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ORIGINAL RESEARCH

Mortality and Risk Factors of Death in Patients with AmpC β-Lactamase Producing *Enterobacterales* Bloodstream Infection: A *Cohort Study*

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Aim: ESCPM bacteria include *Enterobacter* spp, *Serratia, Citrobacter* spp, *Providencia* spp, and *Morganella* spp. These Gram-negative bacilli harbor chromosomally encoded AmpC-type β-lactamases that cause resistance to β-lactam antibiotics, such as penicillins, β-lactam/β-lactamase inhibitors, and first-, second-, and third-generation cephalosporins. Bloodstream infections caused by ESCPM group bacteria (BSI-ESCPM) are difficult to treat.

Purpose: To describe 30-day mortality and analyze potential risk factors for death in patients with BSI-ESCPM.

Patients and Methods: A cohort study of patients aged ≥ 18 years with BSI-ESCPM was conducted at a University Hospital in Brazil, from January 2013 and December 2018. Potential risk factors for death within 30 days of bloodstream infection BSI diagnosis were analyzed using multivariable logistic regression.

Results: Among 138 patients with BSI-ESCPM, 63.0% were males, with a median age of 61 years. Of 155 BSI-ESCPM episodes, 61.3% were hospital-acquired. Primary BSI-ESCPM associated with short-term central venous catheter (37.4%) and BSI-ESCPM secondary to respiratory infection (19.4%) occurred mainly. Mostly, *Enterobacte*r spp. (49.7%) and *Serratia* spp. (29.0%) were isolated. Multidrug-resistance occurred in 27.7% of BSI-ESCPM episodes, involving *Enterobacter* spp. (16.1%) and *Serratia* spp. (7.7%) mainly. The mortality was 24.5%. Developing septic shock within 72 h of BSI-ESCPM diagnosis (OR: 70.26; 95% CI: 16.69–295.77; *P*<0.01) was risk factor for death. Conversely, combined antibiotic therapy (OR: 0.23; 95% CI: 0.05–0.94; *P*:0.04), BSI-ESCPM secondary to urinary infection (OR: 0.11; 95% CI: 0.01–0.99; *P*:0.05), and *Enterobacter* spp. BSI (OR: 0.16; 95% CI: 0.05–0.56; *P*0<0.01) was protective factor against death. Tendency of association between inadequate antibiotic therapy and death (OR: 2.19; 95% CI: 0.51–9.42; *P*:0.29) was observed.

Conclusion: BSI-ESCPM is severe and has serious outcomes such as sepsis-associated deaths. Combined antibiotic therapy was a protective factor against death in patients with BSI-ESCPM. There is a suggestive association between inadequate antibiotic therapy and mortality. The ESCPM group bacteria that are considered to be at moderate to high risk of clinically significant AmpC production were not associated with death.

Keywords: bloodstream infection, *Enterobacterales*, AmpC β-lactamase, mortality, risk factors of death

Introduction

Bloodstream infections (BSI) are a growing public health concern, with *Enterobacterales* among the most common agents of community-acquired and healthcare-associated BSI.[1–3] Infections caused by multidrug-resistant (MDR) microorganisms are a growing threat to human health.[4] *Enterobacterales* are opportunistic pathogens that are usually part of the human intestinal microbiota.[5] They are often resistant to β-lactam antibiotics because of the production of

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AmpC β-lactamases encoded by chromosomal genes (*Citrobacter* spp., *Enterobacter* spp., *Serratia* spp., *Providencia* spp., and *Morganella* spp.–ESCPM group bacteria) and are frequent causes of BSI (BSI-ESCPM).[4,6]

The production of AmpC β-lactamases by the ESCPM group bacteria is as follows: (i) inducibly expressed following exposure to β-lactam antibiotics, and (ii) constitutively expressed after spontaneous mutations with consequent hyperproduction of AmpC β-lactamases. The production of inducible AmpC causes resistance to penicillins, β-lactamase inhibitor-β-lactam combinations, oxyimino-beta-cephalosporins (1st-, 2nd-, and 3rd-generation cephalosporins), cephamycin, and aztreonam.[7–9] AmpC β-lactamases show little hydrolytic activity against cefepime, cefpirome, and carbapenems. Therefore, susceptibility to these antibiotics is usually unaffected. However, the hyperproduction of AmpC in mutants triggers additional resistance to cefepime and cefpirome. Both mechanisms of AmpC production can occur during the treatment of BSI-ESCPM. Consequently, strains that are initially susceptible to these β-lactam antibiotics may develop resistance. *Enterobacter cloacae, Klebsiella aerogenes* (formerly *Enterobacter aerogenes*)[10] and *Citrobacter freundii* are considered as moderate to high risk of clinically significant AmpC production through induction and mutations.[11,12] Consequently, severe infections caused by β-lactams resistant ESCPM group bacteria are difficult to treat and usually associated with high mortality.[13,14] There is no conclusive evidence about the optimal treatment of BSI-ESCPM.[15,16] In this cohort, mortality, and possible causes of death in patients with BSI ESCPM group bacteria are studied.

Material and Methods

Study Design

A prospective cohort study of patients aged ≥ 18 years with BSI-ESCPM, hospitalized at a University Hospital (UH) in Niterói, Brazil, was conducted from January 1, 2013, to December 31, 2018. All BSI-ESCPM episodes detected in each patient were included in the analysis. Death within 30 days of BSI diagnosis, defined as the date of the 1st positive blood culture, was the primary outcome. The epidemiological, clinical, and microbiological characteristics of the study population were analyzed as potential determinants of death. This study was approved by the Board of Ethics in Research of the Federal Fluminense University (BER-FFU) (number 32570). The BER-FFU waived the requirement for informed consent for this study because it was observational, data were analyzed anonymously, and kept confidential. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Setting

This study was conducted in a 287-bed public teaching hospital comprising 13 inpatient units (surgical and clinical wards, intensive care unit, and coronary unit), an emergency room, and an outpatient hemodialysis clinic.

The Detection of the BSI-ESCPM Episodes and Data Collection

Cases were identified through daily laboratory-based surveillance of positive blood culture results issued by the UH Microbiological Laboratory. Once a positive blood culture was detected, BSI was confirmed by patient examination or medical record review. Patients were excluded from the study: 1) if they were dead at the time a positive blood culture result was obtained; 2) and their medical record was not available for review. Each included patient was followed up for 30 days after the BSI-ESCPM diagnosis. The following data were collected by reviewing the medical records: i) Demographics - sex, date of birth, patient origin (community, ambulatory care clinics, UH hemodialysis unit, and transfers from other hospitals), ward of admission, clinical or surgical admission, and date of admission. ii) Clinical - type of admission (emergency and elective), cause of admission, main underlying illness, Charlson comorbidity index,[17] presence of an invasive device up to 48 h before BSI diagnosis, use of antibiotics and surgical procedure within 30 days before BSI diagnosis, clinical outcome within 72 h (sepsis or septic shock), and 30 days (remaining hospitalized, discharge, or death) after BSI diagnosis and date. iii) Characteristics of the BSI episode included: date of positive blood culture, the microorganism(s) detected and its antibiotic susceptibility, type of BSI acquisition (hospital-acquired, healthcare-associated infection, and

community-acquired); source of BSI episode that was classified as i) primary associated with vascular access, mucosal barrier damage, infective endocarditis, and undefined source; and ii) secondary to extravascular site of infection, urinary tract, respiratory tract, gastrointestinal and intra-abdominal tract, skin and soft tissues, and the central nervous system. Pitt bacteremia severity score from the day of BSI onset to 48 h before (upper value was used in the analysis and a value ≥4 was used to define severe BSI),[18–20] C-reactive protein (CRP; mg/dl) serum level from 1 d before to 1 d after BSI onset (the highest value was used in the analysis), and presence of neutropenia (absolute number of neutrophils $<0.5 \times 10^9$/L)[21] from 1 d before to 3 days after BSI onset; and iv) Treatment of the BSI episode included antimicrobial(s) initiated with the date of beginning and ending, if it was empirically initiated or guided by microbiological results), and other approaches such as removal of invasive devices and drainage of abscess.

Definitions

The community-acquired BSI was defined as either an infection detected or incubated at the time of patient admission to the hospital that was not associated with health care. The healthcare-associated BSI were detected in outpatients receiving healthcare. The hospital-acquired BSI was defined as an infection that occurred on or after the 3rd day of hospitalization.[22] The definitions of primary BSI/laboratory-confirmed BSI, central line-associated BSI, BSI associated with mucosal barrier injury and secondary BSI were in accordance with The Centers for Disease Control and Prevention (CDC) definitions.[23]

The multidrug resistant ESCPM pathogens were considered according to the following criteria: non-susceptibility to at least one agent in three or more antimicrobial categories, except for those with intrinsic resistance.[24] Resistance to 1st, 2nd, and 3rd-generation cephalosporin, amoxicillin-clavulanate, and piperacillin-tazobactam was considered intrinsic owing to AmpC-chromosomal production by the ESCPM group.[9]

Appropriate antimicrobial therapy was defined as: (i) at least one antibiotic used in the therapy must have action against the microorganisms(s) isolated from blood, (ii) the antimicrobial must be initiated within 24 h after blood culture is obtained, and (iii) the antimicrobial must be used for at least 72 h.[14] Monotherapy is defined as the use of antibiotics during the treatment period. Otherwise, polytherapy was defined as combined therapy when two or more antibiotics were started within a maximum interval of 24 h and maintained concurrently for 72 h or more, and sequential therapy for the use of two or more antibiotics during the treatment period.

The Pitt bacteremia score is a previously validated scoring system to evaluate the severity of acute illness based on mental status, vital signs, requirement for mechanical ventilation, and recent cardiac arrest, at the day of the positive blood culture and 48 h before. The highest point score during that time is recorded. It ranges from 0 to 14 points [mental status (disoriented: 1; stupor: 2; coma: 4 points); fever (> 37.6°C and < 40°C: 1; > 40°C: 2 points); hypotension (drop in systolic > 20 mm Hg or diastolic > 10 mm Hg or on intravenous pressor agents: 2 points); mechanical ventilation: 2 points; and cardiac arrest: 4 points]. Patients accumulating 4 or more points (Score ≥ 4) is defined as critical illness and have increased risk of death.[18–20]

Microbiological Analysis

BSI episodes were investigated by obtaining at least one blood sample (20 mL) from two different venipuncture sites in each patient using an aseptic technique, as recommended by the Infection Control Division of UH. Each blood sample was inoculated into one aerobic or anaerobic blood culture bottle (10 mL each). Microorganism growth was detected using BacT/ALERT® (BioMérieux). Both microbiological identification and antibiotic susceptibility tests were performed using the Vitek® 2 automated system (BioMérieux). The antimicrobial susceptibility test results were interpreted according to The Clinical and Laboratory Standards Institute, applying the updated versions for the year in which the blood culture was performed.[25,26] Resistance to cefoxitin is considered a phenotypic marker of the presence of chromosomal AmpC.[9]

Statistical Analysis

Descriptive analyses of categorical and continuous variables were presented as proportions and median values, respectively. The $\chi 2$ or Fisher's exact test was used to compare categorical variables, and Student's *t*-test or Mann–Whitney test was used to compare continuous variables, as appropriate.

Death within 30 days of BSI-ESCPM diagnosis was the primary outcome of interest. Mortality was calculated by dividing the number of deaths within 30 days after BSI-ESCPM diagnosis by the total number of BSI-ESCPM cases in the same period. The demographics, clinical and microbiological characteristics of the patients, and BSI episodes were analyzed as potential risk factors for death within 30 days. Inadequate antimicrobial therapy was hypothesized to be the main factor independently associated with death within 30 days. Variables were included in the multivariable logistic regression models if they met the criteria for statistical significance ($P < 0.05$) in the univariate analyses. Additional clinically relevant variables, based on biological plausibility and prior knowledge, were included as a priori variables in the adjusted models. A backward selection approach was applied, using the 10% rule, to identify potential confounders in the final adjusted model. Analyses were performed using the Epi info 7.2.5.0 software (https://epi-info.software.informer.com/7.2/).

Results

Study Population and BSI-ESCPM Episodes

From January 2013 to December 2018, 1394 BSI episodes were detected in the UH. Of these, 11.1% (n: 155) were caused by *Enterobacterales* from the ESCPM group. These 155 BSI-ESCPM episodes occurred in 138 patients during 146 hospitalizations. Among 138 patients, 11% had two or more BSI-ESCPM episodes. Of 155 episodes of BSI-ESCPM, 18% were polymicrobial with two or more microorganisms identified, adding up 184 microorganisms. All the detected BSI-ESCPM episodes were included in the analysis, as shown in Figure 1.

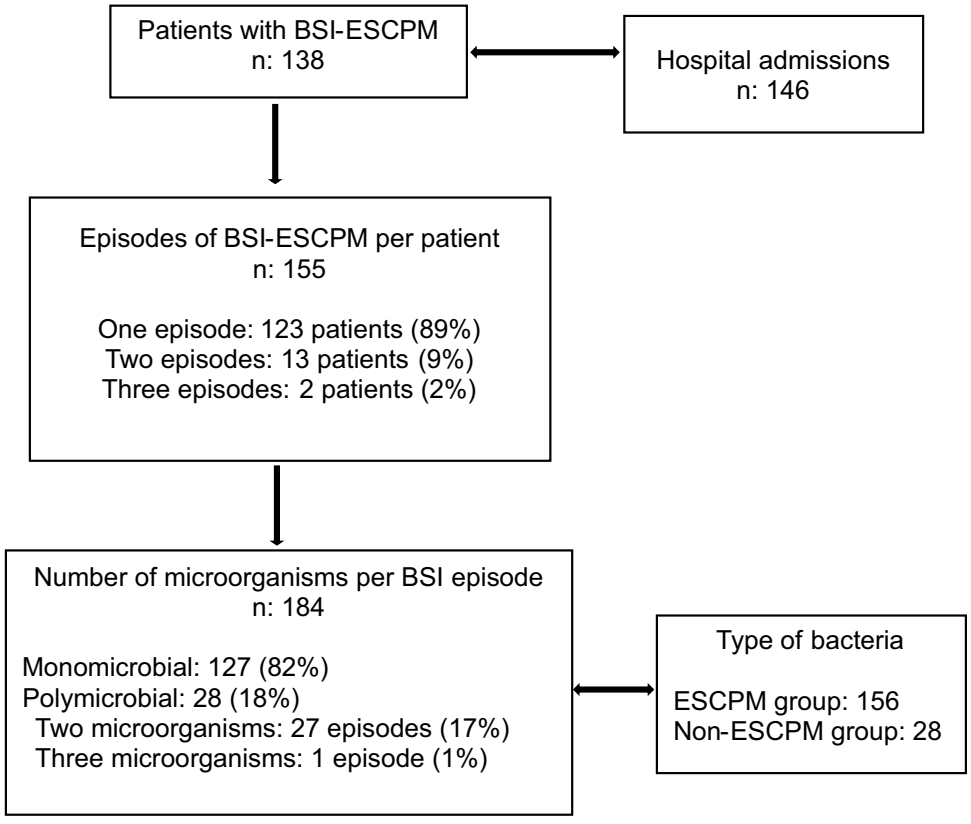

Figure 1 Population and episodes of bloodstream infection due to the ESCPM bacteria group detected at a University Hospital from January 1st, 2013, to December 31st, 2018.
Abbreviations: BSI, bloodstream infection; ESCPM, *Enterobacter* spp. *Serratia* spp. *Citrobacter* spp. *Providencia* spp. *Morganella* spp.

Clinical and Demographic Characteristics of the Study Population

Among the 138 patients, 63.0% (n: 87) were male. The median age of the patients was 60 years (range: 18–85) years. Charlson comorbidity index > 5 was observed in 21.0% (n: 29) of patients, and the most frequently detected underlying disease was kidney disease in 27.5% (n: 38) of patients. These patients had 146 admissions; 80.1% (n: 117) due to a medical emergency. They occurred in the emergency room mostly, 65.8% (n: 96). Infectious diseases (30.1%; n: 44), mainly skin, soft tissue, and osteoarticular infections (10.3%; n: 15), followed by cardiovascular diseases (14.4%; n: 21), were the main reasons for admission.

Clinical Characteristics of the BSI-ESCPM Episodes

The 155 BSI-ESCPM episodes were hospital-acquired (HAI) and occurred mainly in the intensive care unit. Over a third of the episodes involved invasive procedures and antibiotic use, 48 h and within 30 days before BSI diagnosis, respectively. BSI-ESCPM episodes were associated with short-term central venous catheter (37.4%) mainly, followed by those secondary to respiratory infections (19.4%), as details Table 1.

Table 1 Univariate Analysis of Epidemiological and Clinical Characteristics as Risk Factors for 30-Day Death in Bloodstream Infection Due to ESCPM Bacteria Group (*Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., *Morganella* spp.)

Variable, n (%)*	Total n: 155	30-day death n: 38	Survivors n: 117	OR	95% CI	*P* value
Gender, male	97 (62.6)	26 (68.4)	71 (60.7)	1.40	0.64–3.06	0.44
Age in years, median (range)	60 (18–85)	61 (32–85)	60 (18–85)	1.02	1.00–1.05	0.26
Charlson comorbidity index, median (range)	3 (0–14)	4 (0–11)	3 (0–14)	1.04	0.91–1.18	0.56
2–5	102 (65.8)	27 (71.1)	75 (64.1)	1.37	0.62–3.05	0.56
6–14	34 (21.9)	9 (23.7)	25 (21.4)	1.14	0.48–2.72	0.82
Baseline disease (Charlson)						
Moderate/severe renal disease	45 (29.0)	11 (29.0)	34 (29.1)	0.99	0.44–2.23	0.99
Tumor/neoplasm	33 (21.3)	10 (26.3)	23 (19.7)	1.46	0.62–3.43	0.37
Metastatic solid tumor	15 (9.7)	4 (10.5)	11 (9.4)	1.13	0.34–3.79	0.76
Diabetes with organ damage	10 (6.5)	3 (7.9)	7 (6.0)	1.35	0.33–5.49	0.71
Moderate/severe liver disease	9 (5.8)	2 (5.3)	7 (6.0)	0.87	0.17–4.39	0.99
Lymphoma	7 (4.5)	3 (7.9)	4 (3.4)	2.42	0.52–11.34	0.36
Without comorbidity	10 (6.5)	1 (2.6)	9 (7.7)	0.32	0.04–2.65	0.45
Other[a]	26 (16.8)	4 (10.5)	22 (18.8)	0.51	0.16–1.58	0.32
Consecutive BSI-ESCPM episodes in the same patient	17 (11.0)	3 (7.9)	14 (12.0)	0.63	0.17–2.32	0.77
Origin of patient						
Community	124 (80.0)	27 (71.1)	97 (82.9)	0.51	0.22–1.18	0.16
Outpatient clinic and hemodialysis clinic at HUAP	19 (12.3)	9 (23.7)	10 (8.5)	3.32	1.23–8.93	0.02
Another hospital	12 (7.7)	2 (5.3)	10 (8.5)	0.59	0.12–2.84	0.73
Type of admission						
Emergency	124 (80.0)	30 (79.0)	94 (80.3)	0.92	0.37–2.26	0.82
Admission in clinical specialty	139 (89.7)	36 (94.7)	103 (88.0)	2.45	0.53–11.29	0.36
Place of admission						
Emergency room	98 (63.2)	25 (65.8)	73 (62.4)	1.16	0.54–2.50	0.85
Internal medicine	37 (23.9)	6 (15.8)	31 (26.5)	0.52	0.20–1.36	0.20
Surgical ward	11 (7.1)	4 (10.5)	7 (6.0)	1.85	0.51–6.70	0.47
Coronary Unit	6 (3.9)	2 (5.3)	4 (3.4)	1.57	0.28–8.93	0.64
Other[b]	3 (1.9)	1 (2.6)	2 (1.7)	1.55	0.14–17.63	0.57

(*Continued*)

Table 1 (Continued).

Variable, n (%)*	Total n: 155	30-day death n: 38	Survivors n: 117	OR	95% CI	*P* value
Cause of admission						
Infectious disease	44 (28.4)	12 (31.6)	32 (27.4)	1.23	0.55–2.72	0.68
Skin, soft tissues and osteoarticular	15 (9.7)	5 (13.2)	10 (8.5)	1.62	0.52–5.08	0.53
Urinary	9 (5.8)	0 (0.0)	9 (7.7)	0.00	Undefined	0.11
Respiratory	9 (5.8)	5 (13.2)	4 (3.4)	4.28	1.09–16.86	0.04
Others[c]	11 (7.1)	2 (5.3)	9 (7.7)	0.67	0.14–3.23	0.99
Non-infectious causes						
Cardiovascular	22 (14.2)	3 (7.9)	19 (16.2)	0.44	1.12–1.59	0.29
Neurological	17 (11.0)	3 (7.9)	14 (12.0)	0.63	0.17–2.32	0.77
Renal	16 (10.3)	3 (7.9)	13 (11.1)	0.69	0.18–2.55	0.76
Neoplastic	14 (9.0)	3 (7.9)	11 (9.4)	0.83	0.22–3.13	0.99
Hematological	10 (6.5)	4 (10.5)	6 (5.1)	2.18	0.58–8.17	0.26
Gastrointestinal	9 (5.8)	2 (5.3)	7 (6.0)	0.87	0.17–4.39	0.99
Respiratory	9 (5.8)	3 (7.9)	6 (5.1)	1.59	0.38–6.67	0.69
Orthopedic	6 (3.9)	3 (7.9)	3 (2.6)	3.26	0.63–16.87	0.16
Other[d]	8 (5.2)	2 (5.3)	6 (5.1)	1.03	0.20–5.32	0.99
Type of BSI-ESCPM acquisition						
Hospital-acquired	95 (61.3)	22 (57.9)	73 (62.4)	0.83	0.39–1.75	0.70
Intensive care unit	53 (34.2)	16 (42.1)	3 (31.6)	1.57	0.74–3.34	0.24
Clinical ward	35 (22.6)	5 (13.2)	30 (25.6)	0.44	0.16–1.23	0.12
Surgical ward	7 (4.5)	1 (2.6)	6 (5.1)	0.50	0.06–4.29	0.99
Healthcare-associated infection at the HUAP	19 (12.3)	2 (5.3)	17 (14.6)	0.33	007–1.49	0.16
Healthcare-associated infection outside HUAP	2 (1.3)	0 (0.00)	2 (1.7)	0.00	Undefined	0.00
Community-acquired	39 (25.2)	14 (36.8)	25 (21.4)	2.15	0.97–4.75	0.08
Length of hospital-acquired BSI-ESCPM in days, median (range)	25 (6–311)	38 (6–311)	22 (7–306)	1.01	0.99–1.01	0.23
Invasive devices 48 h before BSI-ESCPM diagnosis	56 (36.1)	11 (29.0)	45 (38.5)	0.65	0.29–1.44	0.33
Surgical procedure 30 days before BSI-ESCPM diagnosis	12 (7.7)	1 (2.6)	11 (9.4)	0.26	0.03–2.09	0.30
Antibiotics use 30 days before BSI-ESCPM diagnosis	92 (59.4)	26 (68.4)	66 (56.4)	1.67	0.77–3.64	0.25
Colonization by multi-resistant microorganism	11 (7.1)	2 (5.3)	9 (7.7)	0.67	0.14–3.23	0.99
Source of secondary BSI-ESCPM	91 (58.7)	24 (63.2)	67 (57.3)	1.28	0.60–2.72	0.57
Respiratory tract infection	30 (19.4)	12 (31.6)	18 (15.4)	2.54	1.09–5.93	0.03
Urinary tract infection	25 (16.1)	2 (5.3)	23 (19.7)	0.23	0.05–1.01	0.04
Gastrointestinal/abdominal infection	17 (11.0)	5 (13.2)	12 (10.3)	1.33	0.44–4.04	0.57
Skin and soft tissue infection	12 (7.7)	3 (7.9)	9 (7.7)	1.03	0.26–4.01	0.99
Other[e]	7 (4.5)	2 (5.3)	5 (4.3)	1.24	0.23–6.69	0.68
Source of Primary BSI-ESCPM	64 (41.3)	14 (36.8)	50 (42.7)	0.78	0.37–1.66	0.57
Associated with central venous catheter	58 (37.4)	12 (31.6)	46 (39.3)	0.71	0.33–1.55	0.44
Short-term catheter	38 (24.5)	9 (23.7)	29 (24.8)	0.94	0.40–2.22	0.99
Long-term catheter	20 (12.9)	3 (7.9)	17 (14.5)	0.50	0.14–1.83	0.41
Mucosal barrier injury	4 (2.6)	1 (2.6)	3 (2.6)	1.03	0.10–10.18	0.99
Undefined	2 (1.3)	1 (2.6)	1 (0.9)	3.14	0.19–51.37	0.43
Polymicrobial BSI-ESCPM[f]	28 (18.1)	11 (28.9)	17 (14.5)	2.40	1.00–5.72	0.05

Notes: *Except where otherwise noted next to the variable; [a](n≤ 5): rheumatologic disease (n: 5); leukemia (n: 4); diabetes (n: 3); cerebrovascular disease (n: 3); congestive heart failure (n: 3); chronic pulmonary disease (n: 2); peripheral vascular disease (n: 1); hemiplegia (n: 1); prior myocardial infarction (n: 1); acquired immuno-deficiency syndrome (n: 1); gastric ulcer (n: 2); [b](n≤ 5) dialysis room (n:1), intensive care center (n: 2); [c](n≤ 5): primary bloodstream infection from dialysis catheter (n: 5); abdominal infection (n: 3); tracheostomy cannula infection (n:1); bacterial meningitis (n: 1); feverish syndrome to clarify (n: 1) [d](n≤ 5): urological (n: 4); dermatological (n: 2); endocrinological (n:1); gynecological (n: 1); [e](n≤ 5): central nervous system (n: 4); osteoarticular (n: 3); [f] A polymicrobial infection (*Serratia marcescens* and *Providencia* spp).
Abbreviations: BSI-ESCPM, Bloodstream infection caused by ESCPM bacteria; HUAP, Antônio Pedro University Hospital.

Microbiological Profile of the BSI-ESCPM Episodes

Enterobacter spp. and *Serratia* spp. were the most frequent agents detected, 49% and 29%, respectively. Resistance to cefepime, or cefepime and meropenem was observed in 18.7% and 8.4% of the isolates, respectively. Most MDR *Enterobacter* spp. and *Serratia* spp. were detected (Table 2).

Treatment and Outcome

The initial antibiotic therapy was classified as inadequate in 16.1% of the cases. Therapy was empirically initiated in 78.1% of the episodes. Mostly, combined therapy included meropenem, comprising 14.2% of the BSI-ESCPM episodes. Septic shock within 72 h after BSI-ESCPM diagnosis and Pitt score ≥ 4 were observed in 18.1% and 32.9% of the BSI episodes, respectively, as shown Table 3.

Mortality and Risk Factors of Death

The overall mortality up to 30 days after BSI-ESCPM diagnosis was 24.5% (n: 38) and ranged from 11.8% to 28.0% during the study period (2013–2018). The median time to death was 7.5 (range: 0–29) days. The temporal distribution of the mortality is shown in Figure 2.

The following variables were included in the initial multivariable logistic regression model: i) inadequate empirical antibiotic therapy (primary analysis); ii) BSI secondary to respiratory infection, BSI secondary to urinary infection, BSI caused by *Enterobacter* spp., and septic shock within 72 h after BSI-ESCPM ($P \leq 0.05$) in the univariate analyses); iii) polymicrobial BSI-ESCPM; combined antibiotic therapy, Charlson comorbidity index, and ESCPM group bacteria

Table 2 Univariate Analysis of Microbiological Characteristics as Risk Factors of 30-Day Death in Bloodstream Infection Due to ESCPM Bacteria Group (*Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., *Morganella* spp.)

Variable, n (%)*	Total n: 155	30-day death n: 38	Survivors n: 117	OR	95% CI	*P* value
ESCPM group bacteria (n: 156)[a]						
Enterobacter spp.[b]	77 (49.7)	11 (28.9)	66 (56.4)	0.31	0.14–0.69	0.00
Serratia spp.[c]	45 (29.0)	12 (31.6)	33 (28.2)	1.17	0.53–2.60	0.69
Morganella morganii	12 (7.7)	5 (13.2)	7 (6.0)	2.38	0.71–8.00	0.17
Providencia spp.[d]	12 (7.7)	6 (15.4)	6 (5.2)	3.33	1.01–11.03	0.08
Citrobacter spp.[e]	10 (6.5)	5 (13.2)	5 (4.3)	3.39	0.93–12.44	0.07
ESCPM with moderate to high risk of producing AmpC[f]	87 (56.1)	16 (42.1)	71 (70.7)	0.47	0.22–0.99	0.06
Microorganism different from the ESCPM group in polymicrobial infections	28 (18.1)	10 (26.3)	18 (15.4)	1.96	0.82–4.73	0.15
Enterobacterales[g]	14 (9.0)	5 (13.1)	9 (7.7)	1.82	0.57–5.80	0.33
Gram-positive cocci[h]	8 (5.2)	2 (5.3)	6 (5.1)	1.03	0.20–5.32	0.99
Non-fermenting Gram-negative bacilli[i]	6 (3.9)	3 (7.9)	3 (2.6)	3.26	0.63–16.87	0.16
Multi-resistant ESCPM Group bacteria	43 (27.7)	10 (26.3)	33 (28.2)	0.90	0.40–2.08	0.99
Resistant to cefepime and susceptible to meropenem	29 (18.7)	4 (10.5)	25 (21.4)	0.43	0.14–1.34	0.16
Enterobacter spp.	18 (11.6)	2 (5.3)	16 (13.7)	0.35	0.08–1.60	0.24
Serratia spp.	8 (5.2)	2 (5.3)	6 (5.1)	1.03	0.20–5.32	0.99
Others[j]	3 (1.9)	0 (0.0)	3 (2.6)	0,00	Undefined	0.99
Resistant to cefepime and meropenem	13 (8.4)	5 (13.2)	8 (6.8)	2.06	0.63–6.74	0.38
Enterobacter spp.	7 (4.5)	3 (7.9)	4 (3.4)	2.42	0.52–11.34	0.48
Serratia spp.	4 (2.6)	0 (0.0)	4 (3.4)	0.00	Undefined	0.57
Providencia spp.	2 (1.3)	2 (5.3)	0 (0.0)	0.00	Undefined	0.06

Notes: *Except where otherwise noted next to the variable; [a]One infection was polymicrobial caused by *Serratia marcescens* and *Providencia* spp.; [b]*Enterobacter cloacae* (n: 55); *Klebsiella aerogenes* (formerly *E. aerogenes*; n: 20); *Enterobacter asburiae* (n: 2); [c]*Serratia marcescens* (n: 41); *Serratia liquefaciens* (n: 2); *Serratia fonticola* (n: 1); *Serratia rubidaea and Serratia marcescens* (n: 1); [d]*Providencia stuartii* (n: 6); *Providencia rettgeri* (n: 4); *Providencia rustigianii* (n: 1); *Providencia* spp. (n: 1); [e]*Citrobacter freundii* (n: 5); *Citrobacter koseri* (n: 4); *Citrobacter* spp. (n: 1); [f]*Enterobacter* spp. and *Citrobacter* spp. are described as having a moderate to high risk of inducing AmpC production, with a high risk for resistance to broad-spectrum cephalosporins; [g]*Klebsiella pneumoniae* (n: 8); *Escherichia coli* (n: 2); *Proteus mirabilis* (n: 2); *Proteus vulgaris* (n: 1); *Klebsiella oxytoca* (n: 1); [h]*Staphylococcus aureus* (n: 4); *Staphylococcus epidermides* (n: 2); *Staphylococcus warneri* (n: 1); *Enterococcus faecalis* (n: 1); [i]*Pseudomonas aeruginosa* (n: 5); *Pantoea agglomerans* (n: 1); [j]*Providencia* spp. (n: 2); *Morganella morganii* (n: 1).

Table 3 Univariate Analysis of Severity of Infection and Type of Antibiotic Treatment as Risk Factor for 30-Day Death in Bloodstream Infection Due to ESCPM Bacteria Group (*Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., *Morganella* spp.)

Variable, n (%)*	Total n: 155	30-day death n: 38	Survivors n: 117	OR	95% CI	*P* value
Antibiotic therapy	133 (85.8)	33 (86.8)	100 (85.5)	1.12	0.38–3.28	0.99
Empirical antibiotic therapy[a]	121 (78.1)	30 (79.0)	91 (77.8)	1.07	0.44–2.62	0.99
Inadequate[b]	27 (17.4)	11 (28.9)	16 (13.7)	2.57	1.07–6.18	0.05
Antibiotic therapy in the first 24 h of BSI-ESCPM diagnosis	105 (67.7)	28 (73.7)	77 (65.8)	1.45	0.64–3.29	0.43
Time to onset of antibiotics, in days, median (range)	0 (0–7)	1 (0–7)	0 (0–6)	1.02	0.78–1.34	0.89
Monotherapy	44 (28.4)	11 (29.0)	33 (28.2)	1.04	0.46–2.33	0.99
Meropenem	21 (13.5)	5 (13.2)	16 (13.7)	0.96	0.33–2.81	0.99
Piperacillin-tazobactam	10 (6.5)	3 (7.9)	7 (6.0)	1.35	0.33–5.49	0.71
Cefepime	7 (4.5)	1 (2.6)	6 (5.1)	0.50	0.06–4.29	0.99
Other[c]	6 (3.9)	2 (5.3)	4 (3.4)	1.57	0.28–8.93	0.64
Polytherapy	89 (57.4)	22 (57.9)	67 (57.2)	1.03	0.49–2.15	0.99
Sequential therapy[d]	49 (31.6)	16 (42.1)	33 (28.2)	1.85	0.87–3.96	0.11
Cefepime and vancomycin	5 (3.2)	3 (7.9)	2 (1.7)	4.93	0.79–30.69	0.09
Meropenem and polymyxin	5 (3.2)	2 (5.3)	3 (2.6)	2.11	0.34–13.14	0.60
Other[e]	39 (25.2)	11 (29.0)	28 (24.0)	1.30	0.57–2.94	0.53
Combined therapy[f]	40 (25.8)	6 (15.8)	34 (29.1)	0.46	0.18–1.19	0.14
Meropenem with vancomycin	12 (7.7)	3 (7.9)	9 (7.7)	1.03	0.26–4.01	0.99
Meropenem with polymyxin	7 (4.5)	0 (0.0)	7 (6.0)	0.00	Undefined	0.19
Other[g]	21 (13.6)	3 (7.9)	18 (15.4)	0.47	0.13–1.70	0.29
Other therapeutic approaches	50 (32.3)	8 (21.1)	42 (35.9)	0.48	0.20–1.13	0.11
Removal of vascular catheter	47 (30.3)	8 (21.1)	39 (33.3)	0.53	0.22–1.27	0.22
Time to catheter removal after BSI diagnosis, in days, median (range)	0 (−3-15)	0 (0–5)	0 (−3-15)	0.92	0.70–1.23	0.59
Evolution in the 72 h from the date of BSI-ESCPM						
Without sepsis	97 (62.6)	4 (10.5)	93 (79.5)	0.03	0.01–0.09	0.00
With sepsis	30 (19.4)	10 (26.3)	20 (17.1)	1.73	0.73–4.13	0.24
Septic shock	28 (18.1)	24 (63.2)	4 (3.4)	48.42	4.65–160.04	0.00
Pitt score	51 (32.9)	19 (50.0)	32 (27.4)	2.66	1.25–5.65	0.02
CRP, mg/L, median (range)	12.4 (0.4–49.8)	15.9 (2.4–49.8)	11.6 (0.4–41.3)	1.04	1.00–1.08	0.05

Notes: *Except where otherwise noted next to the variable; [a]Initiation of antibiotic before blood culture result; [b]Antibiotics administered after the blood culture date or at least for 72 h and with antibiotics to which the bacteria were resistant; [c]Antibiotics used in 1 episode: amoxicillin/clavulanate (n: 1); ceftriaxone (n: 1); cefuroxime (n: 1); fluconazole (n: 1); imipenem (n: 1); oxacillin (n: 1); [d]Use of two or more antibiotics during the treatment period; [e]Sequential therapy less than 5: cefepime and meropenem (n: 4); meropenem and vancomycin (n: 4); meropenem and piperacillin/tazobactam (n: 3); amikacin and vancomycin (n: 2); cefepime and meropenem and teicoplanin (n: 2); meropenem and vancomycin and piperacillin/tazobactam (n: 2); meropenem and teicoplanin and polymyxin (n:2); amoxicillin/clavulanic acid and piperacillin/tazobactam and vancomycin (n: 1); azithromycin and clarithromycin (n: 1); azithromycin and piperacillin/tazobactam (n: 1); cefuroxime and ertapenem (n: 1); ciprofloxacin and piperacillin/tazobactam (n: 1); cefepime and clindamycin and meropenem (n:1); cefepime and ciprofloxacin (n: 1); cefepime and meropenem and vancomycin (n: 1); cefepime and piperacillin/tazobactam (n: 1); ceftriaxone and meropenem (n: 1); ciprofloxacin and meropenem and vancomycin (n: 1); clindamycin and oxacillin (n: 1); ertapenem and piperacillin/tazobactam (n: 1); imipenem and polymyxin (n: 1); imipenem and piperacillin/tazobactam (n: 1); meropenem and metronidazole (n: 1); meropenem and tigecycline (n: 1); meropenem and polymyxin and vancomycin (n: 1); meropenem and teicoplanin and polymyxin (n: 1); piperacillin/tazobactam and vancomycin (n: 1); fAntibiotics start with maximum difference of 24h and maintenance for at least 72h; [g]Combination therapy less than 5: gentamicin with vancomycin (n: 3); cefepime with metronidazole (n: 2); piperacillin/tazobactam with vancomycin (n: 2); amikacin with vancomycin (n: 1); amikacin with ertapenem (n: 1); amikacin with meropenem (n: 1); amikacin with cefazolin (n: 1); amikacin with cefuroxime (n: 1); cefepime with meropenem (n: 1); cefepime with teicoplanin (n: 1); cefepime with vancomycin (n: 1); ciprofloxacin with clindamycin (n: 1); imipenem with polymyxin (n: 1); imipenem with teicoplanin (n: 1); meropenem with teicoplanin (n: 1); piperacillin/tazobactam with linezolid (n: 1); piperacillin/tazobactam with teicoplanin (n: 1).

Abbreviations: BSI-ESCPM, Bloodstream infection caused by ESCPM bacteria; CRP, C-reactive protein.

considered at moderate to high risk of clinically significant AmpC production (including prior knowledge and biological plausibility). Tables 1–3 present details of the analysis.

The final model after backward selection included septic shock within 72 h after BSI-ESCPM diagnosis (OR: 70.26; 95% CI: 16.69–295.77), treatment with combined antibiotic therapy (OR: 0.23; 95% CI: 0.05–0.94), BSI due to *Enterobacter* spp. (OR: 0.16; 95% CI: 0.05–0.56), and BSI secondary to urinary infection (OR: 0.11; 95% CI: 0.01–0.99) remained independently associated with 30-day death. There was a tendency for association between inadequate empirical antibiotic therapy and 30-day death (OR: 2.19; 95% CI: 0.51–9.42), as shown in Table 4. The potential interactions between risk factor and protective factors were tested, however no statistically significant associations were detected.

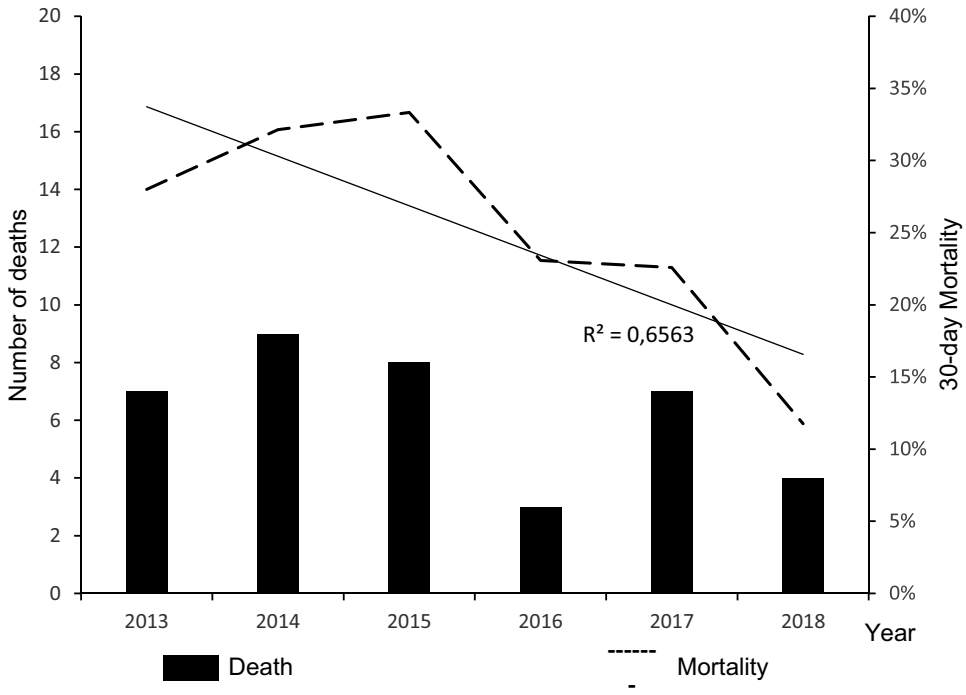

Figure 2 Frequency of deaths within 30 days of the 155 episodes of bloodstream infection caused by ESCPM bacterial group (*Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., *Morganella* spp.).

Table 4 Multivariable Analysis of Risk Factors for 30-Day Death in 155 Episodes of Bloodstream Infection Due to ESCPM Bacteria Group (*Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., *Morganella* spp.)

Variable	OR	IC 95%	*P* value
Septic shock within 72 h after BSI-ESCPM diagnosis	70.26	16.69–295.77	<0.01
Inadequate empirical antibiotic therapy	2.19	0.51–9.42	0.29
Combined antibiotic therapy	0.23	0.05–0.94	0.04
Enterobacter spp. bloodstream infection	0.16	0.05–0.56	<0.01
BSI-ESCPM secondary to urinary tract infection	0.11	0.01–0.99	0.05

Abbreviation: BSI-ESCPM, Bloodstream infection caused by ESCPM bacteria group.

Discussion

In this 6-year cohort of patients with BSI-ESCPM, 30-day mortality was relatively high (24.5%). Shock within 72 h after BSI diagnosis was independently associated with death while combined antibiotic therapy, BSI secondary to urinary infection, and *Enterobacter* spp. BSI were protective factors for death within 30 days of BSI diagnosis. There was a positive association between inadequate empirical antibiotic therapy and 30-day death, however it did not reach statistical significance.

BSI-ESCPM episodes were detected mostly in males and older patients, with a median age of 60 years and a Charlson comorbidity index of three. These findings suggest males, the elderly, and patients with comorbidities are more susceptible to BSI-ESCPM, as described in other studies.[27–29] The following characteristics of these patients can partially explain their higher susceptibility to BSI: (i) lower healthcare, hormonal, and microbiological characteristics of males compared to females could increase the susceptibility to acquiring infection and (ii) the immunosenescence of aging with the greater susceptibility of the elderly to acquire infection.[2,28–30] This may have been partly attributed to UH's characteristics since (i) most patients treated there are males; (ii) UH predominantly cares for patients with chronic diseases; and (iii) there is no emergency room for the general population.

Patients with BSI-ESCPM episodes were admitted to emergency room mainly. This finding can be explained by the greater risk of infection acquisition in patients with medical emergencies[31,32] suggesting that such patients must be closely surveyed for BSI, including BSI-ESCPM. Infectious diseases are the main cause of hospitalization, as reported by others.[28] The hospital preference for caring for patients with chronic diseases who are more susceptible to infections might explain these results.

The proportion of administered antibiotics and invasive procedures was high before the BSI-ESCPM acquisition. These characteristics are associated with an increased risk of HAI.[28,33,34] Not surprisingly, most BSI-ESCPM episodes are HAI, mainly in the ICU, where patients are usually more exposed to antibiotic use and invasive procedures. The presence of a short-term central venous catheter was the main cause of BSI-ESCPM, as described in previous studies[27,29] indicating that a large proportion of BSI-ESCPM episodes could be avoided by adhering to strict protocols to prevent vascular catheter-related infections.

Generally, empirical antibiotic therapy is initiated. A high proportion of patients received inadequate antibiotic therapy. Patients who received inadequate therapy had higher mortality than patients treated with combined therapy, including at least one adequate antimicrobial, as described by others for Gram-negative BSI in general[29,35–37] suggesting that combined antibiotic therapy can increase the proportion of adequate therapy and reduce mortality of BSI-ESCPM.

Enterobacter spp. and *Serratia* spp. were the most common agents of BSI-ESCPM, as seen in other studies.[27–29,33] A high proportion of BSI caused by bacteria resistant to cefepime alone as well as to cefepime and carbapenem was detected, involving *Enterobacter* spp. and *Serratia* spp. mainly. *Enterobacter* spp. and *Citrobacter* spp. are considered to have moderate to high risk of broad-spectrum cephalosporins resistance due to AmpC production.[11,38] However, we found a higher frequency of MDR *Serratia* spp. than MDR *Citrobacter* spp. which could be explained by the low number of BSI due to *Citrobacter* spp. detected. This also suggests *Serratia* spp. has an elevated potential to produce clinically relevant AmpC. Surprisingly, an elevated proportion of carbapenem resistance has been detected in these species. Thus, we wondered whether these species would have an increased risk of acquiring additional mechanisms of antibiotic resistance such as carbapenemase production.

The 30-day mortality rate was high, reinforcing that BSI-ESCPM is a severe infection with an elevated burden.[16,27,33,36] Septic shock within 72 h after BSI-ESCPM diagnosis was identified as a significant risk factor for death, as described by others for BSI in general.[34,35,39–41] These findings emphasize the severity and potential for fatal health outcomes in BSI-ESCPM. Thus, better strategies for managing septic shock are critical for reducing the risk of death in patients with BSI-ESCPM.

Combined antibiotic therapy was a protective factor against death in patients with BSI-ESCPM. Similarly, other studies have described that combined therapy reduces the mortality of Gram-negative bacteria BSI.[42,43] To the best of our knowledge, this finding is unprecedented for BSI-ESCPM. In fact, combined antimicrobial therapy could reduce the selection of mutant ESCPM group bacteria with AmpC hyperproduction and could result in a patient cure.[12] In this study, the combination therapy mainly included meropenem, followed by combined therapies with other drugs that are active against Gram-negative bacteria. However, combination therapy with meropenem did not have a protective effect against death, suggesting that additional combinations of antibiotics had an impact on these results.

A trend towards the association between inadequate empiric antimicrobial therapy and death was detected (OR: 2.19; 95% CI: 0.51–9.42), reinforcing inadequate initial antimicrobial therapy is associated with negative health outcomes in patients with Gram-negative bacteria BSI, as described by others.[35] In the present study, a larger sample size would have provided a greater statistical power to test this association.

BSI-ESCPM secondary to urinary infection was also protective against death within 30 days of diagnosis. Other studies have demonstrated that BSI originating from urinary tract infections is associated with lower mortality rates than BSI originating from other sites of infection. Therefore, these findings corroborate the results of previous studies.[2,44–49]

Surprisingly, *Enterobacter* spp. BSI was a protective factor against 30-day death. This finding differs from those of other studies, in which *Enterobacter* spp. BSI was associated with an increased risk of death[34,49] and most BSI-ESCPM caused by *Enterobacter* spp. occurred in patients with less severe clinical conditions, which can explain the lower risk of death observed compared to other agents in the ESCPM group. In fact, the patients with *Enterobacter* spp. BSI were

preferentially admitted outside the intensive care unit and had BSI secondary to sources of infection other than the respiratory tract, which is associated with high mortality.

This study has some limitations (i) it was a single-center study; therefore, external validation to increase the generalizability of the findings is limited; (ii) only 155 episodes of BSI were detected; this small sample size may have reduced the power of detecting variables associated with death (for instance, the impact of therapy with piperacillin/tazobactam and antibiotic combination therapy without meropenem were not analyzed). Nevertheless, by including all BSI-ESCPM episodes detected during the study, this strengthened our findings; and (iii) BSIs due to different bacterial species were analyzed together. However, their principal mechanism of antimicrobial resistance is similar, and species considered to be at a higher risk of clinically relevant AmpC production were analyzed separately. Despite these limitations, this study presents new information regarding the risk factors for death in patients with BSI-ESCPM.

Conclusion

Finally, BSI-ESCPM is a severe infection with poor outcomes such as sepsis associated with death. Combined antibiotic therapy was found to be a protective factor against death and could reduce the burden of BSI-ESCPM in settings with elevated incidence. A tendency of association between inadequate empirical antibiotic therapy and 30-day death was detected in these patients, and BSI-ESCPM episodes caused by species considered to be at moderate to high risk of clinically significant AmpC production were not associated with a higher risk of death.

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Disclosure

The authors report no conflicts of interest in this work.

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