Metallo-Beta-Lactamases: Epidemiological Profile and Clinical Outcome in Gram-Negative Bacteria

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ABSTRACT

Objectives: *This study seeks to describe the epidemiological profile of MBL-producing Gram-negative bacteria isolated from patients treated at the Walter Cantídio University Hospital (HUWC) in Ceará between January 2022 and December 2024.*
Methods: *This is a descriptive, retrospective study based on laboratory data obtained from HUWC. The samples were processed by automated methods and analyzed according to BrCAST protocols, including single samples per patient with MBL-producing microorganisms, analyzing clinical and microbiological variables and outcomes.*
Results: *A total of 133 infections caused by single strains were analyzed, of which 121 were MBL-producing only and 12 were dual carbapenemase-producing. Klebsiella pneumoniae was the most prevalent pathogen (74.4%), followed by Pseudomonas aeruginosa (5.3%). The NDM gene was identified in 77.4% of cases. Samples were mainly obtained from blood (43.6%) and urine (28.6%), with a higher frequency in the medical ward II B and ICU wards. The mortality rate among those infected was 43.6%. Universal resistance to ceftolozane-tazobactam and ceftazidime-avibactam antibiotics was observed, with greater sensitivity to polymyxin B (75.9%).*
Conclusions: *The high prevalence of multidrug-resistant strains, especially NDM-producing K. pneumoniae, associated with high mortality, highlights the severity of MBL infections. The results reinforce the need for constant microbiological surveillance, strict control of hospital infections, and rational use of antimicrobials to contain the spread of these strains, as well as the optimization of therapeutic protocols to reduce mortality.*

Keywords: *Carbapenems; Carbapenem-resistant Enterobacteriaceae; Microbiology.*

Introduction

Infectious diseases currently represent a major public health challenge, requiring health professionals to employ effective strategies for infection prevention and control[1]. Among the pathogens associated with these diseases, Gram-negative bacteria stand out, as they are responsible for a significant proportion of healthcare-associated infections (HAIs), contributing to increased morbidity and mortality among hospitalized patients[2].

Despite the effectiveness of antibiotics in controlling bacterial infections, the development of antimicrobial resistance by microorganisms has become a major challenge and has contributed to increased mortality among affected patients[3]. Antibiotic resistance can be acquired through several mechanisms, notably the production of enzymes capable of inactivating antimicrobial agents. To overcome this issue, antibiotics that are more effective have been developed to act against resistant bacteria, such as carbapenems. Antibiotics belonging to this class are highly potent and can withstand the

action of various inactivating enzymes, including extended-spectrum beta-lactamases (ESBLs)[3].

However, resistance to carbapenems has become a reality and a challenge for healthcare professionals[3]. Carbapenemases are enzymes that hydrolyze carbapenems and can facilitate the emergence of pan-resistant bacteria[4].

Carbapenemases are classified into three beta-lactamase classes (A, B, and D), with class B corresponding to metallo-beta-lactamases (MBLs). These enzymes require zinc ions at their active site to hydrolyze antibiotics[5]. MBLs are mainly found in some Enterobacterales species, Pseudomonas aeruginosa, and Acinetobacter spp. They are capable of hydrolyzing all beta-lactams except aztreonam. Consequently, infections caused by MBL-producing bacteria represent a major concern today[6].

The detection of bacterial resistance and identification of the underlying resistance mechanism are of fundamental importance in hospital care, strengthening Antimicrobial Stewardship Programs (ASP). This understanding enables comprehensive monitoring of the dissemination of multidrug-resistant strains and the implementation of strategies to prevent outbreaks[7],[8].

Furthermore, understanding resistance mechanisms allows for targeted and effective treatment, avoiding inappropriate and excessive antibiotic use that may otherwise increase selective pressure and resistance development[7],[8].

In this context, the present study aimed to describe the clinical and epidemiological profile of patients infected with MBL-producing Gram-negative bacteria at the University Hospital Complex of the Federal University of Ceará, seeking to understand how these infections affect patient outcomes.

Materials and Methods

This descriptive and retrospective study analyzed the clinical and epidemiological profile of patients infected with metallo-beta-lactamase (MBL)-producing microorganisms treated at the Walter Cantídio University Hospital (HUWC/UFC), part of the Brazilian Hospital Services Company (EBSERH) network. The study was approved by the hospital's Ethics Committee under protocol number 6,717,757, in accordance with Resolution No. 466 of December 12, 2012, of the Brazilian National Health Council[9].

Samples were collected in the hospital environment and processed by the institution's Microbiology Laboratory. Microorganism identification and antimicrobial susceptibility testing (AST) were performed using the automated Vitek-2® system (BioMérieux®, Marcy-l'Étoile, France), except for polymyxin B susceptibility, which was determined manually by broth microdilution. Results were interpreted according to the standards established by the Brazilian Committee on Antimicrobial Susceptibility Testing (BrCAST, 2025). Data were collected and managed using the REDCap electronic data capture tool.

Patients treated between January 2022 and December 2024 were included. Data collected included sex, age, type of biological sample, hospital ward, isolated microorganism, presence and classification of carbapenemase, antimicrobial susceptibility profile, treatment regimen, and clinical outcome. Only one culture per patient was included, selected randomly.

All data were organized in spreadsheets using Microsoft Excel® 2013. Categorical variables were expressed as absolute and relative frequencies. Statistical analyses included the chi-square test, Student's t-test, and binary logistic regression using IBM SPSS Statistics v.22, with $p < 0.05$ considered statistically significant.

Results

A total of 179 positive cultures for MBL-producing bacteria were identified, in addition to 15 bacteria producing dual carbapenemases (serine beta-lactamase and MBL genes). After removing duplicate cultures from the same patient, 133 reports remained, including 12 patients infected with dual-carbapenemase-producing strains and 121 infected with MBL-producing bacteria alone. Of these, 39 cases occurred in 2022, 52 in 2023, and 42 in 2024.

Among the 133 infected patients, 58 (43.6%) were female and 75 (56.4%) were male. Age ranged from 19 to 85 years, with a mean of 57.49 ± 17.13 years. Patients were divided into adults (≤60 years; n = 64, 48.1%) and elderly (>60 years; n = 69, 51.9%). A total of 75 patients (56.4%) were discharged, while 58 (43.6%) died. All of this data is represented in Table 1.

Table 1: Distribution of patients by gender, age group, and clinical outcome, treated between January 2022 and December 2024 at the Hospital Complex of the Federal University of Ceará (HUWC/MEAC).

Demographic characteristics	n	%
Gender		
Male	75	56,40
Female	58	43,60
Age group		
Adult (≤ 60 years)	64	48,10
Elderly (> 60 years)	69	51,90
Clinical outcome		
Discharge	75	56,40
Death	58	43,60
Total	**133**	**100**

Source: Authors

Patients were admitted to all HUWC units; however, the highest incidence of MBL-producing strains occurred in Medical Ward II B (22.6%) and the Intensive Care Unit (ICU) (18.8%). Blood (43.6%) and urine (28.6%) were the most frequent biological samples. Other wards that presented significant occurrences were Medical Ward II A (n = 20, 15.0%), medical ward I (n = 16, 12.0%), renal transplant surgical ward (n = 12, 9.0%), and operating room (n = 10, 7.5%). As for biological samples, the most prevalent were blood (n = 58, 43.6%), followed by urine (n = 38, 28.6%) and tracheal aspirate (n = 15, 11.3%). The complete distribution of patients by ward and sample is shown in Table 2.

Table 2: Distribution of patients by inpatient ward and biological sample, treated between January 2022 and December 2024 at the Hospital Complex of the Federal University of Ceará (HUWC/MEAC).

Epidemiological characteristics	n	%
Inpatient ward		
Medical Ward II B (General Medical Ward)	30	22,60
Intensive Care Unit (ICU)	25	18,80
Medical Ward II A (Cardiology/Pneumology)	20	15,00
Medical Ward I (Hematology/Rheumatology)	16	12,00
Kidney/Liver Transplant Surgery Ward	12	9,00
Surgical Center	10	7,50
Recovery Ward	6	4,50
General Surgical Ward	6	4,50
Kidney Transplant Ward	5	3,90
Bone Marrow Transplant	2	1,50
Hematology Clinic	1	0,80
Biological Sample		
Blood	58	43,60
Urine	38	28,60
Tracheal Aspiration	15	11,30
Ascites fluid	6	4,50
Abdominal fluid	5	3,80
Bronchoalveolar lavage	4	3,00
Tissue	3	2,30
Sputum	1	0,80
Bile	1	0,80
Catheter tip	1	0,80
Purulent secretion	1	0,80
Total	**133**	**100**

Source: Authors

Among isolates, 125 (93.9%) were Enterobacterales, with Klebsiella pneumoniae being the most representative (n = 99, 74.4%). The others were infected by Pseudomonas spp. species, with 7 (5.3%) being Pseudomonas aeruginosa and 1 (0.8%) being Pseudomonas mendocina. The NDM gene was detected in 103 (77.4%) cases, followed by IMP (n = 9, 6.8%) and VIM (n = 1, 0.8%) (Table 3).

Table 3: Distribution of isolates by species and resistance gene, obtained from January 2022 to December 2024 at the Hospital Complex of the Federal University of Ceará (HUWC/MEAC).

Microbiological characteristics	n	%
Species		
Klebsiella pneumoniae	99	74,40
Pseudomonas aeruginosa	7	5,30
Enterobacter cloacae	6	4,50
Escherichia coli	5	3,80
Providencia stuartii	4	3,00
Klebsiella oxytoca	3	2,30
Morganella morganii	2	1,50
Proteus mirabilis	2	1,50
Serratia marcescens	2	1,50
Citrobacter amalonaticus	1	0,80
Providencia rettgeri	1	0,80
Pseudomonas mendocina	1	0,80
Resistance Gene		
NDM	103	77,40
IMP	9	6,80
VIM	1	0,80
Indetermined	20	15,00
Total	**133**	**100**

Source: Authors

Regarding antimicrobial sensitivity profiles, the results were analyzed for the main antibiotics used in the therapeutic protocol for patients infected with carbapenem-resistant bacteria, namely Ceftolozane/Tazobactam (CTZ), Ceftazidime/Avibactam (CZA), Amicacin, Gentamicin, Aztreonam, and Polymyxin B. Among the results presented, it was observed that 100% of patients were carriers of strains resistant to CTZ and CZA. In contrast, polymyxin B was the antimicrobial with the highest percentage of sensitivity (n= 101, 75.9%). All results are shown in Table 4.

Table 4: Sensitivity profile of strains to the main antibiotics used in clinical practice, isolated from patients treated between January 2022 and December 2024 at the Hospital Complex of the Federal University of Ceará (HUWC/MEAC).

Antimicrobial sensitivity profile	Susceptible	Susceptible, increased exposure	Resistant	Not tested
	n (%)	n (%)	n (%)	n (%)
Antibiotic				
Ceftolozone-tazobactam	0 (0)	0 (0)	133 (100)	0 (0)
Ceftazidime-avibactam	0 (0)	0 (0)	133 (100)	0 (0)
Amicacin	42 (31,6)	9 (6,8)	82 (61,65)	0 (0)
Gentamicin	47 (35,35)	1 (0,75)	77 (57,9)	8 (6,0)
Polymyxin B	101 (75,9)	0 (0)	32 (24,1)	0 (0)
Aztreonam	5 (3,8)	2 (1,5)	46 (34,6)	80 (60,1)

Source: Authors

After performing the chi-square test, it was observed that the clinical outcome was associated with gender (p = 0.044) and inpatient wards (p = 0.010), indicating a higher death rate in female patients and in the Intensive Care Unit (ICU) and Medical Ward II B (Table 5). The other variables were not statistically significant when compared with the outcome.

Table 5: Relationship between clinical outcome and gender and sector of origin of patients treated between January 2022 and December 2024 at the Hospital Complex of the Federal University of Ceará (HUWC/MEAC).

Outcome associated factors[1]	Discharge n (%)	Death n (%)	Total n (%)
Inpatient ward			
Medical Ward II B (General Medical Ward)	13 (17,3)	17 (29,3)	30 (22,55)
Intensive Care Unit (ICU)	6 (8)	19 (32,75)	25 (18,8)
Medical Ward II A (Cardiology/Pneumology)	12 (16)	8 (13,8)	20 (15)
Medical Ward I	13 (17,3)	3 (5,2)	16 (12)
Kidney/Liver Transplant Surgery Ward	10 (13,3)	2 (3,4)	12 (9)
Surgical Center	7 (9,3)	3 (5,2)	10 (7,5)
Recovery Ward	2 (2,7)	3 (5,2)	6 (4,5)
General Surgical Ward	4 (5,4)	2 (3,4)	6 (4,5)
Kidney Transplant Ward	5 (6,6)	3 (5,2)	5 (4,75)
Bone Marrow Transplant	2 (2,7)	2 (3,4)	2 (1,5)
Hematology Clinic	1 (1,3)	0 (0)	1 (0,75)
Gender			
Male	48 (64)	27 (46,55)	75 (56,4)
Female	27 (36)	31 (53,45)	58 (43,6)
Total	**75 (56,4)**	**58 (43,6)**	**133 (100)**

[2]Chi-square test revealed p = 0.044 for association between gender and outcome, with 1 degree of freedom. [1]Chi-square test revealed p = 0.010 for association between sector and outcome, with 11 degrees of freedom.

Source: Authors

A binary logistic regression was performed to compare Medical Ward II B and the Intensive Care Unit (ICU) with Medical Ward I, where hematological patients are hospitalized. The regression confirmed an increase in the odds of death in these sectors by approximately 5.7 (OR: 5.667, p = 0.019) and 13.7 (OR: 13.722, p = 0.001) times, respectively.

In addition, another significant association was found between the sector of origin and the treatment used (p = 0.010), indicating greater use of the combination Ceftazidime/Avibactam/Aztreonam (CZA + AZT) in patients from Renal Transplant and Medical Ward I (Table 6).

Table 6: Relationship between treatment used and sector of origin of patients treated between January 2022 and December 2024 at the Hospital Complex of the Federal University of Ceará (HUWC/MEAC).

Inpatient ward	(CZA + AZT)[1] n (%)	(PB + AMC)[2] n (%)	Other n (%)
Medical Ward II B (General Medical Ward)	5 (16,7)	13 (21,7)	12 (27,9)
Intensive Care Unit (ICU)	5 (16,7)	18 (30)	2 (4,65)
Medical Ward II A (Cardiology/Pneumology)	2 (6,7)	9 (15)	9 (20,9)
Medical Ward I	7 (23,3)	8 (13,3)	1 (2,3)
Kidney/Liver Transplant Surgery Ward	6 (20)	2 (3,3)	4 (9,3)
Surgical Center	1 (33,3)	5 (8,3)	4 (9,3)
Recovery Ward	3 (10)	1 (1,7)	2 (4,65)
General Surgical Ward	0 (0)	1 (1,7)	5 (11,65)
Kidney Transplant Ward	1 (33,3)	1 (1,7)	3 (6,9)
Bone Marrow Transplant	0 (0)	2 (3,3)	0 (0)
Hematology Clinic	0 (0)	0 (0)	1 (2,3)
Total	**30**	**60**	**43**

Chi-square test revealed p = 0.010 for association between sector and treatment, with 26 degrees of freedom. 1CZA + AZT: Ceftazidime/Avibactam + Aztreonam. 2PB + AMC: Polymyxin B + Amicacin.

Source: Authors

Discussion

Between 2022 and 2024, 133 patients were identified as carriers of strains capable of producing MBLs. During this same period, the laboratory provided care to a total of 5,492 patients in the hospital and outpatient clinic, of whom 2,057 had positive cultures. In other words, 37.45% of patients were affected by infections, and among these, there was a prevalence of MBL-producing strains of 6.46%.

This rate was higher than that reported in similar studies, which found that 4.5% of the analyzed strains were resistant to carbapenems[10].

Other investigations in this field did not detect the presence of NDM among multidrug-resistant Gram-negative bacteria[11]. Additionally, a multicontinental study reported an overall rate of 4.5% of carbapenem-resistant Enterobacteriaceae (CRE), with a higher prevalence of 5.8% observed in Latin America[12].

Despite the worrying result, it is plausible that this increase can be attributed to the passage of time, due to the significant increase in multidrug-resistant bacteria in recent years[13,14]. A marked increase of approximately tenfold in NDM genes was observed between 2015 and 2020 in another study[14]. However, this observation was not maintained in the present study, since, although there was a significant increase in infections by MBL-producing strains from 2022 to 2023, there was a decrease from 2023 to 2024.

Infections predominantly affected male patients, representing 56.4% of the total. However, mortality was higher in females. These findings are consistent with other similar studies, which also indicate a greater predisposition of males to infections, but greater fragility in females. Another factor that has been shown to increase susceptibility and fragility to infections, according to studies, is age. However, the present study did not identify a significant difference in infections and death rates between populations under and over 60 years of age[15].

The predominance of the NDM gene as the main resistance mechanism found among isolates corroborates the literature, which points to this enzyme as one of the main factors responsible for the global emergence of pan-resistant strains, with the MBL gene being the most common[3,5]. The widespread dissemination of strains carrying this gene in the hospital environment is a cause for concern, given its capacity for horizontal transmission by plasmids, which increases the speed of resistance propagation among different bacterial species[5,16].

The predominance of *Klebsiella pneumoniae* (74.4%) as the main producer of MBLs is consistent with previous studies, which point to this bacterium as one of the major producers of MBLs[6,17].

Furthermore, the higher prevalence of these infections in the Medical Ward II B (22.6%) and ICU (18.8%) sectors is a cause for concern when combined with the results shown by binary logistic regression, in which the risk of death in these sectors was found to be higher. Given the above, it can be inferred that these data are consistent with other studies in the literature, which demonstrate that admission to the intensive care unit is a risk factor for the development of infections by resistant bacteria. Other risk factors include procedures such as mechanical ventilation and intubation, which are highly prevalent in Medical Ward II B, where patients with respiratory problems are concentrated[18,19].

The antimicrobial susceptibility profile showed 100% resistance to CTZ and CZA, which is consistent with the literature, since these antibiotics do not inhibit MBL[20,21]. However, the combination with aztreonam restores the efficacy of CZA, making it a viable treatment option[22].

Aminoglycosides, especially amicacin, are also a promising option for combating such strains, which makes them frequently used in the treatment of patients carrying multidrug-resistant bacteria. Despite this, the effectiveness of treatment may be related to the sensitivity of the strain to the antibiotics in question. Finally, polymyxin B, despite being the antibiotic that showed the greatest sensitivity, has been shown in other studies to have limited action in monotherapy regimens. However, it has synergistic activity with other antibiotics, making it an effective alternative when used in combination[3,23].

The correlation between the therapeutic plan employed and the sector of origin probably stems from the protocols established by the hospital, which provides priority care to hematological patients in critical condition. In this context, studies show that CZA-based therapies have shown superior results to polymyxin B-based therapies in the treatment of patients affected by infections caused by CREs, making it the preferred treatment for these patients[24,25]. In addition, polymyxin B is known to be nephrotoxic, making treatment with this drug unfeasible in patients undergoing kidney transplantation[26].

Furthermore, it is important to note that, for this study, data were collected only from strains with phenotypically detected MBL production. This intrinsic limitation in the study restricts the generalization of the results, since MBL production by many strains of *P. aeruginosa* and, especially, *Acinetobacter* sp. strains could only be detected by molecular biology methods.

Moreover, all results presented in this study, derived from the routine of the hospital's clinical microbiology laboratory, are used by the team as a basis for implementing effective PGA and clinical pharmacy actions, thus helping and guiding therapy in a more assertive manner, in addition to being useful for creating indicators as a way to assess the profile of infections in the hospital and the use of antibiotic therapy by hospitalized patients.

Conclusion

Given the above, it can be inferred that the problem of bacterial resistance is not limited to the treatment of infections but involves a complex and multifactorial challenge, ranging from epidemiological surveillance to the development of new antimicrobial therapies. Thus, this study seeks to contribute to the improvement of local knowledge about the resistance profile and may support

In the context of HUWC, the study indicates the need for more careful attention to patients admitted to the ICU and Medical Ward II B. In addition, Ceftazidime-avibactam was used in only 30 of the 133 patients, revealing a failure of public infrastructure, since this drug, despite showing greater efficacy, is a less accessible treatment.

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