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Carbapenem-resistant Enterobacterales bloodstream infections related to death in two Brazilian tertiary hospitals

Lorena Galvão de Araujo[1], Kehvyn Cedeño[2], Adriele Pinheiro Bomfim[3], Marcio de Oliveira Silva[1,4], Ana Verena Mendes[4], Maria Goreth Barberino[4], Edilane Lins Gouveia[5], Fabianna Márcia M. Bahia[5,6], Mitermayer Galvão dos Reis[1,6,7] and Joice Neves Reis[1,3*]

Abstract

Background Bloodstream infection (BSI) caused by carbapenem-resistant Enterobacterales (CRE) is a major global public health concern due to its high lethality and limited treatment options. In Brazil, CRE was first reported in 2005, with *Klebsiella pneumoniae* carbapenemase (KPC) documented in 2009. Despite ongoing reports, data remain limited in several regions.

Objective To describe the lethality rate and epidemiological and clinical characteristics of BSI patients with Enterobacterales BSI and assess carbapenem resistance to identify major risk factors for CRE infection and lethality.

Methods This prospective laboratory-based surveillance study, which was conducted in two tertiary hospitals (April 2016–December 2018), analyzed BSI cases caused by Enterobacterales. Clinical and demographic data were obtained from medical records. The bacterial isolates were identified by mass spectrometry and by VITEK-2®, with antimicrobial susceptibility testing performed by VITEK-2®. Logistic regression and Kaplan–Meier survival analyses were used to assess the impact of CRE BSI on death.

Results Among 252 patients with enterobacterial BSIs were identified, of which 14.3% had CRE. The overall lethality rate was 37.7%. Compared with carbapenem-susceptible Enterobacterales, CRE-associated BSIs were associated with significantly greater lethality (71.6% vs. 28.4%; $p < 0.001$; OR = 6.53, 95% CI [3.01–15.41]). The association remained significant after adjusting for age, comorbidities, Pitt bacteremia score, Enterobacterales species, BSI type, and sepsis. All CRE BSI cases were hospital-acquired.

Conclusions CRE accounts for 14.3% of BSIs and is strongly associated with increased lethality. Given the limited epidemiological data in Brazil, this study provides valuable epidemiological insights that may inform local treatment protocols for Enterobacterales infections.

Keywords Enterobacterales, Microbial resistance, Bloodstream infection, Carbapenem resistance

*Correspondence:
Joice Neves Reis
joice@ufba.br
[1]Program of Biotechnology in Health and Investigative Medicine, Instituto Gonçalo Moniz/FIOCRUZ–, Salvador, Brazil
[2]Global Health Disparities Research Training Program, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[3]Faculty of Pharmacy, Federal University of Bahia, Ondina, Salvador, Bahia 40170-115, Brazil
[4]São Rafael Hospital, São Marcos, Salvador, Bahia 41253-190, Brazil
[5]Bahia Hospital, Pituba, Salvador, Bahia 40280-000, Brazil
[6]Faculty of Medicine, Federal University of Bahia, Salvador, Bahia 40170-115, Brazil
[7]Yale School of Public Health, Yale University, New Haven, USA

Introduction

Bloodstream infections (BSIs) caused by carbapenem-resistant Enterobacterales (CREs) have emerged as a significant global public health threat because of their high lethality rates and limited treatment options [1]. In Brazil, the first description of carbapenemase-producing Enterobacterales was in 2005, with the identification of IMP-1 in a *Klebsiella pneumoniae* isolate in the state of São Paulo [2], followed by the detection of *Klebsiella pneumoniae* carbapenemase (KPC) in 2009 [3]. Since then, numerous studies across the country have documented a sharp increase in CRE cases [4, 5]. Polymyxin remains one of the few treatment options for BSI caused by CRE in low- and middle-income countries, as the newer beta-lactamase inhibitors are often prohibitively expensive [6]. However, with CRE now endemic in Brazil [7], polymyxin usage has increased [8], leading to higher rates of polymyxin resistance [9]. Despite these concerning trends, epidemiological and microbiological data remain limited in certain states. Although new antibiotics have become available in recent years to treat infections caused by CRE, finding effective therapeutic options remains challenging [10]. In addition to antimicrobial therapy, several factors have been associated with increased mortality in patients with infections caused by multidrug-resistant (MDR) gram-negative bacteria, including the Charlson comorbidity index (CCI), elevated Pitt bacteremia score (PBS), presence of sepsis or septic shock, delayed initiation of appropriate therapy, use of combination therapy and recent hospitalization within the past six months [11, 12].

In 2019, the Centers for Disease Control and Prevention (CDC) classified CRE as one of the five urgent threats to human health, with CRE infections resulting in 13,100 hospitalizations and over 1,000 deaths in the United States in 2017 alone [13]. The SENTRY study further demonstrated a statistically significant increase in CRE rates across Latin America over a 20-year period, increasing from 0.8 to 6.4% [14]. In Brazil, CRE incidence specifically increased from 1.1% (1997–2000) to 12.7% (2013–2016) [14].

The primary objectives of this study were to describe the sociodemographic and clinical characteristics of patients, report the lethality rate, determine the rate of carbapenem resistance among enterobacterial isolates and identify key risk factors associated with death in patients with CRE BSI. As a secondary objective, the study also explored the antimicrobial susceptibility profile of Enterobacterales isolates, including resistance to polymyxins and other first-line antibiotics used in the treatment of CRE infections in Brazil. We recognize that such epidemiological data are essential for developing targeted antimicrobial stewardship strategies and identifying patients at increased risk of poor outcomes.

Methods

Study design and population

We performed a cross-sectional study involving patients with positive blood cultures for Enterobacterales, identified through active surveillance in two tertiary hospitals that manage medium- to high-complexity cases. The first site, Hospital da Bahia, a 295-bed facility with four intensive care units (ICUs) and high-complexity services, was studied from April 2016 to December 2018. The second site, Hospital São Rafael, with 250 beds, including over 70 designated for critical care, was studied between March 2017 and February 2018.

Inclusion criteria

Medical records with a positive blood culture for Gram-negative bacterial infection were included in the dataset.

Exclusion criteria

As this was a retrospective study, records were excluded if they involved any of the following: repeated culture data, polymicrobial infections, unknown antibiogram results, subsequent positive blood cultures within 28 days of the initial episode, or patients under 18 years of age.

Definitions

Bloodstream infection (BSI) was defined as the presence of a positive blood culture accompanied by signs and symptoms of infection. Primary bloodstream infections were defined as those with no identifiable source of infection. In contrast, bacteremias associated with infections at other body sites, such as the lungs or urinary tract, were classified as secondary [15]. Community-acquired infection (CAI) was defined as a BSI occurring ≤ 48 h after hospital admission, without any of the following healthcare-associated risk factors: previous hospitalization, surgery, dialysis, or residence in a long-term care facility within the 12 months prior to the BSI. Healthcare-associated infection (HCAI) was defined as a BSI occurring more than 48 h after hospital admission or in cases where healthcare-associated risk factors, as listed above, were present. Carbapenem-resistant Enterobacterales (CRE) were defined according to the CDC criteria: isolates resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem or imipenem) or those that were carbapenemase producers. For Enterobacterales species with intrinsically high minimum inhibitory concentrations of imipenem, such as *Proteus* spp., *Morganella* spp. and *Providencia* spp., susceptibility to meropenem and ertapenem was used to determine whether they met the CRE definition [16].

Microbial isolation, identification and antimicrobial susceptibility testing

Blood cultures were performed on a BacT/ALERT® 3D system (bioMeriéux-France) at both hospitals. Microbial identification was performed via MALDI-TOF MS (bioMeriéux-France), as described by Barberino et al. [17], at Hospital São Rafael, whereas at Hospital da Bahia, VITEK 2® (bioMeriéux-France) was used. The antimicrobial susceptibility profile was determined in both hospitals via VITEK 2®. The broth microdilution method was used to determine polymyxin resistance. The tests and the interpretative criteria were performed according to the Clinical and Laboratory Standard Institute recommendations (33rd edition, 2023) [18].

Data collection

The medical records of all eligible patients were retrospectively reviewed to collect demographic and clinical data, including inpatient unit data, length of hospital stay, hospitalization during the previous six months, previous health care, previous infections, comorbidities, presented symptoms, possible sources and risk factors for bacteremia, antibiotic use in the previous six months, empiric and culture-guided treatment and clinical outcomes at 30 days, intensive care unit admission, and discharge. The Pitt bacteremia score (PBS) was used to assess the severity of BSI, whereas the Charlson comorbidity index (CCI) was used to evaluate the severity of underlying conditions at admission.

Statistical analysis

Descriptive statistics were used to characterize the study sample's sociodemographic and clinical features. Categorical variables were reported as percentages and frequencies, while continuous variables were presented as medians with interquartile ranges (1st–3rd quartiles). Crude logistic regression models estimated associations between covariates and CRE, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated via the generalized linear model. Associations with p-values < 0.05 were considered statistically significant. For contingency tables where cell values were zero, an OR with Fisher's correction was applied, as recommended by Ruxton & Neuhäuser [19]. Due to the limited number of cases for some species, logistic regression models compared infection with a specific Enterobacterale (one of five categories - *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, *E. cloacae*, *Citrobacter freundii*) against infection with any of the other species (a merged group). Each regression used 'Other bacterium' as the reference category.

Two adjusted logistic regression models were constructed to explore the association between CRE and lethality. The first model included variables selected based on literature findings [20–26], while the second used stepwise regression to identify predictors, with a significance threshold of 0.10 for forward selection and 0.15 for backward elimination. A Kaplan-Meier survival curve was constructed to compare lethality between patients with BSI caused by carbapenem-susceptible Enterobacterales (CSE) and those caused by CRE. Lethality was assessed based on the proportion of deaths among patients with BSI confirmed by a positive blood culture for Enterobacterales. Time was measured in days, calculated as the interval between the date of blood culture collection and the last day in the hospital (either death or discharge). The survival analysis covered a 72-day period for both groups, as shown in Fig. 2. A log-rank test was used to compare the survival curves. All analyses were performed using RStudio (version. 2023.03.0 + 386).

Lethality rate was calculated as the percentage of people who died from BSI after being diagnosed with it.

Results

A total of 320 cases were identified, of which 68 were excluded from the analysis for the following reasons: repeated culture information ($n = 16$), polymicrobial infection ($n = 43$), unknown antibiogram ($n = 2$), subsequent positive blood cultures within 28 days of the initial episode ($n = 1$), and age younger than 18 years ($n = 6$). This resulted in a final study sample of 252 cases (71.3%) included in the analysis (Fig. 1).

During the study period, 252 patients with Enterobacterales bacteremia were identified. The characteristics of these patients are summarized in Table 1. The majority of them were male ($n = 136$, 54.0%), with a median age of 68.0 years (interquartile range [IQR]: 55.8 and 79.3). Primary BSIs accounted for 28.2% of the cases. Secondary BSIs accounted for 181 (71.8%) cases, with the most common sources being urinary tract infection (105 cases, 58.3%), intra-abdominal infection (38 cases, 21.1%), and respiratory tract infection (21 cases, 17.2%). The median CCI was 5.0 (IQR: 3.0 and 7.0), and the median PBS was 2.0 (IQR: 0.0 and 8.0). A QSOFA score of ≥ 2 was observed in 60.9% of the patients. Most cases (78.2%) involved patients admitted to intensive or semi-intensive care units (ICUs) and 76.6% ($n = 193$) of the episodes were HCAI.

Escherichia coli was the most common pathogen among all BSI cases, identified in 119 cases (47.2%), followed by 76 cases of *Klebsiella pneumoniae* (30.2%). Among the 252 BSI episodes, 36 (14.3%) were caused by CRE. One *E. coli* and 14 *K. pneumoniae* isolates were found to be resistant to colistin. Others Enterobacterales isolated on BSI are summarized on Table 1. The overall lethality rate was 37.7 per 100 cases, while the 30-day lethality rate was 31.0 per 100 cases.

Lethality rates were stratified for *E. coli* and *K. pneumoniae*, they two most frequently identified

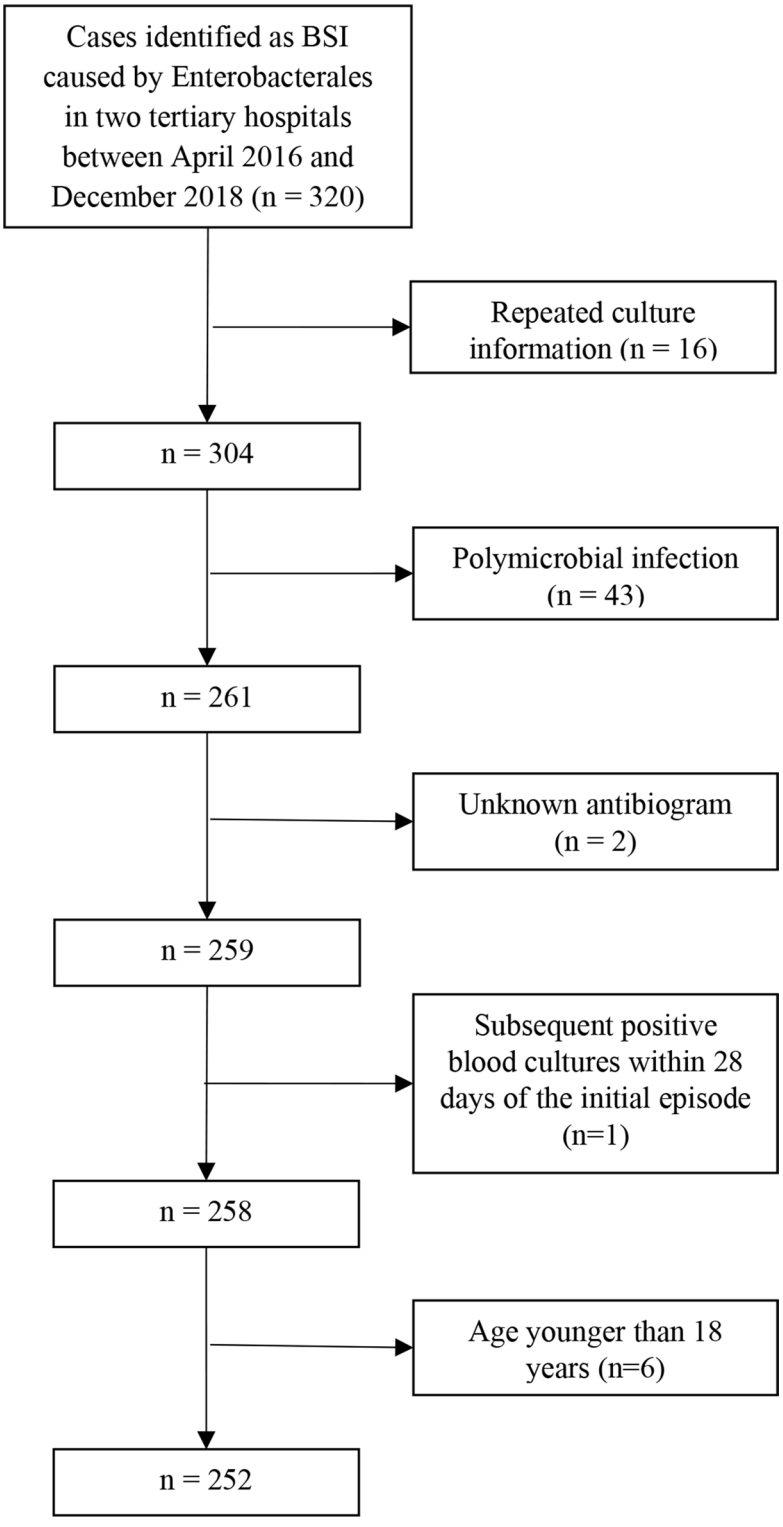


Fig. 1 Flow chart of the study sample

Table 1 Univariate analysis of the sociodemographic and clinical characteristics of patients with BSI caused by enterobacterales ($n = 252$)

Characteristics	*n* (%)
Age, years	
Median (1qt-3qt)	68.0 (55.8–79.3)
≤ 68	127 (50.4)
> 68	125 (49.6)
Sex at birth	
Male	136 (54.0)
Female	116 (46.0)
Charlson Comorbidity Index[a]	
Median (1qt-3qt)	5.0 (3.0–7.0)
< 3	58 (23.2)
≥ 3	192 (76.8)
Type of BSI	
Primary	71 (28.2)
Secondary[※]	181 (71.8)
QSOFA score [b]	
< 2	97 (39.1)
≥ 2	151 (60.9)
Pitt bacteremia score[c]	
Median (1qt-3qt)	2.0 (0.0–8.0)
< 4	146 (58.2)
≥ 4	105 (41.8)
Enterobacterales	
E. coli	119 (47.2)
K. pneumoniae	76 (30.2)
P. mirabilis	15 (6.0)
E. cloacae	14 (5.6)
Other[‡]	28 (11.1)
Carbapenem resistance	
No	216 (85.7)
Yes	
Polymyxin resistance[+, d]	36 (14.3)
No	100 (87.0)
Yes	15 (13.0)
Sepsis	
No	98 (38.9)
Yes	154 (61.1)
ICU admission	
No	55 (21.8)
Yes	197 (78.2)
Type of infection	
HCAI	193 (76.6)
CAI	59 (23.4)
Died	
No	157 (62.3)
Yes	95 (37.7)
Died in 30 days or less	
No	174 (69)
Yes	78 (31)

[※]It includes urinary, respiratory and intra-abdominal infections

[+]Only for *E. coli* and *K. pneumoniae* isolates

[‡]Other include: *K. oxytoca*, *E. aerogenes*, *S. marcescens*, *Citrobacter koseri*, *Citrobacter Braakii*, *M. morganii*, *P. stuartii*

Missing values: [a]$n = 2$| [b]$n = 4$| [c]$n = 1$| [d]$n = 137$

Enterobacterales isolates (119 and 76, respectively). A total of 30 deaths occurred among patients with *E. coli* BSI, yielding a case fatality rate of 25.2%. For *K. pneumoniae*, 39 deaths were recorded, resulting in a case fatality rate of 51.3%.

All *E. coli* isolates ($n = 119$) were susceptible to carbapenem and tigecycline antibiotics, and only one strain was resistant to colistin. Susceptibility to cephalosporins (including cefepime, ceftazidime, ceftriaxone and cefuroxime) ranged from 72.0 to 74.8%. In contrast, lower susceptibility to carbapenems was observed among *K. pneumoniae* isolates (66.7 – 69.7%), and 14 isolates demonstrated resistance to colistin. The lowest susceptibility rates were observed for cephalosporins (36.0 – 37.0%). For *Proteus mirabilis* ($n = 15$), susceptibility to carbapenems ranged from 53.8 to 66.7%, with amikacin exhibiting the highest in vitro activity (71.4%). Among the 13 *Enterobacter cloacae* isolates tested, 11 (85.7%) were susceptible to carbapenems, and all were susceptible to colistin (100%). This information can be verified in Table 2.

Table 3 presents the association analysis, showing the frequency distribution of each covariable by outcome (carbapenem-resistant vs. carbapenem-susceptible Enterobacterales, CRE vs. CSE). Significant associations were found with variables QSOFA score, PBS, specific causative agents (lower odds for *E. coli*, higher odds for *K. pneumoniae* and *P. mirabilis*), presence of sepsis, admission to intensive or semi-intensive care units, and infection type (CAI vs. HCAI). Higher PBS and QSOFA scores were associated with increased odds of CRE infection. Among the pathogens, *E. coli* showed the lowest association with CRE, (no resistant isolates identified), while *K. pneumoniae* exhibited strongest association, accounting for 69.4% of CRE cases (25/36) with highest odds (OR = 7.35, 95% CI [3.46–16.54]). No CRE cases were identified among CAIs. Also, BSI caused by CRE was significantly associated with increased lethality, with a greater proportion of deaths among patients with CRE compared to those with CSE (28.4% vs. 5.7%, p-value < 0.001 and OR = 6.53, 95% CI [3.01–15.41]).

To evaluate risk factors for lethality in patients with CRE BSIs, adjusted logistic regression models were applied, using CSE BSIs as reference group (OR = 1.00). Resistance to polymyxin was excluded from the adjusted model due to missing data and the intrinsic resistance of certain bacterial species. In the crude analysis, patients with CRE BSIs had a significantly higher risk of death compared to those with CSE BSIs (OR = 6.53, 95% CI: 3.01–15.41). This association remained significant in model 1 after adjusting for age, CCI, PBS, Enterobacterales species (*K. pneumoniae* vs. other Enterobacterales), type of BSI and presence of sepsis (Model 1, aOR = 4.09. 95% CI: 1.55–11.88). In model 2, a similarly elevated

Table 2 Antibiotic susceptibility profiles of *E. coli*, *K. pneumoniae*, *P. mirabilis* and *E. cloacae* isolates (*n* = 252)

Antibiotic	E. coli *n* (%) (*n*=119)	K. pneumoniae *n* (%) (*n*=76)	*P.* mirabilis *n* (%) (*n*=15)	E. cloacae *n* (%) (*n*=14)	Other *n* (%) (*n* = 28)
Amikacin	113 (96.6)[a]	68 (91.9)[a]	10 (71.4)[b]	13 (92.9)[a]	28 (100)
Ampicillin/Sulbactam	48 (40.3)[c]	22 (29.7)[a]	9 (64.3)[b]	0 (0.0)[a]	3 (12.5)[d]
Cefepime	89 (74.8)	27 (36.0)[b]	9 (60.0)	9 (69.2)[b]	22 (78.6)
Ceftazidime	86 (74.8)[d]	27[e] (37.0)	7 (53.8)[a]	5 (62.5)[f]	12 (75.0)[g]
Ceftriaxone	88 (74.6)[b]	27 (36.0)[b]	7 (53.8)[a]	5 (62.5)[f]	12 (75.0)[c]
Cefuroxime	85 (72.0)[b]	25 (32.9)	7(53.8)[a]	1 (10.0)[d]	3 (18.8)[c]
Ciprofloxacin	74 (64.3)[d]	33 (44.6)[a]	9 (60.0)	12 (85.7)	23 (82.1)
Polymyxin	58 (98.3)[h]	33 (70.2)[i]	ND	ND	ND
Gentamicin	106 (92.2)[d]	43 (58.1)[a]	9 (60.0)	12 (85.7)	24 (85.7)
Piperacillin/Tazobactam	112 (94.1)	31 (40.8)	9 (64.2)[b]	8 (61.5)[a]	20 (80.0)[e]
Tigecycline	106 (100.0)[g]	62 (84.9)[h]	0 (0.0)[h]	9 (90.0)[d]	14 (82.4)[k]
Ertapenem	119 (100.0)	51 (67.1)	10 (66.7)	12 (85.7)	24 (85.7)
Imipenem	116 (100.0)[e]	50 (66.7)[b]	7 (53.8)[a]	12 (85.7)	16 (76.2)[l]
Meropenem	119 (100.0)	53 (69.7)	10 (66.7)	12 (85.7)	25 (89.3)

Missing values: [a]*n* = 2| [b]*n* = 1| [c]*n* = 12| [d]*n* = 4| [e]*n* = 3| [f]*n* = 6| [g]*n* = 13| [h]*n* = 61| [i]*n* = 29| [j]*n* = 8| [k]*n* = 11| [l]*n* = 7

adjusted odds ratio was observed, although with greater variability; the association remained statistically significant (Table 4).

A survival curve was generated to compare lethality over time between patients with CRE BSIs and those with CSE BSIs. Time was measured in days, defined as the difference between the last day in the hospital (either death or discharge) and the day the blood culture was performed. The graph was divided into fractions of time, to present how many people had died and how many had been discharged (survived) from the hospital as time passed. The survival curve for CRE BSIs declined faster than did the curve for CSE BSIs. Notably, the median survival time for patients with CSE BSIs was 20 days longer than that for patients with CRE BSIs (36 days vs. 16 days, respectively). This difference was statistically significant (p value = 0.0013). Despite the overall differences between the groups, the majority of deaths occurred within the first few days of hospitalization (Fig. 2).

Discussion

In this cohort of patients with Enterobacterales BSI, lethality was high at 37.7%. CRE-associated BSIs were linked to significantly greater lethality (71.6% vs. 28.4%; $p < 0.001$). Consistent with previous studies on BSI epidemiology, most infections occurred in male and elderly patients [27–29]. Regarding the source of BSI, 71.8% of cases were secondary to infections from other sites. This was similar to a research in Greece, by Chandroulis et al. [30] where 77.1% of the cases were Secondary BSI. On the other hand, this frequency was higher than reported in other studies; 44.1% in the study by Leal et al. in Brazil [31], and 22.4% in the studies performed in Tenerife, Spain, by Sante et al. [32]. This difference may be attributed to the higher rate of HCAI in our cohort than in the populations in the referenced studies.

As expected, *E. coli* and *K. pneumoniae* were the predominant pathogens isolated from Enterobacterales BSIs, aligning with findings from other BSI cohorts [33, 34]. Specifically regarding CRE, *K. pneumoniae* was the most frequently isolated species, consistent with results from Zhou et al. [35] across 18 hospitals and Li et al. [36] from a single hospital; both conducted in China. Similar results have also been reported in countries neighboring Brazil. The study by Krapp et al. [37]., conducted in 15 hospitals across Peru, found *E. coli* and *K. pneumoniae* as the most frequent Enterobacterales in routine blood cultures from a multicenter prospective hospital-based surveillance study. Authors didn't find carbapenem resistance among *E. coli* isolates, compared with a prevalence of 11.0% among *K. pneumoniae*. Indeed, *K. pneumoniae* is well-known for its ability to acquire and disseminate resistance genes, making it a leading cause of healthcare-associated infections [31].

Among the 252 episodes of BSI, 36 (14.3%) were caused by CRE. This frequency is lower than that reported by AMANATI et al. [38], which was 39.3%, although their study also included non-fermenting gram-negative BSI cases. In contrast, another study found that 6.4% of Enterobacterales isolates in Latin America exhibited carbapenem resistance between 2013 and 2016 [14]. This study included other sources of BSI, which may explain the lower CRE frequency compared to our findings. A large national laboratory-based study reported an increase in the frequency of bla_{NDM} from 4.1% in 2015 to 39.4% in 2022, while the frequency of bla_{KPC} decreased from 74.5% in 2015 to 55.1% in 2022. Although this study included infections other than BSI, it used data from three public laboratory information systems, primarily

Table 3 Sociodemographic and clinical characteristics of patients with BSI caused by enterobacterales, stratified by carbapenem resistance, *n* = 252

	Carbapenem			
Variable	**Susceptible** ***n*** **= 216** **n (%)**	**Resistant** ***N*** **= 36** **n (%)**	**OR (95% CI)**	**p value**
Age (years)				
≤ 68	109 (85.8)	18 (14.2)	Ref.	0.959
> 68	107 (85.6)	18 (14.4)	1.02 (0.50–2.07)	
Biological sex				
Male	115 (84.6)	21 (15.4)	Ref.	0.571
Female	101 (87.1)	15 (12.9)	0.81 (0.39–1.65)	
Charlson Comorbidity Index[a]				
< 3	51 (87.9)	7 (12.1)	Ref.	0.565
≥ 3	163 (84.9)	29 (15.1)	1.30 (0.56–3.37)	
Type of BSI				
Primary	57 (80.3)	14 (19.7)	Ref.	0.126
Secondary	159 (87.8)	22 (12.2)	0.56 (0.27–1.20)	
QSOFA score [b]				
< 2	92 (94.8)	5 (5.2)	Ref.	**< 0.001**
≥ 2	72 (75.0)	24 (25.0)	6.13 (2.40–18.92)	
Pitt bacteremia score [c]				
< 4	136 (93.2)	10 (6.8)	Ref.	**< 0.001**
≥ 4	79 (75.2)	26 (24.8)	4.48 (2.11–10.20)	
Bacterium [+]				
E. coli *	119 (100.0)	0 (0.0)	0.00 (0.00–0.09)	**< 0.001**
K. pneumoniae	51 (67.1)	25 (32.9)	7.35 (3.46–16.54)	**< 0.001**
P. mirabilis	10 (66.7)	5 (33.3)	3.32 (0.98–10.03)	**0.039**
E. cloacae	12 (85.7)	2 (14.3)	1.00 (0.15–3.88)	> 0.999
Other	24 (85.7)	4 (14.3)	1.00 (0.28–2.80)	> 0.999
Sepsis				
No	90 (91.8)	8 (8.2)	Ref.	**0.027**
Yes	126 (81.8)	28 (18.2)	2.50 (1.14–6.11)	
ICU admission				
No	164 (83.2)	33 (16.8)	Ref.	**0.045**
Yes	52 (94.5)	3 (5.5)	3.49 (1.19–14.91)	
Type of infection				
HCAI *	157 (81.3)	36 (18.7)	Ref.	**< 0.001**
CAI	59 (100)	0 (0)	0.00 (0.00–0.30)	
Died				
No	148 (94.3)	9 (5.7)	Ref.	**< 0.001**
Yes	68 (71.6)	27 (28.4)	6.53 (3.01–15.41)	

[+] Each Enterobacterales species was evaluated against all other species combined (e.g., *E. coli* vs. non-*E. coli* Enterobacterales)

*Fisher test approach was used for the OR

Missing values: [a]*n* = 2 | [b]*n* = 4 | [c]*n* =1

Bold p values means statistically significant ($p < 0.05$)

Ref - means reference value

focused on carbapenem-resistant organisms, which may explain the higher prevalence of CRE observed compared to our real-world dataset [5].

We identified polymyxin resistance in 29.8% (*n* = 14) of the isolates tested, the majority of which were *K. pneumoniae* (13 of 14 isolates), with only one *E. coli* isolate resistant to this antimicrobial. This rate is higher than those previously reported in Brazil, yet consistent with the rising trend of colistin resistance observed in clinical Enterobacterales isolates from the Hospital das Clínicas in São Paulo, where resistance increased from 6.6% in 2010 to 9.4% in 2014 [39]. Similarly, Pereira et al. [40] reported a 15% rate of polymyxin resistance among KPC-producing *K. pneumoniae* isolates from several Brazilian states in 2013.

Table 4 Logistic regression models for the association between carbapenem-resistant enterobacterales BSI and lethality outcomes ($n = 252$)

Levels	OR_{crude} (95% CI)	$aOR_{Model\ 1}$ (95% CI)	$aOR_{Model\ 2}$ (95% CI)
CSE	1.00	1.00	1.00
CRE	6.53 (3.01–15.41)	4.09 (1.55–11.88)	4.96 (1.85–14.51)

Models' description:

Crude: $n = 252$; $R^2 = 0.99$; AIC = 313.58

Model 1 (based in literature): Adjusted for age, Charlson score, Pitt Bacteremia Score, Enterobacterales *(E. coli, K. pneumoniae, Proteus mirabilis, E. cloacae, Citrobacter freundii)*, Type of BSI, and sepsis. $n = 249$; $R^2 = 0.351$; AIC = 248.31

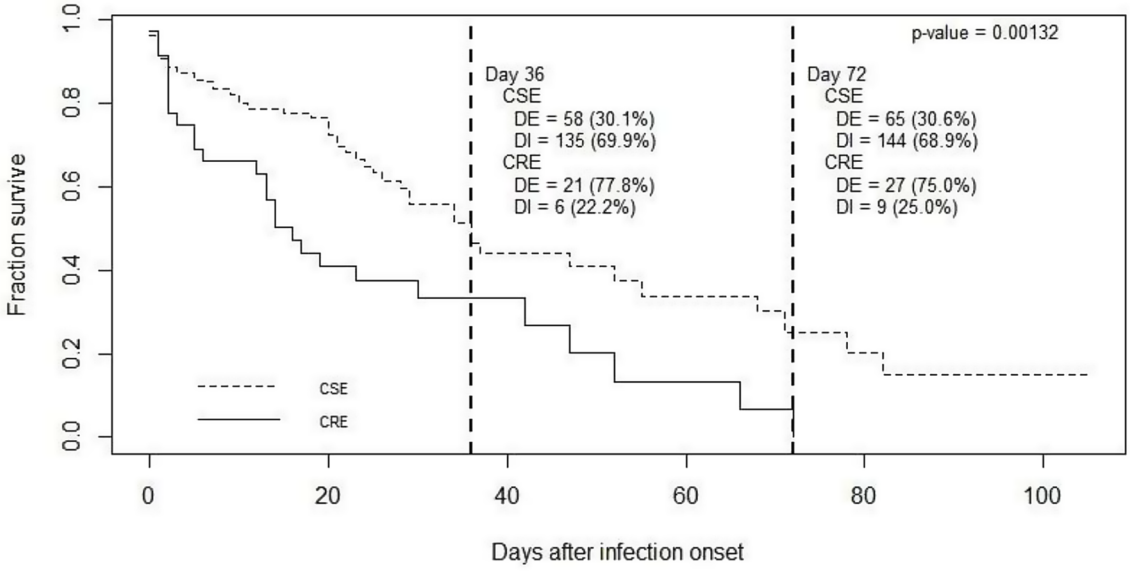
Model 2 (Stepwise recommendation): Adjusted for Charlson score, Bacterium infection, and Sepsis. $n = 250$; $R^2 = 0.380$; AIC = 237.45

These findings emphasize the critical needs for policies that ensure access to effective and affordable antimicrobials in low- and middle-income countries. One such option is ceftazidime-avibactam (CAZ-AVI), a novel β-lactam/β-lactamase inhibitor combination with in vitro activity against CRE producing Ambler class A and some class D (e.g., OXA-48) β-lactamases [34–41]. However, the availability of CAZ-AVI in Brazil remains limited, restricting its widespread use in clinical practice.

Overall lethality in our sample was 37.7 per 100 cases, which is consistent with the findings of Villegas et al. [29], who reported similar lethality rates in a multicenter observational study conducted between 2013 and 2014 across 11 hospitals in seven Latin American countries (the sample size was almost the same [$n = 255$]). This underscores the high lethality associated with Enterobacterales BSI. However, this lethality rate is lower than those reported in studies focused exclusively on CRE BSI [27, 42]. In this analysis, CRE infection was significantly associated with death, reinforcing the findings of these earlier studies. This association remained significant after adjusting for age, CCI, PBS, type of Enterobacterales, type of BSI, and presence of sepsis.

Our study revealed a significant association between qSOFA and PBS with CRE BSI, suggesting that patients with CRE infections present with more severe illness than those with CSE BSI. This association with critical illness was further supported by a higher frequency of sepsis and ICU admission in the CRE group.

By examining both HCAI and CAI, differences in the multidrug-resistant (MDR) profile between these two groups were assessed. We identified 23.4% ($n = 59$) of the BSI cases as CAI, and none of the isolates from CAI were resistant to carbapenems. This finding aligns with other studies indicating that CRE is predominantly associated with HCAI [35]. However, this contrasts with earlier data from a multicentric study in Latin America by Villegas et al. [29], which reported that 19% of BSIs caused by carbapenemase-producing Enterobacterales were CAIs. Additionally, the PANORAMA cohort study, which



CSE = Carbapenem-Susceptible Enterobacterales; CRE = Carbapenem-Resistant Enterobacterales
DE = Number of deaths at that time; DI = number of Discharged at that time (survived)
The p-value was based on the comparison of both Survival Curves using the log-rank test.

Fig. 2 Survival curve of carbapenem resistance in patients with bloodstream infection (BSI) caused by Enterobacterales in two tertiary referral hospitals in Salvador, Brazil ($n = 252$). CSE = Carbapenem-Susceptible Enterobacterales; CRE = Carbapenem-Resistant Enterobacterales DE = Number of deaths at that time; DI = number of Discharged at that time (survived) The p-value was based on the comparison of both Survival Curves using the log-rank test

examined BSI caused by Enterobacterales in low- and middle-income countries, classified 9% of CRE - BSIs as CAIs [43].

This study contributes to the growing body of evidence on the epidemiology and clinical outcomes of CRE bloodstream infections (BSIs), using a clear and standardized definition of infection. However, several important limitations must be acknowledged. Antibiotic susceptibility testing was conducted according to individual hospital protocols, and not all isolates were tested against the full panel of antibiotics. In particular, a large proportion of isolates ($n = 90$) lacked susceptibility data for polymyxins—primarily among carbapenem-susceptible isolates—which may introduce bias and partially explain the observed high prevalence of polymyxin resistance. Additionally, the findings reflect the epidemiological profile of only two healthcare institutions and, as such, may not be generalizable to other settings or the broader population. Despite these limitations, the study provides valuable insight into the local epidemiology of antimicrobial resistance in Enterobacterales, offering important data to inform public health strategies and clinical decision-making.

Conclusions

In conclusion, this study highlights the high lethality associated with CRE - BSI, with a significantly higher lethality rate observed in CRE-related BSIs compared to carbapenem-susceptible Enterobacterales (CSE) infections. The findings underscore the increased severity of CRE infections, with more frequent ICU admissions and a higher incidence of sepsis. Our results also reveal that healthcare-associated infections (HCAI) are more strongly associated with CRE, supporting the notion that CRE is primarily a concern in hospital settings. This study contributes to the growing body of evidence on the epidemiology and clinical outcomes of CRE BSIs, emphasizing the need for continued surveillance, effective infection control measures, and alternative therapeutic strategies, especially in regions with high CRE prevalence. Given the lack of epidemiological data in Brazil, this study provides valuable epidemiological insights and could help guide local treatment protocols for Enterobacterales infections.

Abbreviations

aOR	Adjusted odds ratio
BSI	Bloodstream infection
CAI	Community-acquired infections
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CI	Confidence intervals
CRE	Carbapenem-resistant Enterobacterale
CSE	Carbapenem-susceptible Enterobacterale
Fiocruz	Fundação Oswaldo Cruz
HCAI	Healthcare-associated infection
ICU	Intensive care unit
KPC	Klebsiella pneumoniae carbapenemase
MALDI TOF/MS	Matrix-Assisted Laser Desorption Ionization-Time of Flight/ Mass Spectrometry
MDR	Multidrug-resistant
HCAI	Healthcare-associated infection
ICU	Intensive care unit
OR	Odds ratios
qSOFA	Quick sequential organ failure assessment score
PBS	Pitt Bacteremia Score

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Author contributions

"LGA" contributed to the conceptualization of the research project and its methodology; collected clinical and epidemiological information through medical records review; analyzed and interpreted the data; wrote (original draft preparation); and reviewed and edited the manuscript. "KC" analyzed and interpreted the data, prepared the draft and reviewed the manuscript. "ELG", "FMMB", "AVM", "MGR" and "MGB" contributed to the conceptualization of the research project and its methodology and reviewed and edited the manuscript. "APB" performed the microbiological and molecular tests and reviewed and edited the manuscript. "JNR" contributed to the conceptualization of the research project and its methodology; was responsible for the project administration; supervised the procedures carried out in this research; analyzed and interpreted the data; and reviewed and edited the manuscript. All the authors have read and approved the final manuscript.

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Data availability

The datasets used in the current study are not publicly available to maintain the privacy and confidentiality of the participants but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2013) and the Brazilian National Health Council Resolution No. 466/12, which regulates research involving human subjects in Brazil. The research protocol was reviewed and approved by the Research Ethics Committee of the Nursing School of Federal University of Bahia (UFBA) (CAAE 30904614.2.0000.5531; 2.170.080), the Medical Board and Ethics Committee of São Rafael Hospital (CAAE 79250817.4.0000.0048) and the Medical Board and Ethics Committee of the Hospital da Bahia (CAAE 30904614.2.3006.5606). Both the Medical Boards and Ethics Committee of São Rafael Hospital and Hospital da Bahia provided ethical clearance for conducting this study and waivered the requirement to obtain informed consent from the patients whose medical records were analyzed in this study, as it involved an internal, retrospective review of patient charts without any acquisition of identifying patient information. Permission was obtained to review patient charts. The data were accessible only to authorized members of the core study team.

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests. JNR is an Editorial Board Member in BMC Infectious Diseases.

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