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# Assessment of epidemiological characteristics and outcomes in patients presenting bacteremia by Gram-negative bacilli in intensive care units belonging to a tertiary care teaching hospital. A retrospective cohort study

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**Palavras-chave**
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**Abstract:** Bloodstream infections (BSI) are a major problem in intensive care units (ICUs), with increasing rates despite medical advancements. These infections are closely tied to patient deaths and are influenced by various risk factors identified through ICU research. Infections caused by antibiotic-resistant Gram-negative bacilli (GNBs) negatively impact patients, especially in underdeveloped countries like Brazil. This study investigated nosocomial BSI caused by GNB among ICU patients at Federal University of Uberlândia between 2012 and 2014. The research focused on understanding the epidemiology of these infections, their effect on mortality rates, and the corresponding risk factors involved. In a three-year study, 110 nosocomial bloodstream infections were caused by GNB, mainly from the lower respiratory tract with 57 cases (51.8%). Out of the 115 microorganisms identified in this study, microorganisms from the Enterobacteriaceae family accounted for 58.3% (67) of the episodes. Klebsiella pneumoniae (20.9%), Acinetobacter baumannii (20.0%) and Pseudomonas aeruginosa (19.1%) were the most frequent microorganisms. In our cohort, the overall mortality rate was of 39.5%, when only cases of BSI caused by GNB are analyzed, this percentage rises to 45.5%. This study revealed that septic shock and mechanical ventilation were significant mortality risk factors. Notably, patients with BSI caused by GNB, particularly MDR strains, experienced a faster progression towards death within the initial 20 days of hospitalization compared to those with infections from different microorganisms.

**Avaliação das características epidemiológicas e dos desfechos em pacientes com bacteremia por bacilos Gram-negativos em unidades de terapia intensiva pertencentes a um hospital universitário terciário. Um estudo de coorte retrospectivo**

**Resumo:** As infecções na corrente sanguínea (ICS) são um grande problema nas unidades de terapia intensiva (UTIs), com taxas crescentes apesar dos avanços médicos. Essas infecções estão intimamente ligadas às mortes dos pacientes e são influenciadas por vários fatores de risco identificados por meio de pesquisas em UTIs. Infecções por bacilos Gram-negativos (BGNs) resistentes a antibióticos afetam negativamente pacientes, especialmente em países subdesenvolvidos como o Brasil. Este estudo investigou infecções hospitalares na corrente sanguínea causadas por BGNs em pacientes de UTI na Universidade Federal de Uberlândia entre 2012 e 2014. A pesquisa teve como foco compreender a epidemiologia dessas infecções, seu efeito nas taxas de mortalidade e os fatores de risco correspondentes envolvidos. Neste período de três anos, 110 infecções hospitalares na corrente sanguínea foram causadas por BGNs, principalmente do trato respiratório inferior com 57 casos (51,8%). Dos 115 microrganismos identificados neste estudo, os microrganimos da família Enterobacteriaceae corresponderam a 58,3% (67) dos episódios. *Klebsiella pneumoniae* (20,9%), *Acinetobacter baumannii* (20,0%) e *Pseudomonas aeruginosa* (19,1%) foram os microorganismos mais frequentes. A taxa de mortalidade geral de pacientes com infecção de corrente sanguínea foi de 39,5%, sendo 45,4% atribuídos a pacientes com infecções por BGNs, especialmente organismos multirresistentes (MDR). Este estudo revelou que o choque séptico e a ventilação mecânica foram fatores significativos de risco de mortalidade. Notavelmente, pacientes com infecções na corrente sanguínea causadas por BGNs, particularmente cepas MDR, apresentaram um prognóstico desfavorável nos primeiros 20 dias de hospitalização em comparação com aqueles com infecções por microorganismos diferentes.

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## Introdução

Bloodstream infections (BSI) stand as one of the foremost hospital-acquired infections affecting Intensive Care Unit (ICU) patients (RUSSOTO *et al*., 2015). Despite the remarkable progress in modern medicine, the frequency of BSIs in ICUs remains on an upward trajectory, with this form of infection serving as a robust and independent predictor of mortality (VINCENT *et al*., 2020).

Recent studies focusing on ICU patients have highlighted that a various risk factors have been identified as playing a role in the elevated occurrence of these infections within the ICU setting, consequently leading to unfavorable patient outcomes (WARREN *et al*., 2001; YANG *et al*., 2022).

On a global scale, Gram-negative organisms stand as the most prevalent bacteria isolated from individuals afflicted with nosocomial BSIs. These organisms exhibit a higher potential for antibiotic resistance, a trait that has seen a surge in prevalence, particularly within developing nations like Brazil (ROSENTHAL *et al*., 2020; ALLEGRANZI *et al*., 2011; PONCE-DE-LEON *et al*., 2011; SILVA *et al*., 2012; GISKE *et al*., 2008). In such regions, there is a greater likelihood for patients to receive empiric antibiotic treatments that may not be appropriately targeted, thus contributing to the observed heightened mortality rates linked to these infections (KOLLEF; MICEK, 2014).

In the current study, our focus was directed towards assessing the epidemiological aspects of nosocomial BSIs caused by Gram-negative bacilli (GNB) in individuals admitted to an adult ICU. Furthermore, we aimed to investigate the influence of these infections on mortality rates.

## Methods

### Study design, settings and patients

A retrospective cohort study was conducted from January 2012 to December 2014 in an adult clinical/surgical ICU with 30 beds, situated within a 530-bed tertiary care hospital in Uberlândia, Minas Gerais, Brazil. The study included patients aged ≥18 years old who experienced their initial episode of BSI caused by GNB.

Variables potentially linked to the primary outcome of 30-day mortality following a diagnosis of sepsis/bacteremia were subjected to analysis. These variables encompassed demographics (age and gender), comorbidities, Charlson comorbidity index, Average Severity Index Score (ASIS), invasive devices, origin of infection, bacterial isolates, antimicrobial susceptibility profile, and the prescribed antibiotic regimen.

### Bacterial isolates and clinical microbiology

A sum of 115 isolates derived from 110 patient blood samples were encompassed within this study. The cultivation process employed the BACT/Alert test developed by bioMérieux. For microbial identification and subsequent antimicrobial susceptibility assessments, the VITEK II automated system, also by bioMérieux, was utilized. This analysis encompassed various antimicrobial categories, namely aminoglycosides, carbapenems, cephalosporins, and fluoroquinolones. The requisite data were subsequently extracted from the patients' medical records.

### Definitions

*Bloodstream infections (BSI)*: A result of bacterial dissemination in the bloodstream. In this context, they are classified as primary BSI when an infection occurs in association with a central line, or when the microorganisms identified in blood samples are not related to another site. Conversely, secondary infections are defined when the microorganisms identified in blood samples originate from another site (RUSSOTO *et al*., 2015).

*Multidrug resistant (MDR):* Microorganism resistance to at least three distinct antimicrobial classes, including aminoglycosides, carbapenems, fluoroquinolones, β-lactamase inhibitors, extended-spectrum cephalosporins, folate pathway inhibitors, polymyxins, and tetracyclines (MAGIORAKOS *et al*., 2012).

*Severe sepsis:* The manifestation of the following symptoms or signs, in the absence of any other documented cause: body temperature > 38 °C or < 36 °C, heart rate > 90 beats per minute, white blood cell count > 12,000 cells/mm³ or < 4,000 cells/mm³, respiratory rate > 20 breaths per minute, or partial pressure of carbon dioxide (PaCO2) < 32 mmHg (SINGER *et al*., 2016).

*Septic Shock:* Patients diagnosed with septic shock may be recognized as exhibiting sustained hypotension necessitating the use of vasopressors to sustain a blood pressure of ≥65 mmHg, along with a serum lactate level exceeding 2 mmol/L (18 mg/dL) (SINGER *et al*., 2016). In this study, the classification of severe sepsis and septic shock was made by the physician and documented in the patient's medical record.

*Appropriate antimicrobial therapy*: Refers to the situation where the patient is administered suitable antimicrobial treatment within the initial 48 hours subsequent to the collection of the initial set of positive blood cultures. Additionally, the microorganism isolated should exhibit susceptibility to the antimicrobial agents as determined by an in vitro antimicrobial susceptibility test (ZILBERBERG *et al*., 2014).

**Statistical analyses**

Comparison was made between the groups of patients who survived and those who did not survive during their time in the care unit. Statistical analyses were conducted using GraphPad Prism for Windows (version 6.0; La Jolla, California, United States). Where applicable, categorical variables were compared using Fisher's exact test and the chi-square test. A significance level of $P \leq 0.05$ was deemed as statistically significant.

For the multivariate analysis, BioEstat for Windows (version 5.0; Mamirauá: Belém, Pará-Brasil) was employed. Variables were included in the model using a forward stepwise logistic regression approach, with a criteria of $P \leq 0.05$ for inclusion.

**Ethics statement**

The present study received the ethical approval of the Ethics Board of the Federal University of Uberlândia, under protocol number 7882318.2.0000.5152 (June, 2018).

**Results and discussions**

A total of 110 cases of BSI caused by GNB in patients in the ICU were included in our study. These cases comprised 50 (45.4%) fatal cases and 60 survival cases within 30 days after the onset of BSI. Among these 110 patients, 40.9% (45) had a comorbidity in the form of heart failure. In terms of the comorbidity index, 40% (44) of these patients had a Charlson score of ≥3. This variable demonstrated statistical significance in the univariate analysis ($P = 0.0008$) (Table1).

This study revealed a notable association between patients and a heightened utilization of invasive procedures, including central vascular catheterization (98.2%), urinary catheterization (90.9%), and mechanical ventilation (81.8%). Regarding the source of origin of bacteremia, a substantial proportion, 70.9% (78), was categorized as secondary bacteremia. Among these cases, 51.8% (57) were attributed to an origin in the respiratory tract (table 1).

Among the 110 patients with BSI caused by GNB, 70.9% (78) received inappropriate empirical treatment after the onset of BSI. Furthermore, the presence of septic shock ($P = 0.0050$) and, as previously mentioned, the use of mechanical ventilation ($P = 0.0076$), were identified as significant predictors of an elevated risk of mortality on these patients (Table1).

**Table 1 -** Characteristics of patients presenting bloodstream infections (BSI) caused by Gram-negative bacilli (GNB) and mortality predictors within 30 days from the first BSI episode of adult patients admitted to the Intense Care Unit (ICU) of the Clinical Hospital belonging to the Federal University of Uberlândia, Brazil, between January 2012 and December 2014.

| Characteristics | BSI[1] by GNB[2] | | | Univariate P[4] (OR[5]) | Multivariate P (OR) |
|---|---|---|---|---|---|
| | Total *N*[3] =110 (%) | Death *N* = 50 (%) | Survivors *N* = 60 (%) | | |
| **Demographics** | | | | | |
| Male/Female | 82 (74.6)/28 (25.4) | 33 (66.0)/17 (34.0) | 49 (81.7)/11 (18.3) | 0.0604 (2.29) | - |
| Age (average ± SD[6]) | 55.5 ±19.9 | 59.8 ±19.8 | 51.8 ±19.5 | - | - |
| Length of ICU[7] stays in days (average ± SD) | 15.8 ±9.0 | 12 ±6.4 | 18.9 ±12.1 | - | - |
| **Admission reason** | | | | | |
| Surgical | 58 (52.7) | 29 (58.0) | 29 (48.3) | 0.3119 (1.48) | - |
| Clinical | 27 (24.5) | 16 (32.0) | 11 (18.3) | 0.0972 (0.48) | - |
| Traumatology | 25 (22.7) | 5 (10.0) | 20 (33.3) | 0.0036 (4.50)* | 0.4065 (0.61) |
| **Comorbidity/underlying disease** | | | | | |
| Heart Failure | 45 (40.9) | 25 (50.0) | 20 (33.3) | 0.0767 (2.00) | - |
| Chronic renal failure | 38 (34.5) | 26 (52.0) | 12 (20.0) | 0.0004 (4.33)* | 0.8243 (1.16) |
| Diabetes mellitus | 26 (23.6) | 14 (28.0) | 12 (20.0) | 0.3254 (1.56) | - |
| COPD[8] | 11 (10.0) | 8 (16.0) | 3 (5.0) | 0.1071 (3.62) | - |
| Neoplasia | 9 (8.2) | 7 (14.0) | 2 (3.3) | 0.0763 (4.72) | - |
| HIV[9] | 4 (3.6) | 3 (6.0) | 1 (1.7) | 0.3281 (3.77) | - |
| Immunocompromise | 77 (70.0) | 41 (82.0) | 36 (60.0) | 0.0133 (3.04)* | 0.1737 (2.09) |

**Table 1-** Characteristics of patients presenting bloodstream infections (BSI) caused by Gram-negative bacilli (GNB) and mortality predictors within 30 days from the first BSI episode of adult patients admitted to the Intense Care Unit (ICU) of the Clinical Hospital belonging to the Federal University of Uberlândia, Brazil, between January 2012 and December 2014 (*continued*).

| **Clinical score** | | | | | |
|---|---|---|---|---|---|
| ASIS[10] ≥4 | 89 (80.9) | 44 (88.0) | 45 (75.0) | 0.0945 (2.44) | |
| Charlson ≥3 | 44 (40.0) | 29 (58.0) | 15 (25.0) | 0.0008 (4.14)* | 0.1570 (2.48) |
| **Severity of infection** | | | | | |
| Sepsis and severe sepsis | 70 (63.6) | 27 (54.0) | 43 (71.7) | 0.0551 (2.15)* | 0.2349 (0.41) |
| Septic shock | 40 (36.4) | 23 (46.0) | 17 (28.3) | 0.0051 (0.46)* | 0.0050 (5.59)* |
| **Invasive device/procedures** | | | | | |
| CVC[11] | 108 (98.2) | 50 (100.0) | 58 (96.7) | 0.4996 (4.34) | |
| Urinary catheter | 100 (90.9) | 49 (98.0) | 51 (85.0) | 0.0208 (8.65)* | 0.454 (2.83) |
| Mechanical ventilation | 90 (81.8) | 47 (94.0) | 43 (71.7) | 0.0026 (6.19)* | 0.0076 (4.77)* |
| Hemodialysis catheter | 12 (10.9) | 11 (22.0) | 1 (1.7) | 0.001 (16.64)* | 0.120 (6.64) |
| **Classification of bacteremia** | | | | | |
| Primary | 32 (29.1) | 9 (18.0) | 23 (38.3) | 0.0194 (0.35)* | - |
| Secondary | 78 (70.9) | 41 (82.0) | 37 (61.7) | 0.0194 (2.83) | 0.253 (1.94) |
| Lung | 57 (51.8) | 29 (58.0) | 28 (46.7) | 0.2362 (1.58) | - |
| Urine | 11 (10.0) | 3 (6.0) | 8 (13.3) | 0.3390 (0.57) | - |
| Others[12] | 10 (9.1) | 9 (18.0) | 1 (1.7) | 0.0166 (10.4) | 0.712 (0.91) |
| **Antibiotic therapy** | | | | | |
| Use of antimicrobial of last generation[13] | 105 (95.4) | 48 (96.0) | 57 (95.0) | 0.8020 (1.26) | - |
| Inappropriate antimicrobial therapy | 78 (70.9) | 34 (68.0) | 44 (73.3) | 0.5397 (1.29) | - |
| **Microorganisms** | | | | | |
| Enterobacteriaceae | 63 (57.3) | 27 (54.0) | 36 (60.0) | 0.0623 (0.46) | - |
| GNB Non-fermenting | 47 (42.7) | 23 (46.0) | 24 (40.0) | 0.5265 (0.78) | - |
| MDR[14] pathogen | 56 (50.9) | 30 (60.0) | 43 (43.3) | 0.0817 (1.96) | - |
| Death | 50 (45.4) | - | - | - | - |

[1]Out of the 115 microorganisms identified in this study, 27 isolates (23.5%) exhibited resistance to carbapenems, 59 (51.3%) displayed resistance to third and fourth generation cephalosporins, and 44 (38.3%) were found to be resistant to fluoroquinolones. Among the isolates from the Enterobacteriaceae family, *K. pneumoniae* was the predominant species, constituting 58.3% of the cases. Notably, a significant majority of the isolates were classified as MDR at 48.7% (Table 2).

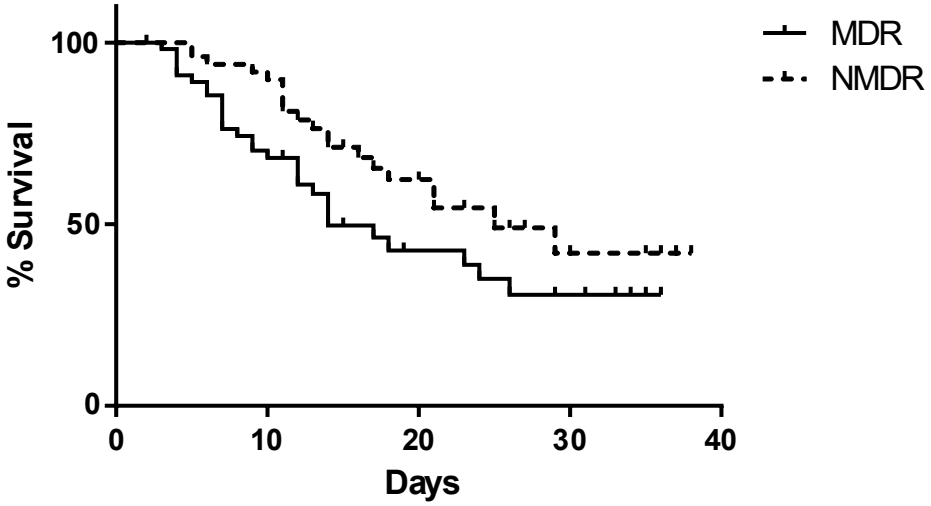
[1]Bloodstream infection; 2Gram-negative bacilli; 3Number; 4P value; 5Odds ratio; 6Standard deviation; 7Intense Care Unit; 8Chronic Obstructive Pulmonary Disease; 9Human Immunodeficiency Virus; 10Average Severity Index Score; 11Catheter Vascular Central; 12Tracheal secretion, cerebrospinal fluid, surgical site secretion; 13Carbapenems, extended spectrum cephalosporins and polymyxins; 14Multidrug resistant; *Statistically significant.

**Table 2 -** Etiology and resistance profile of Gram-negative bacilli (GNB) isolated from the first bacteremia episode of patients admitted to the Intensive Care Unit (ICU) of the Clinical Hospital belonging to the Universidade Federal de Uberlândia (UFU), Brazil, between January 2012 and December 2014.

| Microrganisms | Total | Antibiotic class | | | | | MDR[8] |
|---|---|---|---|---|---|---|---|
| | | 1GC[1] and 2GC[2] | 3GC[3] and 4GC[4] | CARB[5] | AMG[6] | FQ[7] | |
| ***Enterobacteriacae*** | **67 (58.3)** | **46 (68.6)** | **38 (56.7)** | **3 (4.5)** | **17 (25.4)** | **20 (29.8)** | **32 (47.8)** |
| *K. pneumoniae* | 24 (20.9) | 17 (70.8) | 15 (62.5) | 2 (8.3) | 7 (29.2) | 8 (33.3) | 14 (58.3) |
| *S. marcescens* | 16 (13.9) | 8 (50.0) | 3 (18.7) | 0 (0.0) | 1 (6.2) | 3 (18.7) | 3 (18.7) |
| *E. cloacae* | 14 (12.2) | 14 (100.0) | 14 (100.0) | 0 (0.0) | 8 (57.1) | 6 (42.8) | 11 (78.6) |
| *E. coli* | 9 (7.8) | 4 (44.4) | 4 (44.4) | 0 (0.0) | 1 (11.1) | 2 (22.2) | 4 (44.4) |
| Others[9] | 4 (3.5) | 3 (75.0) | 2 (50.0) | 1 (25.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) |
| **GNB non fermenting** | **48 (41.7)** | **8 (16.7)** | **21 (43.7)** | **24 (50.0)** | **13 (27.1)** | **24 (50.0)** | **24 (50.0)** |
| *P. aeruginosa* | 22 (19.1) | 8 (36.4) | 6 (27.3) | 12 (54.5) | 7 (31.8) | 7 (31.8) | 9 (40.9) |
| *A. baumannii* | 23 (20.0) | 0 (0.0) | 15 (65.2) | 11 (47.8) | 6 (26.1) | 17 (73.9) | 14 (60.9) |
| Others[10] | 3 (2.6) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | **1 (33.3)** |
| **Total** | **115 (100.0)** | 54 (46.9) | 59 (51.3) | 27 (23.5) | 30 (26.1) | 44 (38.3) | 56 (48.7) |

The overall 30-day mortality rate of patients with a BSI caused by GNB was 45.5%. However, this rate was significantly higher for patients with MDR-BSI compared to patients with non-MDR BSI (*P* = 0.001) (Figure 1).

**Figure 1** - Cumulative survival for patients with Bloodstream infection BSI by Gram-negative bacilli (GNB) Multidrug resistant (MDR) versus GNB Non-resistant microorganism (NMDR) isolated from the first bacteremia episode of patients admitted to the Intensive Care Unit (ICU) of the Clinical Hospital of the Federal University of Uberlândia, Brazil, between January 2012 and December 2014 (P = 0.001). (**Created in GraphPad Prism**).




BSIs are major contributors to morbidity and mortality, primarily in low-income countries like Brazil. In a recent study involving ICU patients, the crude mortality rates varied from 35% to 53%, with BSIs accounting for 16% to 40% of these cases (WAREEN *et al*., 2001). Within our BSI cohort, the overall mortality rate was 39.5%, of which 45.4% was linked to patients with GNB infections. Existing literature suggests that various risk factors are connected to mortality in BSI patients (KOLLEF *et al*., 2014; YANG *et al*., 2022), although in our present study, all these factors demonstrated significance according to the univariate analysis. The only factor independently associated with BSI patient mortality caused by GNB was septic shock progression.

Severe sepsis and septic shock progression are among the leading causes of mortality in Brazilian ICUs, occurring at a rate of 35.3% among patients hospitalized for more than 24 hours (SILVA *et al*., 2004), however, in developed countries, this mortality rate decreases to 11.4% (SAKR *et al*., 2013).

Pneumonia emerged as the predominant origin of Gram-negative bacteremia among ICU-acquired BSIs, a finding consistent with several other studies (SLIGL; TAYLOR; BRINDLEY, 2006). Our study's findings demonstrate that 51.8% of secondary BSIs were linked to respiratory tract issues. Moreover, in 18.2% of all patients, an evident source of infection couldn't be discerned, mirroring the outcomes documented by Russoto *et al*. (2015).

In the current study, the majority (95.4%) of patients with BSIs were receiving advanced-generation antibiotic regimens, as previously documented by the same research unit (BRAGA *et al*., 2019). This trend was further substantiated by a multicenter study encompassing 19 ICUs nationwide (SILVA *et al*., 2019). This approach has been necessitated by the pervasive prevalence of resistance phenotypes in clinically significant Gram-negative microorganisms.

The considerable levels of antibiotic resistance, alongside local variations in species distribution and drug susceptibilities within specific patient groups, should serve as guiding factors for the empirical treatment of nosocomial BSIs (WISPLINGHOFF *et al*., 2004). The emergence of extensive-spectrum resistance within GNB is particularly alarming, given the limited therapeutic alternatives (BOUCHER *et al*., 2009). Among the prominently significant pathogens, there has been an escalation in the prevalence of Enterobacteriaceae microorganisms exhibiting resistance to third-generation cephalosporins, notably Extended-spectrum beta-lactamase (ESBL) producers, along with the occurrence of carbapenem-resistant microorganisms (HIDRON *et al*., 2008). Furthermore, isolates of *P. aeruginosa* and *A. baumannii* that manifest this antibiotic resistance profile have also been identified.

Notably, patients experiencing BSIs attributed to GNB, particularly those classified as MDR, demonstrated a swifter progression towards mortality within 20 days of hospitalization, in comparison to individuals with infections arising from alternative microorganisms, particularly Gram-positive cocci. This accelerated course could potentially be linked to delayed diagnosis, initiation of antimicrobial therapy, and the heightened pathogenicity exhibited by GNB.

The present investigation is constrained by several limitations. Primarily, it adopted an observational rather than a randomized study design, introducing an inherent risk of unaccounted biases between the two groups. Moreover, the study's exclusive focus on a single center curtails the generalizability of the findings, especially considering the substantial representation of immune-suppressed patients within the examined population.

**Conclusions**

The current study established a distinct association between BSIs caused by GNB and in-hospital mortality, independent of antimicrobial resistance. The majority of BSI of this study were categorized as secondary infections, with a notable prevalence of pathogens from the Enterobacteriaceae family, particularly *K. pneumoniae*. Meanwhile, non-fermenting GNBs were most commonly represented by *A. baumannii*. Within the latter group, a concerning resistance to carbapenems was prominent, while a significant proportion of Enterobacteriaceae microorganisms exhibited resistance to broad-spectrum cephalosporins.

Epidemiological studies of this nature, with larger and more comprehensive sample sizes, should be actively encouraged. Such studies can offer substantial additional backing to the Hospital Infection Control Commission, healthcare practitioners, ICU staff, and national regulatory bodies in terms of the essential epidemiological insights necessary for effectively managing healthcare-associated infections. The prevailing situation, especially evident in Brazil, underscores the swift proliferation of multiple antimicrobial-resistant Gram-negative bacteria. This alarming trend has resulted in a notably constrained array of available therapeutic alternatives.

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