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Predictors of outcome in patients with severe sepsis or septic shock due to extended-spectrum β-lactamase-producing Enterobacteriaceae

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ABSTRACT

Purpose: There are few data in the literature regarding sepsis or septic shock due to extended-spectrum β-lactamases (ESBL)-producing Enterobacteriaceae (E). The aim of this study was to assess predictors of outcome in septic patients with bloodstream infection (BSI) caused by ESBL-E.
Methods: Patients with severe sepsis or septic shock and BSI due to ESBL-E were selected from the INCREMENT database. The primary endpoint of the study was the evaluation of predictors of outcome after 30 days from development of severe sepsis or septic shock due to ESBL-E infection. Three cohorts were created for analysis: global, empirical-therapy and targeted-therapy cohorts.
Results: 367 septic patients were analysed. Overall mortality was 43.9% at 30 days. *Escherichia coli* (62.4%) and *Klebsiella pneumoniae* (27.2%) were the most frequent isolates. β-lactam/β-lactamase inhibitor (BLBLI) combinations were the most empirically used drug (43.6%), followed by carbapenems (29.4%). Empirical therapy was active in vitro in 249 (67.8%) patients, and escalation of antibiotic therapy was reported in 287 (78.2%) patients. Cox regression analysis showed that age, Charlson Comorbidity Index, McCabe classification, Pitt bacteremia score, abdominal source of infection and escalation of antibiotic therapy were independently associated with 30-day mortality. No differences in survival were reported in patients treated with BLBLI combinations or carbapenems in empirical or definitive therapy.
Conclusions: BSI due to ESBL-E in patients who developed severe sepsis or septic shock was associated with high 30-day mortality. Comorbidities, severity scores, source of infection and antibiotic therapy escalation were important determinants of unfavorable outcome.

1. Introduction

Bloodstream infections (BSI) caused by extended-spectrum β-lactamases (ESBL)-producing Enterobacteriaceae (E) are associated with high rates of treatment failure and increased mortality, particularly when appropriate antimicrobial therapy is delayed [1,2,3,4,5]. The choice of an early effective empirical antibiotic therapy in critically ill patients with sepsis and/or septic shock is crucial to reduce the high rates of complications and unfavorable outcome [5].

Previous publications resulting from the INCREMENT project [6,7,8,9,10] highlighted the necessity to identify peculiar clinical and therapeutic features of BSI due to ESBL strains. The role of carbapenems, considered the first choice for the treatment of severe infections caused by ESBL strains [11,12,13,14,15], was redefined also for the high incidence of carbapenem-resistant Enterobacteriaceae strains observed in the last few years [16]. Attention is now focused on promotion of carbapenem-sparing strategies and evaluation of efficacy of other drugs, like β-lactam/β-lactamase inhibitor combinations (BLBLI) that remain active against a considerable proportion of ESBL-E; however, the role of these drugs is controversial for the treatment of serious infections due to ESBL pathogens [17,18,19].

There are few data in the literature concerning sepsis or septic shock due to ESBL-E infections. Thus, it is important for physicians to recognize peculiar clinical characteristics of sepsis or septic shock due to ESBL-E infections, to enable them to promptly identify patients at high risk of unfavorable outcome. The aim of this additional study from the INCREMENT project was to assess the predictors of outcome in septic patients with severe sepsis or septic shock caused by ESBL-producing strains.

2. Materials and methods

2.1. Study Design and Patients

The INCREMENT project is a retrospective international cohort study including patients with clinically significant BSI due to ESBL- or carbapenemase-producing Enterobacteriaceae from January 2004 to December 2013. Characteristics of the INCREMENT study were previously explained [15,16,17,18,19]. This analysis was reported according to the STROBE recommendations [20].

Patients with severe sepsis or septic shock and clinically significant BSI due to ESBL-E were selected from the original database. Data from patients were collected from charts up to 30 days after the diagnosis of BSI; if needed, patients or relatives were contacted by phone.

The INCREMENT project was approved by the Spanish Agency of Medicines (AEMPS; code JRB-ANT-2012-01) and the Hospital Universitario Virgen Macarena Institutional Review Board (code 1921); the need to obtain written informed consent was waived. Approval was also gained at participating centers according to local requirements.

2.2. Variables, Microbiology and Definitions

Data collected from all patients included: demographics, acquisition of infection, comorbidities by calculation of Charlson comorbidity index, McCabe classification, Pitt bacteremia score, source of BSI according to clinical and microbiological data, antimicrobial therapy, in vitro susceptibility to empirical and targeted antibiotic regimens, length of stay after BSI, and mortality.

Enterobacteriaceae were identified using standard microbiological techniques in each participating center. ESBL production was screened and confirmed according to CLSI recommendations [21]; selected isolates from each center had been characterized by polymerase chain reaction (PCR) and DNA sequencing using established methods [17]. Nosocomial acquisition was considered when symptoms of infection started >48 h after hospital admission or within 48 h of hospital discharge. Healthcare acquisition was considered if patients had attended hemodialysis or received intravenous chemotherapy in the past 30 days, had been admitted to an acute-care hospital for at least 2 days or had surgery in the past 90 days, or resided in a nursing home or long-term care facility. Other infections were considered community-acquired.

Three categories were used for McCabe classification: (1) nonfatal (mild and only a few comorbidities), (2) ultimately fatal (risk of death within four years or multiple comorbidities) and (3) rapidly fatal (risk of death during stay, intensive or terminal care patients) underlying diseases.

Antimicrobial therapy administered before the susceptibility results were available was considered empirical; therapy administered after microbiological report was considered targeted/definitive.

Severe sepsis was defined as sepsis with sepsis-induced organ dysfunction or tissue hypoperfusion (manifesting as hypotension, elevated lactate levels, or decreased urine output); and septic shock as severe sepsis plus persistently low blood pressure following the administration of intravenous fluids [22].

Administered BLBLI were amoxicillin-clavulanate (AMC), piperacillin-tazobactam (PTZ), or ampicillin-sulbactam (AMS), quinolones were ciprofloxacin or levofloxacin, aminoglycosides were gentamicin or amikacin, and carbapenems included imipenem, meropenem, and ertapenem. Therapy was considered as monotherapy if no other drugs with intrinsic activity against Gram-negative organisms were co-administered, irrespective of isolate susceptibility.

Active empirical therapy was considered appropriate antibiotic therapy for all patients with an etiological diagnosis according to susceptibility test criteria. Antimicrobial treatment was rated as inadequate if one or more of the organisms present were known to have intrinsic resistance or were found to be resistant through susceptibility testing.

Escalation of antibiotic therapy was defined as the switch to or addition of a drug class or classes with a broader spectrum or additional coverage after 48 h from the initial antibiotic therapy.

2.3. Global, Empirical-therapy and Targeted-therapy cohorts

Three non-mutually exclusive cohorts were constructed to analyse predictors of mortality, including therapeutic variables. The global cohort (GC) included all patients analysed but explored only pre-treatment variables to identify factors associated with mortality, irrespective of antibiotic therapies. The impact of empirical therapy was investigated in the empirical-therapy cohort (ETC), which included the patients who received a monotherapy that began within the first 24 h after blood cultures were taken and continued for at least 48 h (except for patients who died in ≤48 h, who were included if they received at least 1 complete day of therapy). The impact of targeted therapy was investigated in the targeted-therapy cohort (TTC), which included the patients who received a monotherapy once the susceptibility profile was available; the targeted drug must have started in ≤5 days and been administered for at least 50% of the total duration of therapy (except for patients who died while on targeted therapy, who were included if they received at least 1 complete day of therapy).

2.4. Endpoints and Statistical Analysis

The primary endpoint of the study was the evaluation of predictors of outcome at 30 days after development of septic shock due to ESBL infection.

Separate analyses were performed for the three cohorts. To detect significant differences between groups, we used the chi-square test or Fisher exact test for categorical variables, and the 2-tailed *t* test or Mann-Whitney test for continuous variables, when appropriate. In univariate and multivariate analysis of survival, the Cox regression model was used to determine the effects of different variables on outcome at 30 days. The cumulative survival was evaluated using Kaplan-Meier product-limit estimators. The final multivariable Cox regression model was selected through forward stepwise regression based on Akaike Information Criterion.

Statistical significance was established at ≤ 0.05. All reported *P* values are 2-tailed. The results were obtained using the statistical software R (version 3.3.4; Vienna, Austria).

3. Results

The INCREMENT database includes 1005 patients with BSI due to ESBL-E; of these, 367 (36.5%) patients with severe sepsis or septic shock were analysed. The number of cases per center in the global cohort ranged from 4 to 50; wards of hospitalization at the time of ESBL-E isolation in this study population are reported in Fig. 1.

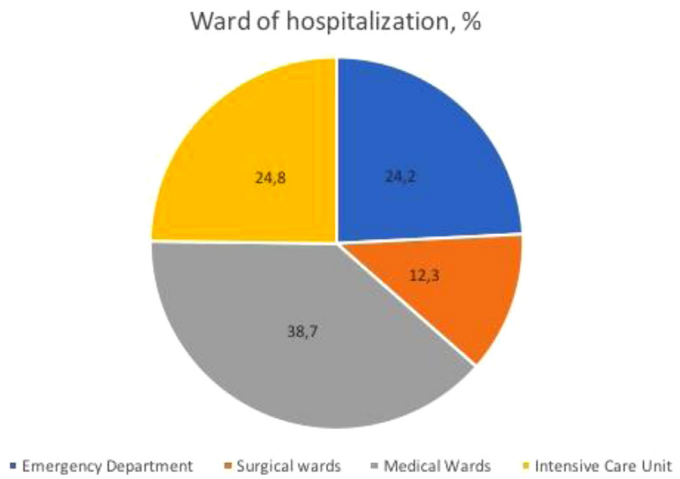

Fig. 1. Wards of hospitalization at time of ESBL-E isolation.
Legend. ESBL-E: extended-spectrum beta-lactamases-producing Enterobacteriaceae.

Baseline characteristics and clinical features of survivors and non-survivors at 30 days are compared in Table 1. Overall, mortality at 30 days was observed in 161 (43.9%) patients. Comparison between the two patient groups showed that nosocomial acquisition of infection (64.5% vs. 50%, $P = 0.002$), pneumonia (17.4% vs. 8.3%, $P = 0.012$), admission in the intensive care unit (ICU; 32.2% vs. 18.9%, $P = 0.004$), a higher Charlson Comorbidity index (3 points vs. 2 points, $P = 0.005$), a higher Pitt bacteremia score (4 points vs. 3 points, $P < 0.001$), need of non-invasive mechanical ventilation (NIV) or mechanical ventilation (MV; 44% vs. 21.3%, $P < 0.001$), and need of vasopressor agents (91.9% vs. 65%, $P < 0.001$) were more frequently observed in non-survivors. Conversely, a urinary source of infection (44.7 vs. 24.8, $P < 0.001$) was more frequently reported in survivors compared with patients with poor outcome. Finally, time to appropriate antibiotic therapy (4 days vs. 3 days, $P = 0.01$) was longer in non-survivors compared with survivors.

Etiologies of infection are described in Table 2. Overall, *Escherichia coli* (62.4%) and *Klebsiella pneumoniae* (27.2%) were the most frequent isolates; in vitro resistance to antibiotics prescribed in empirical therapy was observed in 4/5 (80%) strains of *Serratia marcescens*, 23/29 (79.3%) of *Enterobacter* spp, 123/229 (53.7%) of *E. coli*, and 41/100 (41%) of *K. pneumoniae*. Comparison between survivors and non-survivors showed a more frequent isolation of *E. coli* (67.5% vs. 55.9%, P=0.03) in survivors, whereas *K. pneumoniae* was more frequently isolated in non-survivors (34.2% vs. 21.8%, $P = 0.012$), compared with survivors.

Table 3 shows a comparison of antibiotics used in empirical and definitive regimens among survivors and non-survivors. BLBLI was the most empirically used class (43.6%), followed by carbapenems (29.4%), and cephalosporins (19.3%). Carbapenems (56.4%), and BLBLI (10.4%) were more frequently used as definitive therapy. Combination therapy was used empirically in 119 (32.4%) patients and as a definitive regimen in 93 (25.3%) patients. Empirical antibiotics were active in vitro in 249 (67.8%) patients, and escalation of antibiotic therapy was reported in 287 (78.2%) patients. Comparison between non-survivors and survivors showed that a carbapenem in a definitive antibiotic regimen (42.9% vs. 67%, P<0.001) and a combination of antibiotics as definitive therapy (16.7% vs. 32%, P<0.001) were more frequently used in survivors.

Table 1
Comparison of baseline characteristics and clinical features of survivors and non-survivors at 30 days in the global cohort.

Variables	All patients N=367 (%)	Survivors N=206 (%)	Non-survivors N=161 (%)	*P*
Age, median (IQR)	69 (57-78)	68 (56-77)	70 (57-80)	0.30
Male sex	216 (58.9)	127 (61.7)	89 (55.3)	0.26
Acquisition of infection				
Community	46 (12.5)	30 (14.5)	16 (9.9)	0.26
Healthcare	106 (28.9)	70 (33.9)	36 (22.3)	**0.01**
Nosocomial	207 (56.4)	103 (50)	104 (64.5)	**0.002**
Source of infection				
Primary BSI	22 (6)	10 (4.9)	12 (7.5)	0.41
Urinary	132 (36)	92 (44.7)	40 (24.8)	**<0.001**
Biliary	36 (9.8)	23 (11.2)	13 (8.1)	0.42
SSTI	7 (1.9)	4 (1.9)	3 (1.9)	1.0
Abdominal	50 (13.6)	22 (10.7)	28 (17.4)	0.09
Pneumonia	45 (12.3)	17 (8.3)	28 (17.4)	**0.012**
Osteoarticular	2 (0.5)	2 (1)	0	0.59
CNS	1 (0.3)	0	1 (0.6)	0.90
Other	93 (25.3)	60 (29.1)	33 (20.4)	0.085
McCabe classification, nonfatal	145 (39.5)	97 (47)	48 (29.8)	**<0.001**
Charlson Comorbidity Index, median (IQR)	3 (1-5)	2 (0-4)	3 (2-8)	**0.005**
Pitt bacteremia score, median (IQR)	3 (2-5)	3 (1-4)	4 (2-7)	**<0.001**
Comorbidities				
Diabetes	124 (33.8)	60 (29.1)	64 (39.7)	**0.027**
COPD	77 (21)	37 (17.9)	40 (24.8)	0.09
Myocardial infarct	47 (12.8)	20 (9.7)	27 (16.7)	0.12
Congestive heart failure	70 (19.1)	31 (15)	39 (24.2)	**0.027**
Peripheral arterial disease	40 (10.9)	16 (7.8)	24 (14.9)	**0.046**
Dementia	41 (11.2)	22 (10.7)	19 (11.8)	0.83
Immunological disease	16 (4.4)	9 (4.3)	7 (4.3)	1.0
Ulcerative disease	23 (6.3)	12 (5.8)	11 (11.1)	0.81
Liver disease	58 (15.8)	31 (15)	27 (16.7)	0.68
Kidney disease	84 (22.9)	41 (19.9)	43 (26.7)	0.12
Cancer	148 (40.3)	88 (42.7)	60 (37.2)	0.43
Neurological disease	77 (21)	36 (17.4)	41 (25.4)	0.08
AIDS	8 (2.2)	6 (2.9)	2 (1.2)	0.47
ICU admission	91 (24.8)	39 (18.9)	52 (32.2)	**0.004**
Need of NIV or MV	115 (31.3)	44 (21.3)	71 (44)	**<0.001**
Need of vasopressor agents	282 (76.8)	134 (65)	148 (91.9)	**<0.001**
Time to appropriate antibiotic therapy, days, median (IQR)	3 (1-5)	3 (1-4)	4 (2-5)	**0.01**

Legend. IQR: inter-quartile range; BSI: bloodstream infection; SSTI: skin and soft tissue infection; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; AIDS: acquired immune deficiency syndrome; ICU: intensive care unit; NIV: non-invasive mechanical ventilation; MV: mechanical ventilation.

Table 2
Etiology of infection among survivors and non-survivors at 30 days and rate of resistance to empirical therapy.

Pathogens	Survivors N = 206 (%)	Non-Survivors N = 161 (%)	*P*	Resistance to empirical therapy N° resistant isolates/total isolates (%)
Escherichia coli	139 (67.5)	90 (55.9)	**0.03**	123/229 (53.7)
Klebsiella pneumoniae	45 (21.8)	55 (34.2)	**0.012**	41/100 (41)
Enterobacter spp	17 (8.3)	12 (7.5)	0.93	23/29 (79.3)
Serratia marcescens	3 (1.5)	2 (1.2)	1.0	4/5 (80)
Proteus spp	0	2 (1.2)	0.37	0
Citrobacter spp	1 (0.5)	0	1.0	0
Morganella morganii	1 (0.5)	0	1.0	0

As reported in Table 4, univariate and multivariate Cox regression analysis of predictors of outcome at 30 days in the GC showed that age (hazard ratio [HR] 1.11, confidence interval [CI] 95% 1.02-1.22, $P = 0.021$), McCabe classification (HR 1.39, CI 95% 1.12-1.72, $P = 0.003$), Pitt bacteremia score (HR 1.14, CI 95% 1.09-1.19, $P < 0.001$), and abdominal source of infection (HR1.66, CI 95% 1.08-1.89, $P = 0.02$) were independently associated with death.

Based on inclusion criteria (see Methods section), 31 patients were excluded from ETC and TTC to investigate the impact of therapy on 30-day mortality.

The Table 5 shows univariate and multivariate Cox regression analysis of predictors of outcome at 30 days in 106 patients of the ETC: McCabe classification (HR 1.45, CI 95% 1.14-1.83, $P = 0.002$), Pitt bacteremia score (HR 1.14, CI 95% 1.08-1.19, $P<0.001$), and escalation of antibiotic therapy (HR 1.9, CI 95% 1.1-3.26, $P = 0.02$) were independently associated with death.

Univariate and multivariate Cox regression analysis of predictors of outcome at 30 days in 230 patients of the TTC is reported in Table 6. Charlson Comorbidity Index (HR 1.20, CI 95% 1.11-1.30, $P < 0.001$) and Pitt bacteremia score (HR 1.16, CI 95% 1.09-1.24, $P < 0.001$) were associated with death, whereas quinolones in definitive therapy had a protective role (HR 0.29, CI 95% 0.11-0.8, $P = 0.016$).

Finally, Kaplan-Meier analysis of 30-day survival of patients with or without escalation of antibiotic therapy is reported in Fig. 2.

Table 3
Comparison between antibiotics administered in empirical and definitive therapy to survivors and non-survivors at 30 days in the global cohort.

Antibiotics	Empirical therapy			Definitive therapy		
	Survivors N = 206 (%)	Non-survivors N = 161 (%)	*P*	Survivors N = 206 (%)	Non-survivors N = 161 (%)	*P*
Cephalosporin	43 (20.9)	28 (17.4)	0.48	3 (1.5)	1 (0.6)	0.80
BLBLI	94 (45.6)	66 (41)	0.43	27 (13.1)	11 (6.8)	0.07
Aminoglycosides	22 (10.7)	21 (13)	0.59	16 (7.8)	8 (5)	0.39
Quinolones	30 (14.6)	25 (15.5)	0.91	14 (6.8)	6 (3.7)	0.29
TMP/SMX	1 (0.5)	0	1.0	8 (3.9)	4 (2.5)	0.65
Fosfomycin	2 (1)	0	0.59	0	0	-
Tetracycline	2 (1)	2 (1.2)	1.0	0	0	-
Monobactams	1 (0.5)	1 (0.6)	1.0	0	0	-
Colistin	1 (0.5)	1 (0.6)	1.0	3 (1.5)	1 (0.6)	0.79
Carbapenem	61 (29.6)	47 (29.2)	0.44	138 (67)	69 (42.9)	**<0.001**
Tigecycline	0	0	-	6 (2.9)	2 (1.2)	0.47
Chloramphenicol	0	0	-	1 (0.5)	0	1.0
Combination therapy	150 (72.8)	111 (68.9)	0.54	88 (42.7)	49 (30.4)	**0.001**
Median length of therapy (IQR)	3 (1-4)	2 (1-4)	0.1	11 (5-14)	7 (3-10)	**<0.001**
Active empirical therapy	143 (69.4)	106 (65.8)	0.54			
Escalation of antibiotic therapy	154 (74.7)	133 (82.6)	0.09			

Legend. BLBLI: ß-lactam/ß-lactamase inhibitor; TMP/SMX: Trimethoprim/sulfamethoxazole: IQR: inter-quartile range.
Note. BLBLI: amoxicillin/clavulanate or ampicillin/sulbactam or piperacillin-tazobactam
Quinolones: ciprofloxacin or levofloxacin
Aminoglycosides: gentamicin or amikacin
Carbapenem: meropenem or imipenem or ertapenem

Table 4
Univariate and Multivariate Cox regression analysis of predictors of outcome at 30 days in 367 patients in the global cohort.

VARIABLES	UNIVARIATE			MULTIVARIATE		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.1	1.01-1.21	0.031	1.11	1.02-1.22	0.021
Male sex	0.84	0.62-1.15	0.284			
Acquisition of infection						
Healthcare	0.95	0.53-1.71	0.863			
Nosocomial	1.38	0.81-2.34	0.233			
Source of infection						
Primary BSI	1.08	0.6-1.94	0.807			
Urinary	0.59	0.41-0.84	0.003			
Biliary	0.81	0.46-1.44	0.478			
SSTI	0.82	0.26-2.57	0.735			
Abdominal	1.46	0.97-2.19	0.07	1.66	1.08-1.89	0.02
Pneumonia	0.45	1.04-2.36	0.3			
ICU admission	1.4	1.01-1.95	0.047			
Charlson Comorbidity Index	1.05	0.99-1.11	0.083			
McCabe classification	1.54	1.25-1.89	<0.001	1.39	1.12-1.72	0.003
Pitt bacteremia score	1.14	1.09-1.19	<0.001	1.14	1.09-1.19	<0.001
Comorbidities						
Diabetes	1.42	1.03-1.95	0.033			
COPD	1.28	0.89-1.84	0.175			
Myocardial infarct	1.29	0.85-1.96	0.238			
Congestive heart failure	1.28	0.87-1.84	0.19			
Peripheral arterial disease	1.41	0.91-2.18	0.12			
Dementia	1.08	0.67-1.75	0.752			
Immunological disease	0.82	0.39-1.76	0.617			
Ulcerative disease	1.08	0.58-1.99	0.816			
Liver disease	1.11	0.73-1.68	0.629			
Kidney disease	1.31	0.92-1.87	0.132			
Cancer	0.85	0.62-1.18	0.334			
AIDS	0.43	0.11-1.72	0.232			
Need of NIV or MV	1.93	1.4-2.64	<0.001			
Need of vasopressor agents	1.37	1.01-2.08	0.044			

Legend. HR: hazard ratio; CI: confidence interval; BSI: bloodstream infection; SSTI: skin and soft tissue infection; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; AIDS: acquired immune deficiency syndrome; NIV: non-invasive mechanical ventilation; MV: mechanical ventilation.

4. Discussion

This study highlights the high mortality associated with BSI due to ESBL-E at 30 days from diagnosis in patients who developed severe sepsis or septic shock. Furthermore, some clinical characteristics, such as source of infection (specifically from urinary tract, abdominal or pneumonia), indicators of severity (comorbidities and admission in ICU) and need of respiratory support and/or vasopressor agents, were important determinants of outcome in this setting.

Cox regression analysis identified age, McCabe classification, Charlson Comorbidity Index, Pitt bacteremia score, abdominal

Table 5
Univariate and Multivariate Cox regression analysis of predictors of outcome at 30 days in 106 patients in the empirical-therapy cohort.

VARIABLES	UNIVARIATE			MULTIVARIATE		
	HR	CI 95%	*P*	HR	CI 95%	*P*
Age	1.09	0.99-1.19	0.075			
Male sex	0.82	0.59-1.13	0.226			
Acquisition of infection						
Healthcare	0.95	0.52-1.74	0.861			
Nosocomial	1.36	0.79-2.35	0.270			
Source of infection						
Primary BSI	1.19	0.66-2.15	0.562			
Urinary	0.56	0.39-0.82	0.003			
Biliary	0.87	0.49-1.54	0.639			
SSTI	0.85	0.27-2.68	0.786			
Abdominal	1.42	0.93-2.17	0.104			
Pneumonia	1.79	1.18-2.72	0.006			
ICU admission	1.58	1.12-2.23	0.009			
Charlson Comorbidity Index	1.06	0.99-1.12	0.069			
McCabe classification	1.55	1.25-1.93	<0.001	1.45	1.14-1.83	0.002
Pitt bacteremia score	1.16	1.11-1.22	<0.001	1.14	1.08-1.19	<0.001
Comorbidities						
Diabetes	1.37	0.98-1.92	0.062			
COPD	1.45	1.01-2.1	0.047			
Myocardial infarct	1.43	0.92-2.21	0.111			
Congestive heart failure	1.43	0.98-2.09	0.06			
Peripheral arterial disease	1.25	0.77-2.03	0.357			
Dementia	0.98	0.58-1.65	0.934			
Immunological disease	0.79	0.35-1.80	0.58			
Ulcerative disease	1.09	0.57-2.07	0.797			
Liver disease	1.12	0.73-1.73	0.593			
Kidney disease	1.43	0.99-2.05	0.056			
Cancer	0.91	0.65-1.27	0.578			
AIDS	0.44	0.11-1.78	0.249			
Need of NIV or MV	1.96	1.41-2.72	<0.001			
Need of vasopressor agents	1.69	1.14-2.49	0.008			
Cephalosporin	0.87	0.57-1.31	0.494			
BLBLI	0.95	0.69-1.32	0.763			
Aminoglycosides	1.06	0.67-1.68	0.808			
Quinolones	1.12	0.73-1.73	0.595			
Tetracycline	1.34	0.33-5.44	0.677			
Carbapenem	1.02	0.72-1.44	0.914			
Combination therapy	0.78	0.65-1.11	0.12			
Escalation of antibiotic therapy	1.92	1.12-3.28	0.017	1.9	1.1-3.26	0.02
Time to appropriate antibiotic therapy	1.2	0.87-2.34	0.25			

Legend. HR: hazard ratio; CI: confidence interval; BSI: bloodstream infection; SSTI: skin and soft tissue infection; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; AIDS: acquired immune deficiency syndrome; NIV: non-invasive mechanical ventilation; MV: mechanical ventilation.

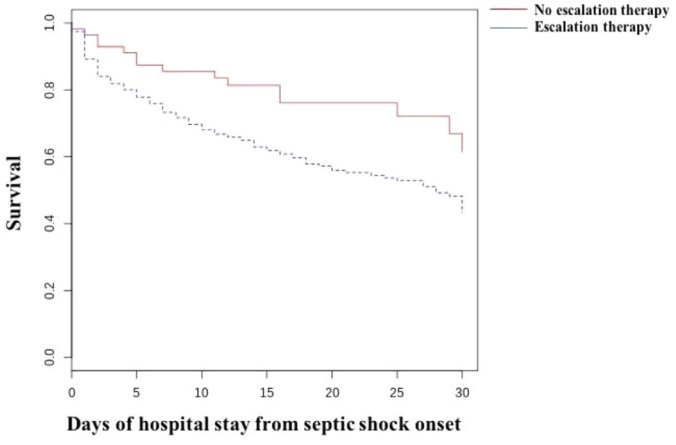

Fig. 2. Kaplan-Meier curves of 30-day survival of patients with or without escalation of antibiotic therapy*.
*$P<0.001$.

source of infection and escalation of antibiotic therapy (after microbiological report and/or worsening of clinical conditions) as factors independently associated with unfavorable outcome at 30 days. Finally, the use of a quinolone in definitive therapy was associated with 30-day survival.

As reported in the literature, the severity of clinical conditions (expressed by age, McCabe classification, Charlson Comorbidity Index and Pitt bacteremia score) at time of BSI onset plays a central role in determining the decreased survival in patients with infections due to ESBL-E [23]. Furthermore, the progression to sepsis and septic shock is the crucial mechanism associated with high rates of mortality observed in this setting of critically ill patients with BSI due to ESBL strains [24,25,26]. Progression to septic shock may also explain the apparently low effectiveness of an adequate initial antibiotic therapy, because septic shock is associated with a lethal cascade of events that is unlikely to be interrupted even by an appropriate initial antimicrobial treatment. In addition, most of our patients were severely ill and would probably have been unable to survive their infections independently of the administration of an adequate initial antimicrobial treatment. Finally, the lack of homogeneity in management and treatment of septic patients could partly explain the high rates of mortality.

Importantly, the need for an antibiotic therapy escalation after microbiological report and/or worsening of clinical conditions was independently associated with unfavorable outcome at 30 days, which confirms previous observations about an initial inadequate antimicrobial treatment as a major risk factor for mortality [27].

Table 6
Univariate and Multivariate Cox regression analysis of predictors of outcome at 30 days in 230 patients in the targeted-therapy cohort.

VARIABLES	UNIVARIATE			MULTIVARIATE		
	HR	CI 95%	*P*	HR	CI 95%	*P*
Age	1.1	1.01-1.21	0.031			
Male sex	1.19	0.62-1.15	0.284			
Acquisition of infection						
Healthcare	0.95	0.53-1.72	0.863			
Nosocomial	1.38	0.81-2.34	0.233			
Source of infection						
Primary BSI	1.73	0.79-3.76	0.169			
Urinary	0.68	0.41-1.13	0.137			
Biliary	1.53	0.79-2.99	0.208			
SSTI	1.71	0.54-5.41	0.365			
Abdominal	0.92	0.44-1.92	0.829			
Pneumonia	1.52	0.87-2.68	0.144			
ICU admission	1.4	1.01-1.95	0.047			
Charlson Comorbidity Index	1.05	0.99-1.11	0.083	1.20	1.11-1.30	<0.001
McCabe classification	1.54	1.25-1.89	<0.001			
Pitt bacteremia score	1.14	1.09-1.19	<0.001	1.16	1.09-1.24	<0.001
Comorbidities						
Diabetes	1.42	1.03-1.95	0.033			
COPD	1.29	0.89-1.84	0.175			
Myocardial infarct	1.29	0.85-1.96	0.238			
Congestive heart failure	1.28	0.89-1.84	0.19			
Peripheral arterial disease	1.41	0.91-2.18	0.12			
Dementia	1.08	0.67-1.75	0.752			
Immunological disease	0.66	0.21-2.09	0.475			
Ulcerative disease	1.08	0.58-1.99	0.816			
Liver disease	1.11	0.73-1.68	0.629			
Kidney disease	1.31	0.92-1.87	0.132			
Cancer	0.85	0.62-1.18	0.334			
AIDS	0.43	0.11-1.72	0.232			
Need of NIV or MV	1.88	1.18-3.0	0.008			
Need of vasopressor agents	1.32	0.79-2.18	0.287			
Cephalosporin	1.46	0.1-4.91	0.708			
BLBLI	1.64	0.33-1.13	0.114			
Aminoglycosides	0.59	0.29-1.20	0.142			
Quinolones	0.54	0.24-1.22	0.141	0.29	0.11-0.8	0.016
TMP/SMX	1.01	0.32-3.19	0.992			
Colistin	0.5	0.07-3.61	0.493			
Carbapenem	0.96	0.54-1.71	0.883			
Tigecycline	0.3	0.04-2.2	0.239			
Combination therapy	0.59	0.39-1.22	0.24			

Legend. HR: hazard ratio; CI: confidence interval; BSI: bloodstream infection; SSTI: skin and soft tissue infection; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; AIDS: acquired immune deficiency syndrome; NIV: non-invasive mechanical ventilation; MV: mechanical ventilation.

Moreover, severe infections could have an unfavorable outcome despite the administration of adequate antimicrobial treatment, due to the inability to raise plasma drug concentrations above the target minimum inhibitory concentration (MIC). This latter finding may be the cause of underexposure at the infection site, particularly in critically ill patients, as septic patients usually require rapid and aggressive fluid resuscitation therapy, with a subsequent increase in the extracellular fluid volume that could raise the volume of distribution of drugs [28]. Differences in rates of mortality could be related to the source of bacteremia. Several studies demonstrated a relationship between source of infection and clinical response [29], with bacteremia secondary to urinary tract infection usually associated with the lowest mortality rate [30]. In our population, as reported in the literature [29], the abdominal source of infection was an independent determinant of unfavorable outcome.

An important finding of this analysis was the impact of empirical and definitive antibiotic regimens on 30-day outcome, particularly for patients treated with carbapenem or BLBLI. The spread of carbapenemase-producing Enterobacteriaceae promoted several studies about alternative therapies such as BLBLI. BLBLI has been evaluated for the treatment of these infections [18,31], but no definitive data were reported about the efficacy of BLBLI in the treatment of severe infections compared with carbapenems [14,32]. The use of carbapenems should be optimized, with a role as empirical therapy only for patients who have high risk factors for colonization/infection, based also on geographical patterns of resistance for ESBL strains not susceptible to BLBLI, and on patients who are affected by non-urinary source of bacteremia [33]. In the remaining subjects, in whom clinical conditions or risk factors may not require immediate ESBL antimicrobial coverage, a guided therapy once culture results are obtained may be sufficient [34]. For these reasons, data from international trials should assess 30-day mortality associated with the use of BLBLI or carbapenems in the setting of ESBL infections [35]. Interestingly, our analysis showed quinolones were protective as definitive therapy. When active in vitro, quinolones were a reasonable choice in less critically-ill patients with urinary source of infection. The interpretation of these data is limited by the retrospective design of the study and only randomized trials could address a possible role of quinolones. However, their use should be carefully evaluated considering the high rates of resistance reported, particularly in areas with increased consumption of these antibiotics [36,37].

The retrospective nature of the study is a limitation and all the considerations about the impact of empirical or targeted regimens on survival should be taken with caution. Nevertheless, our series of septic shock associated with ESBL-E bacteremia is the largest ever reported in literature. Another study limitation is the

lack of information of other variables that may influence the outcome, such as source control, circulatory management and pharmacokinetic/pharmacodynamic (PK/PD) variables. Finally, no data were recorded on long-term survival over 30 days; thus, we cannot provide more consistent information on the risk of recurrence of infection and emergence of resistant strains to the antibiotic regimen used. However, in the database very strict criteria were applied for the cataloguing of antibiotic regimens, and an important strength of this study is the multicenter, international participation in the INCREMENT project.

5. Conclusions

In conclusion, these data highlight the high 30-day mortality associated with BSI due to ESBL-E in patients who developed severe sepsis or septic shock. The results also show the importance of some clinical characteristics, such as source of infection and indicators of severity, as determinants of patient outcome in this setting. These data confirm there are no differences in empirical and definitive antibiotic therapy of BSI, particularly for BLBLI and carbapenems, in these critically ill patients. However, randomized clinical trials are needed to confirm these observations.

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Competing Interests

None to declare.

Ethical Approval

The INCREMENT project was approved by the Spanish Agency of Medicines (AEMPS; code JRB-ANT-2012-01) and the Hospital Universitario Virgen Macarena Institutional Review Board (code 1921).

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