9.7% vs 16.1% (day 14); and 9.7% vs 19.4% (day 30), respectively ($p>0.1$ by chi-squared test for all comparisons; $p=0.2$ by log rank test). The 30-day mortality rates according to the MICs of AMC and PTZ in patients treated with these antibiotics are shown in table 3; mortality rates were 11.4% (4/35) for those treated with PTZ and 8.1% (3/37) for those treated with AMC ($p=0.4$, Fisher test). For patients who received empirical therapy with BLBLI, mortality at day 30 with respect to definitive therapy was as follows: 5.9% (2/34) for those continuing with a BLBLI, and 9.4% (3/32) for those who changed to a carbapenem ($p=0.6$, Fisher test); 2 out of 6 patients (33.3%) who changed to another antimicrobial died. For patients empirically treated with carbapenems who continued with carbapenem as their

definitive therapy, mortality was 16.7% (5/30) (p >0.1 for comparison with previous groups); one patient who switched to a fluoroquinolone died.

We calculated a propensity score for receiving empirical therapy with a carbapenem by constructing a non parsimonious model using logistic regression. From the crude comparison results of patients empirically treated with BLBLI and carbapenems (table 2), the following variables were introduced into the model: age, gender, Charlson index, nosocomial acquisition, Pitt score, neutropenia, cancer, diabetes mellitus, urinary tract disease, chronic renal insufficiency, source, and presentation with severe sepsis or shock. The model showed a p value of 0.53 for the Hosmer-Lemeshow goodness-of-fit test, and an area under the ROC curve of 0.80, showing good predictive ability. When adjusted for the propensity score in the Cox regression model in order to evaluate an association with mortality, empirical therapy with BLBLI showed a HR of 1.14 (95% CI: 0.29–4.40; p =0.84).

Since the crude analysis revealed several variables associated with mortality, namely, source other than biliary or urinary tract, Pitt score, and presentation with severe sepsis or septic shock (data not shown), several Cox regression models were performed, including propensity score plus combinations of pairs of those variables. Because there were only 13 deaths, a comprehensive model including all variables could not be performed. The adjusted HRs (95% CI) for empirical therapy with BLBLI in the different models ranged from 0.93 (0.25–3.51) to 1.27 (0.30–5.35), with p values of between 0.73 and 0.93. The inclusion of definitive therapy with BLBLI or carbapenem did not alter the results.

Median (interquartile range) post-bacteremia hospital stay was 12 (8–27) and 13 (9–22) days for patients who received empirical therapy with BLBLI or carbapenems, respectively (p=0.8, log rank test). Empirical therapy with BLBLI with respect to

carbapenems showed no association with increased length of stay in survivors, after controlling for the propensity score (HR=1.07; 95% CI: 0.35–3.02; p=0.9).

Definitive therapy cohort (DTC)

Overall, 174 patients were included in the DTC, 54 of whom received definitive therapy with a BLBLI (36 AMC, 18 PTZ), and 120 with carbapenem (84 IMP, 16 MER, and 20 ERT). The dosage regimens were similar to those specified for the ETC. The characteristics of patients by treatment received are shown in table 2. The most frequent ESBLs produced by the isolates were CTX-M-14 in 50 cases (53.6%), SHV-12 (15.9%), and CTX-M-15 (13.8%); there were similar distributions for those treated with BLBLI and carbapenems. Mortality rates for patients receiving definitive therapy with BLBLI or carbapenem were 1.9% vs 4.2% (at 7 days); 5.6% vs 11.7% (at 14 days); and 9.3% vs 16.7% (at 30 days), respectively (p >0.2 by chi-squared test for all comparisons; p=0.4 by log rank test). Ten patients received sequential therapy with oral AMC (none died); the treatment of 4 patients was de-escalated from IMP or MER to ERT (none died).

Crude analysis showed that source other than urinary or biliary tract, Pitt score, and presentation with severe sepsis or shock were associated with increased mortality; in the multivariate analysis carried out using Cox regression, definitive therapy with BLBLI or carbapenem showed no association with mortality (table 4).

Median (interquartile range) hospital stays following bacteremia were 13 (8–22) and 15 (10–25) days for patients receiving definitive therapy with BLBLI and carbapenems, respectively (p=0.4, log rank test). After controlling for other variables associated with increased length of stay (nosocomial acquisition, source other than

urinary or biliary tract, ICU admission, Charlson comorbidity index and Pitt score), the HR for definitive therapy with BLBLI was 1.32 (95% CI: 0.91–1.90; p=0.13).

DISCUSSION

This study could not find, for patients with BSI due to ESBL-EC, an association between empirical or definitive therapy using an active BLBLI and increased mortality or length of stay, in comparison with carbapenems. These results suggest that BLBLI, if active in vitro, should be considered a reasonable alternative to carbapenems for treating such infections under certain conditions.

Concerning empirical therapy, although it was not statistically significant, the fact that crude mortality was higher in patients empirically treated with carbapenems strongly suggests that patients treated with them may have been more severely ill than those treated with BLBLI. We controlled for confounding by calculating a propensity score for receipt of carbapenems as empirical therapy and by performing multivariate analysis using Cox regression. There were no trends that favoured the protective effect of carbapenems on mortality or length of stay. We also controlled for potential confounders in the definitive therapy cohort.

Several questions have arisen about the potential efficacy of BLBLI in infections caused by ESBL producers. Firstly, PTZ activity against *E. coli* producing different types of ESBL is significantly reduced in vitro when high inoculum of bacteria is used [23,24]. However, a similar effect has been seen with non-ESBL producing isolates [24], suggesting that the clinical significance of the inoculum effect, if any, would also apply to non ESBL-producing isolates. It is remarkable that AMC shows no inoculum effect [24].

Secondly, data from experimental intraabdominal infection in rats suggested that imipenem was more active than PTZ against TEM-26-producing *K. pneumoniae* and showed the response to PTZ might be dose-dependent [25,26]. However, PTZ showed good results against a TEM-3-producing *K. pneumoniae* in an endocarditis model using rabbits [27]. PTZ and AMC, to our knowledge, have not been tested against enterobacteria producing the most frequent ESBLs (namely, CTX-M and SHV enzymes) in animal models.

Finally, Zimhony et al reported treatment failure with PTZ in a patient with prosthetic valve endocarditis caused by CTX-M-2 and OXA-2-producing *Klebsiella pneumonia* due to the development of resistance during therapy [28]. We are not aware of other cases in which development of resistance to BLBLI has occurred in vivo. Obviously, ESBL-producing enterobacteria may be BLBLI-resistant as a result of additional resistance mechanisms, such as hyperproduction of TEM-1 or SHV-1, production of OXA-1 (frequent in the *E. coli* clonal group ST 131 CTX-M-15 producer [29]) or porin loss (which may also affect carbapenems); Pitout et al reported that the Vitek automated system may fail to detect PTZ resistance, particularly in the case of CTX-M-15 and OXA-1-producing *E. coli*, and recommended using alternative susceptibility testing methods [30].

After reviewing other published series that specify outcome data for patients with BSI due to ESBL-producing enterobacteria and empirically treated with active BLBLI and carbapenems [13,16,31-39], we found that 17 out of 106 treated with BBLBI and 14 out of 138 treated with carbapenem, respectively, died (16% vs 10%, p=0.1). It is difficult to draw any conclusion from these studies because of the heterogeneous nature of the microorganisms, definitions of mortality and patient types included; furthermore, BLBLI doses were frequently not specified. If only BSI caused

by *E. coli* are taken into account, the mortality of those treated with BLBLI was 2.7% (1 out of 36). The lower rate may be partly due to the fact that the MICs of PTZ and AMC against ESBL-producing ESBL-EC are frequently lower than against other enterobacteria [9,10], as discussed below. We have previously shown high cure rates for cystitis patients treated with AMC [14].

One question of interest is the MIC of the isolates and the BLBLI dosage. Stochastic models have shown a 99% probability of attaining the pharmacokinetic/ pharmacodynamic target (PIT) (time above the MIC, >50%) against ESBL producers by using 4,500 mg every 6 hours when the MIC of the isolate is $\leq$8 mg/L, but only 57% when the MIC is 16 mg/L [40]; our results also showed increased mortality for higher MICs of PTZ. A higher PIT has been shown with PTZ using more frequent dosing (3,375 every 4 hours) or extended infusions [41,42]. In this regard, the dose used was rarely specified in previous studies. In many countries, the usual dose for PTZ is 3,375 mg every 6 to 8 hours, while the most frequent dose in our study was 4,500 mg every 6 hours. There are no similar studies for AMC, although our data would suggest that 1,200 mg every 8 hours over 1 hour is adequate for most patients.

In deciding whether BLBLI can be used as empirical monotherapy, the susceptibility of local isolates to these compounds should be taken into account. Recent data showed susceptibility prevalence to PTZ in ESBL-EC ranging from 62% to 87% in different areas of the world; the data for ESBL-producing *K. pneumoniae* ranged from 26% to 47% [6,8]. In a recent nationwide study in Spain, 69% of ESBL-EC isolates were susceptible to AMC [9]; however, most of the isolates are resistant to ampicillin-sulbactam. We do not think that these data support BLBLI use as monotherapy for severe infections potentially caused by ESBL-EC; we do, however, think that our results suggest that PTZ or AMC are suitable options for definitive therapy once the

susceptibility results are known, thus providing an opportunity for using a carbapenem-spare regimen. In this way, patients who receive carbapenems could be de-escalated to an active BLBLI, and patients following any inadequate empirical therapy might be changed to an active BLBLI instead of to a carbapenem.

Some limitations of our study should be considered when interpreting the results. Firstly, this is not a randomised study and confounding due to unmeasured variables may have occurred. Randomised trials for comparing empirical regimens are difficult to perform in this setting, but would be desirable for comparing definitive treatments. Secondly, we integrated patients drawn from different cohorts, although the methodologies used were very similar. Thirdly, although this is the largest series published, its statistical power is limited. Finally, our results are applicable only to BSI due to ESBL-EC, particularly originating in the urinary and biliary tracts, the infection source of 2/3 of our patients. More data for other more difficult-to-treat infections, such as pneumonia, or for other microorganisms such as *K. pneumoniae*, would be needed. Also, our data extend to AMC and PTZ, but not to other BLBLIs.

In conclusion, our results suggest that AMC or PTZ, if used at adequate dosages, are suitable options for the definitive therapy of susceptible ESBL-EC strains causing BSI, mainly in the urinary and biliary tracts, which could help prevent overuse of carbapenems.

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Conflicts of interests. J. Rodríguez-Baño has been a consultant for Wyeth, Merck, and Pfizer, has served as speaker for Wyeth, Merck, Pfizer, Astra-Zeneca and GlaxoSmithKline, and has received research support from Merck and Wyeth. A. Pascual has been a consultant for Merck and Pfizer, has served as speaker for Wyeth, Astra-Zeneca, Merck, and Pfizer and has received research support from Merck and Pfizer and Wyeth. M.D. Navarro, P. Retamar, and E. Picón had no conflict of interest.

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Table 1. Characteristics of the six prospective cohort studies supplying patients with bloodstream infections caused by extended-spectrum β-lactamase-producing *E. coli* included in the present study.

Reference	Number of participating centers	Years	Features of included patients	No. of patients in cohort/no. of patients with bacteremia	No. of patients included in cohort: empirical therapy	Patients included in post-hoc analysis (definitive therapy)
13	1	2001–2005	BSI, community and hospital-acquired	43/43	19	39
14	11	2002–2003	All types of infections, community onset	122/7	2	4
15	2*	2006–2007	All types of infections, community and hospital-acquired	80/19	10	15
16	13	2004–2006	BSI, community-onset	95/95	30	55
17	13	2004–2006	BSI, hospital-acquired	96/96	33	51
9	44	2006	All types of infections, community and nosocomial	304/27	9	10
Total	-	-	-	740/287	103	174

*Only cases in one center had eligible patients.
BSI: bloodstream infection.

Table 2. Characteristics of patients with bloodstream infections caused by extended-spectrum β-lactamase-producing *E. coli*, according to therapy. Data expressed as number of patients (percentages), except where specified. P values were calculated by chi-squared test, except where specified.

	Empirical therapy cohort			Definitive therapy cohort		
	BLBLI (n=72)	Carbapenem (n=31)	P	BLBLI (n=54)	Carbapenem (n=120)	p
Median age, years (IQ range)	69 (59–80)	60 (52–78)	0.1[a]	67 (56–83)	70 (55–78)	0.3[a]
Male gender	29 (40.3)	11 (35.5)	0.6	34 (63)	70 (58.3)	0.5
Nosocomial acquisition	26 (36.1)	24 (77.4)	<0.001	18 (33.3)	67 (55.8)	0.006
Median Charlson index (IQ range)	2 (1–5)	2 (1–5)	0.6[a]	2.5 (1–5)	3 (1–5)	0.5[a]
Cancer	21 (31.9)	11 (35.5)	0.7	15 (27.8)	43 (35.8)	0.2
Immunosuppression	5 (6.9)	5 (16.1)	0.1[b]	3 (5.6)	15 (12.5)	0.1
Neutropenia	2 (2.8)	3 (9.7)	0.1[b]	0	7 (5.8)	0.1[b]
Urinary or biliary tract as source	52 (72.2)	18 (58.1)	0.1	42 (77.8)	79 (65.8)	0.1
ICU admission	7 (9.9)	2 (6.7)	0.7[b]	4 (7.4)	18 (15.4)	0.1
Severe sepsis/shock at presentation	14 (19.4)	9 (29.0)	0.2	8 (14.8)	32 (26.7)	0.08
Median Pitt score (IQ range)	1 (0–2)	1 (0–2)	0.7[a]	1 (0–2)	1 (1–2)	0.04[a]

CTX-M enzyme	57 (80.3)	25 (86.2)	0.4	43 (82.7)	95 (81.2)	0.8
Definitive therapy with carbapenem	32 (44.4)	30 (93.7)	<0.001	-	-	-
Definitive therapy with BLBLI	34[c] (47.2)	0	<0.001	-	-	-
Empirical therapy with carbapenem	-	-	-	0	30 (25)	<0.001
Empirical therapy with BLBLI	-	-	-	45[c] (83.3)	38 (31.7)	<0.001
Empirical therapy with cephalosporins	-	-	-	7 (13)	39 (32.5)	0.006
Empirical therapy with fluoroquinolones	-	-	-	2 (3.7)	13 (10.8)	0.1[b]
Appropriate empirical therapy	-	-	-	34 (63)	64 (53.3)	0.2
Mortality day 7	2 (2.8)	3 (9.7)	0.1 [b]	1 (1.9)	5 (4.2)	0.6[b]
Mortality day 14	7 (9.7)	5 (16.1)	0.3	3 (5.6)	14 (11.7)	0.2
Mortality day 30	7 (9.7)	6 (19.4)	0.1	5 (9.3)	20 (16.7)	0.1
Median days of hospital stay after BSI (IQ range)	12 (8–28)	13 (9–25)	0.7[a]	13 (8–22)	13 (10–25)	0.04[a]

BLBLI: β-lactam-β-lactamase inhibitor association. IQ: interquartile.
[a]Mann-Whitney test. [b]Fisher test. [c] These numbers are different because empirical therapy was inappropriate in 11 patients in the definitive therapy cohort and thus could not be included in the empirical therapy cohort.

Table 3. 30-day mortality in patients who received empirical therapy with an active β-lactam-β-lactam inhibitor, according to MIC of the antimicrobial used. Data expressed as number of patients who died/number of patients treated.

MIC (mg/L)	≤1	2	4	8	16
Piperacillin-tazobactam	0/10	0/8	1/4	2/6	1/7
Amoxicillin-clavulanate	-	-	1/12	2/25	-

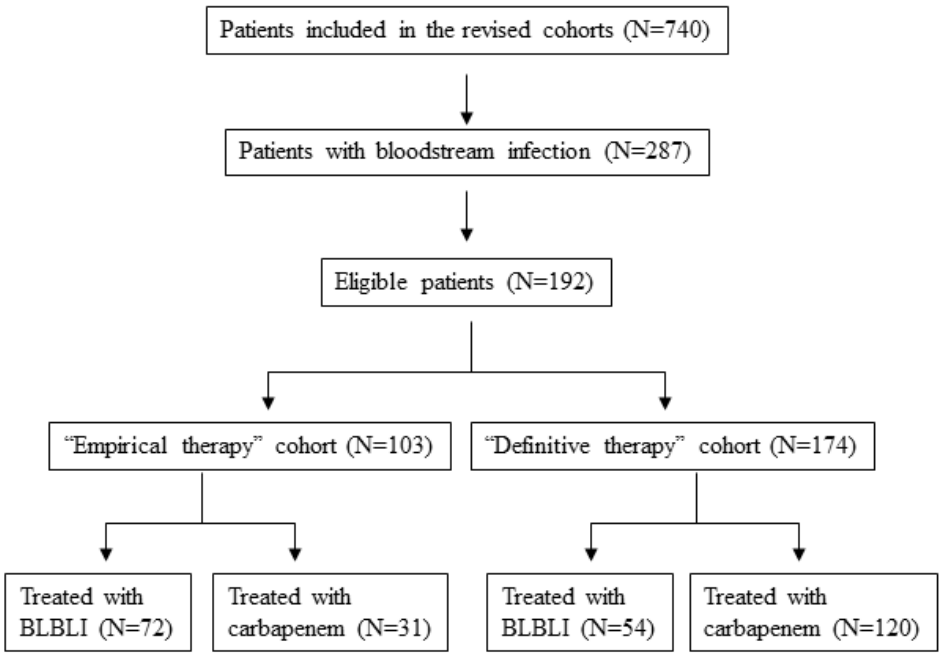
Table 4. Analysis of the association between different variables and mortality by Cox regression in the definitive therapy cohort.

	Crude analysis		Adjusted analysis	
	HR (95% CI)	P	HR (95% CI)	P
Male gender	1.2 (0.46–2.29)	0.9	-	
Age[a]	1.00 (0.97–1.02)	0.9	-	
Nosocomial BSI	0.99 (0.45–2.22)	0.9	-	
Charlson index[a]	1.02 (0.88–1.28)	0.7	-	
Neutropenia	1.78 (0.88–13.32)	0.5	-	
High risk source[b]	2.07 (0.94–4.54)	0.06	-	
Pitt score[a]	1.49 (1.26–1.78)	<0.001	1.38 (1.12–1.70)	0.002
Severe sepsis or shock[c]	3.64 (1.66–7.99)	0.001	2.10 (0.87–5.05)	0.09
Empirical therapy with BLBLI	0.56 (0.18–1.73)	0.3	-	
Inappropriate empirical therapy	1.76 (0.78–3.93)	0.1	-	
Definitive therapy with BLBLI[d]	0.66 (0.24–1.76)	0.4	0.76 (0.28–2.07)	0.5

[a]Per unit. [b]Other than urinary and biliary tract. [c]At presentation. [d]Reference: Definitive therapy with carbapenem.

Figure 1. Flow chart of patients included in the study.

Figure 1.


Patients included in the revised cohorts (N=740)
Patients with bloodstream infection (N=287)
Eligible patients (N=192)
"Empirical therapy" cohort (N=103)
"Definitive therapy" cohort (N=174)
Treated with BLBLI (N=72)
Treated with carbapenem (N=31)
Treated with BLBLI (N=54)
Treated with carbapenem (N=120)