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Brazilian Study on the Prevalence of Carbapenemase Producing Organisms and Their Relation with Patients' Death Rate

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Authors' contributions

This work was carried out in collaboration among all authors. Author ALFV conceived the study, performed the statistical analysis, and wrote the protocols. Author PCPS was co-supervisor of the work and helped in the writing of the manuscript. Authors MVSR and LFE conceived the study and helped write the final manuscript. Authors MCSAT, GMD, MSBH, AJD, GSC, LGR, LSSS and MALA contributed to the realization of the microbiological techniques. Author IFNL helped in the design of the microbiological assays and author GRBC was the supervisor of the study. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Determine the clinical characteristics of patients and the microbiological characteristics of the isolated Gram-negative microorganisms; Analyze the relationship between hospitalization sectors and the occurrence of bacteria resistant to carbapenems; Determine the prevalence of Gram-negative in clinical sectors of a University Hospital from Fortaleza, Brazil; Relate the prevalence to resistent Gram-negative bacteria with patients' death rate.
Study Design: This is a descriptive, retrospective and cross-sectional study, carried out between January and December 2022 at a university hospital in Fortaleza, Brazil.
Place and Duration of Study: Microbiology Sector of the Central Laboratory of the Walter Cantídio University Hospital between January 2022 and December 2022.
Methodology: All reports that showed a positive culture for Gram-negative bacilli and that carried out antibiotic sensitivity testing were included in the study. Their identification (ID) and the Antibiotic Sensitivity Test (TSA) were carried out using the automated system VITEK® 2 (BioMérieux®, Marcyl'Etoile, France), which uses the OBSERVA system for data archiving. The data was collected on a specific form and collected through patient reports issued by the hospital system. The forms were reviewed by a microbiologist pharmacist from the microbiology service. The data were analyzed and audited in the Excel® program for statistical validation using the SPSS Statistics® program, version 17.0.
Results: 398 samples positive for Gram-negative microorganisms were collected. These samples referred to 236 patients admitted to different sectors of the hospital. It was seen that the Surgical Center concentrated a greater number of patients, representing 66 individuals (28%). The most frequently isolated species (n=217) were Klebsiella pneumoniae (n= 70; 23%) and Pseudomonas aeruginosa (n= 70; 23%), followed by Escherichia coli (n= 43; 14%) and Acinetobacter baumannii (n = 34; 11%), respectively. It was observed that 29.9% of GNB were isolated from blood samples, this being the most prevalent biological site. Bloodstream infection (BSI) was identified as the biological site with the highest number of cases, recording 65 (29.9%) positive isolates in the blood. It was found that 131 isolates of Gram-negative bacteria presented resistance mechanisms, with resistance to carbapenems being the most prevalent, corresponding to 42.75% of cases originating from enterobacteria. It was found that admission to the adult ICU increases the chances of death by 6.017 (OR) times in patients who isolated carbapenem-resistant GNBs ($p < 0.001$).
Conclusion: The study analyzed the microbial profile of patients at a university hospital, identifying a significant association between death and microbial resistance, especially with Klebsiella pneumoniae. Bloodstream infections were frequent, being the site with the highest number of cases. The predominant resistance mechanism was Carbapenem-Resistant Enterobacteriaceae (CRE). The results highlight the need for continuous monitoring and control of antimicrobial resistance to guide epidemiological strategies.

Keywords: Gram negative bacilli; carbapenemase; nosocomial infection; Carba-5 test.

1. INTRODUCTION

Recognized by the World Health Organization (WHO) as one of the main threats to public health globally, antibiotic resistance has emerged as a factor of extreme concern regarding the spread of diseases caused by bacteria, especially those classified as highly multidrug-resistant (MDR) Gram-negative bacilli (GNB). This phenomenon not only has a significant

impact on the high rates of illness and deaths, but also has direct implications for the world economy, substantially increasing the costs related to medical care. [1,2]. Additionally, medical interventions such as surgical procedures, chemotherapy treatments that suppress the immune system, and organ transplants are becoming progressively more complex and, in certain scenarios, even unfeasible, given the imperative demand for antibiotics capable of effectively combating MDR pathogens [3].

According to information from the World Health Organization (WHO), annually, at least 700,000 people lose their lives due to infections that do not respond to drug treatments, and, if adequate measures are not adopted, it is estimated that by 2050 infections caused by antibiotic-resistant bacteria (ARBs) could result in 10 million deaths worldwide. This number would surpass the mortality rates associated with diseases such as cancer and diabetes, exerting a substantial impact on the global economy, with estimates in the order of at least 100 trillion dollars [4,5].

The production of β-lactamases represents one of the main examples of an enzymatic mechanism adopted by resistant bacteria. These enzymes play a crucial role in protecting the cell wall as they unfold the amide bond present in the ring of β-lactam molecules such as penicillins, cephalosporins, and carbapenems. This process prevents these antibiotics from binding to penicillin-binding proteins (PBPs), compromising their ability to inhibit enzymes responsible for bacterial cell wall synthesis [6]. The β-lactamases, according to Ambler's classification, are divided into four classes based on their biochemical characteristics and are grouped into two distinct categories according to their catalytic mechanism: the serine-β-lactamases (classes A, C, and D) and the metallo-β-lactamases, which belong to class B [7].

Given the current situation of restriction in therapeutic options, the World Health Organization (WHO) in 2017 issued a list that identifies multidrug-resistant bacteria in high-priority categories. The pathogens classified as critical for research and development of new antibiotics were all Gram-negative bacteria (GNB), especially *Acinetobacter baumannii*, *Pseudomonas aeruginosa and* extended-spectrum beta-lactamase-producing enterobacteria (ESBL). These organisms are known to cause serious infections, including blood infections and pneumonia, and pose a significant threat, especially in hospital settings, nursing homes, and among patients who require medical devices, such as ventilators and blood catheters, for their medical care (WHO, 2017).

Therefore, the present study aims to analyze the microbiological profile and sensitivity pattern of isolated specimens in patients admitted to a university hospital in Fortaleza, Brazil.

2. MATERIALS AND METHODS

This is a descriptive, retrospective, and cross-sectional study conducted between January and December 2022 at a university hospital in Fortaleza, Brazil. The hospital under study has a quaternary level of health care and is integrated into the Unified Health System (SUS). The study was conducted in accordance with the guidelines and regulatory standards for research involving human beings (Resolution 466/12, National Health Council) and was approved by the Research Ethics Committee of the hospital (Opinion number: 3,697,674).

All reports that showed positive culture for gram-negative bacilli and that performed the antibiotic susceptibility test were included in the study. Duplicate results and repeats of bacterial isolates corresponding to the same patient were excluded.

The biological materials of the patients were analyzed at the Microbiology Laboratory of the institution, where their identification (ID) and the Antibiotic Susceptibility Test (AST) were performed through the *VITEK® 2 automated system (BioMérieux®, Marcyl'Etoile, France),* which uses the OBSERVA system for data archiving. Version 11.0 of the Brazilian Committee on Antimicrobial Susceptibility Testing (BrCAST) standardization was used to interpret the susceptibility data.

The detection of carbapenemases was performed using the Carba-5 test. This test is performed for carbapenem-resistant Gram-negative bacteria and consists of a rapid phenotypic test for the detection of serine-β-lactamase enzymes, KPC (K) and OXA-48 (O), and metallo-β-lactamases, VIM (V), IMP (I) and NDM (N) (NG BIOTECH, 2022).

The data were collected in a specific form through the patient reports issued by the hospital

system. The forms were reviewed by a pharmacist microbiologist from the microbiology service. The data were analyzed and audited in Excel® for statistical validation using SPSS Statistics®, version 17.0, in which the chi-square test and odds ratio tests were performed to analyze the possible significance of categorical variables, considering a 95% confidence interval and $p < 0.05$. The results of the study were expressed in tables and graphs at absolute and relative frequencies.

3. RESULTS AND DISCUSSION

During the study period, 398 samples positive for Gram-negative microorganisms were collected. These samples were from 236 patients admitted to different sectors of the hospital, including wards (such as operating room, surgical clinic III, kidney transplant surgical clinic, medical clinic I, recovery room, and bone marrow transplantation) and the Intensive Care Unit. It should be noted that 88 patients had more than one culture.

Table 1 describes the clinical profiles of the patients. Of the 236 reports analyzed, 117 (49.6%) corresponded to male patients and 119 (50.4%) to female patients. The age range was from 10 to 92 years, with a mean age of 55.6 years.

When the inpatient unit was analyzed, it was seen that the operating room concentrated 66 (28%) patients, followed by the Intensive Care Unit with 60 (25.4%) patients and the medical clinic I with 40 (17%) patients. The latter is composed of patients followed by the Hematology and Bone Marrow Transplantation (BMT) services, most of whom have immunosuppression.

When the length of hospital stay was analyzed, a variation was observed that lasted from 1 to 150 days, generating an average of 36 days. Considering the clinical outcome of the patients, it was seen that 160 (67.8%) were discharged from the hospital and 76 (32.2%) died.

Table 1. Clinical and demographic characteristics of the study patients associated with the presence or absence of relevant microbial resistance profiles evaluated in the period from January to December 2022 at a university hospital in Fortaleza, Ceará, Brazil

Variables	N	%
Sex		
Male	117	49,6
Female	119	50,4
Age		
Average (years)	55,6	-
Minimum-Maximum	10-92	-
Inpatient Unit		
Operating Room	66	28
Surgical Clinic III	19	8
Renal Transplant Surgery Clinic	29	12,3
Internal Medicine I	40	17
Recovery Room	16	6,8
Bone Marrow Transplant (BMT)	6	2,5
ICU Adult	60	25,4
Length of Stay		
Average (days)	36	-
Minimum-maximum (days)	1-150	-
Clinical Outcome		
Discharge	160	67,8
Death	76	32,2

Source: Prepared by the author based on the database of the Microbiology Laboratory. Caption: ICU, Intensive Care Unit

Table 2 presents the occurrence of Gram-negative bacteria isolated from clinical specimens of patients. A total of 303 microbiological reports were analyzed, where the most frequent species (n=217) were *Klebsiella pneumoniae* (n= 70; 23%) and *Pseudomonas aeruginosa* (n= 70; 23%), followed by *Escherichia coli* (n= 43; 14%) and *Acinetobacter baumannii* (n = 34; 11 %), respectively. The other isolated species had a combined occurrence of 28%.

Table 2. Gram-negative bacteria isolated from clinical specimens of patients hospitalized in critical sectors evaluated during the period from January to December, 2022 at a university hospital in Fortaleza, Ceará, Brazil

Gram-negative microorganisms isolated	%
Klebsiella pneumoniae	23
Pseudomonas aeruginosa	23
Escherichia coli	14
Acinetobacter baumanii	11
Stenotrophomonas maltophilia	4
Enterobacter cloacae	4
Proteus mirabilis	4
Burkholdeira cepacia complex	3
Other Gram Negatives Isolated	13

Source: Prepared by the author based on the database of the Microbiology Laboratory

It should be noted that, for this analysis, repeated results of bacterial isolation that correspond to the same patient were not considered, excluding 95 results.

Distributions of Gram-negative bacteria were observed in different clinical samples (Table 3). It was observed that 29.9% of the GNB were isolated from blood samples, which was the most prevalent biological site, followed by isolates from the respiratory tract, representing 26.3%, of which 21.2% came from tracheal aspirate and 5.1% from bronchoalveolar lavage.

Based on the mentioned data, bacterial species were found more frequently. Among them, the species *Klebsiella pneumoniae* (23%) and *Pseudomonas aeruginosa* (23%) deserve to be highlighted. These pathogens were also shown to be more frequent in a study on non-fermenting Gram-negative bacteria conducted at a teaching hospital in João Pessoa/PB [8].

Bloodstream infection (BSI) was identified as the biological site with the highest number of cases, with 65 (29.9%) positive isolates in the blood. Subsequently, respiratory tract infection presented 21.2% of positive cases in tracheal aspirate samples and 5.1% in bronchoalveolar lavage. *Klebsiella pneumoniae* was the most frequent species found in ICS. These results are in agreement with the study by Lima [9], which reported a prevalence of 47.14% of positive cases of ICS, highlighting *Klebsiella pneumoniae* as the most prevalent bacterium in this site.

In infections related to the respiratory system, it was observed that *Pseudomonas aeruginosa* was the most frequent species, with 22 positive isolates in tracheal aspirate, in addition to 11 cases in bronchoalveolar lavage. This bacterium is described in the literature as an opportunistic pathogen, as it rarely causes pathology in healthy patients, but represents a great threat to critically ill patients in the hospital environment [10]. In addition, this agent has a remarkable ability to form biofilm on medical device surfaces, including metals, plastics, and biotic surfaces. This ability is closely linked to the development of tissue necrosis and the occurrence of ventilator-associated pneumonia (VAP) [11,10]. A study by Santo *et al.* [12] evaluated the profile of microorganisms isolated from patients admitted to a hospital in Paraná and identified that *Pseudomonas aeruginosa* (25.0%) was the most prevalent bacterium in tracheal aspirate isolates among Gram-negative bacteria, which corroborates the results found in this study.

By analyzing the antibiograms performed, it was possible to characterize, in Table 4, the Gram-negative bacterial isolates in relation to their mechanisms of antibiotic resistance. It was found that 131 isolates of Gram-negative bacteria presented such resistance mechanisms, with resistance to carbapenems being the most prevalent, corresponding to 42.75% of the cases from enterobacteria, in addition to 22.90% observed in *Pseudomonas aeruginosa* and 18.32% in *Acinetobacter baumannii*. Resistance expressed by the ESBL enzyme was identified less frequently, occurring in 16.03% of the cases.

These results are similar to the data found in the study by Freitas *et al*. [13] who reported a resistance rate of 68.8% to carbapenems in *Klebsiella pneumoniae* isolates. However, there is a divergence from the study by Quillici [14] regarding the most frequent resistance mechanism since the presence of ESBL was reported first.

Table 3. Distribution of the most frequent Gram-negative bacteria per clinical sample isolated from patients from January to December 2022 at a university hospital in Fortaleza, Ceará, Brazil

Pathogens	Clinical specimens				
	Tracheal aspirate	Bronchoalveolr lavage	Blood	Urine	Others*
Acinetobacter baumannii	13	2	10	6	3
Escherichia coli	3	-	10	12	18
Klebsiella pneumoniae	8	2	28	18	14
Pseudomonas aeruginosa	22	7	17	3	21
TOTAL: n (%)	46 (21,2)	11 (5,1)	65 (29,9)	39 (18,0)	56 (25,8)

Source: Prepared by the author based on the database of the Microbiology Laboratory.
**To facilitate the analysis of data in relation to sites of infection, for samples described as 'other', secretions, surgical wound, tissue fragments, biological fluids, and catheter tip were included*

Table 4. Prevalence of resistance mechanisms in Gram-negative isolates

Resistance mechanism	N	%
ESBL	21	16,03%
CRE	56	42,75%
CRAB	24	18,32%
CRPA	30	22,90%

Source: Prepared by the author based on the database of the Microbiology Laboratory.
Caption: ESBL, Extended Spectrum Enterobacterium; CRE, Carbapenem-Resistant Enterobacteria; CRAB, Acinetobacter baumannii Carbapenem-Resistant; CRPA, Pseudomonas aeruginosa Resistant to Carbapenems.

Table 5. Clinical outcome associated with carbapenem resistance in patients from January to December, 2022 at a university hospital in Fortaleza, Ceará, Brazil

Inpatient unit		Clinical outcome			p-value (CI 95%)
		Discharge	Death	OR	
Adult ICU	N	10	38	6,017	< 0,001
	%	20,8%	79,2%		
Infirmary	N	38	24	-	-
	%	61,3%	38,7%		
Total	N	48	62	-	-
	%	43,6%	56,4%		

Source: Prepared by the author based on the database of the Microbiology Laboratory.
**CI, confidence index; OR, odds ratio; ICU, intensive care unit.*

By analyzing the possible relationship between carbapenem resistance in the hospitalization sectors and the outcome of the patients (Table 5), an evaluation of the significance of this relationship was performed. A multivariate statistical analysis was performed using binary regression. The test result was significant, showing that admission to the adult ICU increases the chances of death by 6.017 (OR) in patients who isolated carbapenem-resistant GNBs ($p < 0.001$).

In this study, it was found that patients who were affected by carbapenem-resistant Gram-negative bacteria during their stay in the adult Intensive Care Unit (ICU) had a higher mortality rate, reaching 79.2%. Statistical analysis revealed a significant association between carbapenem resistance in the adult ICU and the patients' fatal clinical outcome ($p < 0.001$). These findings corroborate the results obtained by Souza et al. [15], who demonstrated that patients with Carbapenem-Resistant Enterobacteria (CRE) admitted to the ICU had a higher incidence of death (70.2%; $p < 0.001$) compared to patients in other sectors [16-17].

4. CONCLUSION

In conclusion, this study enabled the knowledge of the microbial profile of culture results of patients admitted to a university hospital, which is of fundamental importance for local epidemiological studies and for the control of microbial resistance. The study population consisted mostly of patients from the operating room, ICU, and hematological medical clinic sectors, and found a statistically significant association between the outcome death and the clinically relevant resistance profiles evaluated. A higher frequency of isolation of *Klebisiella pneumoniae* was observed, and bloodstream infection (BSI) was identified as the biological site with the highest number of cases. It was found that the most prevalent resistance mechanism among the isolated Gram-negative bacteria was CRE (Carbapenem-Resistant Enterobacteria). The outcome of death was statistically significantly associated with patients who isolated carbapenem-resistant Gram-negative bacteria during ICU stay. Further studies should be periodically conducted in order to monitor changes in the microbiological profile and control the increase in antimicrobial resistance.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this article.

ETHICAL APPROVAL

This research belongs to an Umbrella Project approved by the Research Ethics Committee of the Federal University of Ceará/Walter Cantídio University Hospital, according to approval opinion number 3,697,674. The research was developed in accordance with the requirements of Resolution No. 466 of December 12, 2012, of the National Health Council (CNS) of the Ministry of Health, considering the respect for human dignity and the special protection due to participants in scientific research involving human beings.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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