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ORIGINAL ARTICLE

Retrospective study of the impact of KPC and NDM genes on multidrug-resistant infections: in a reference hospital in Piauí, Brazil.

Estudo retrospectivo do impacto dos genes KPC e NDM em infecções multirresistentes: em um hospital de referência no Piauí, Brasil.

Estudio retrospectivo del impacto de los genes KPC y NDM en infecciones multirresistentes: en un hospital de referencia en Piauí, Brasil.

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ABSTRACT

Background and Objectives: *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metallo-beta-lactamase (NDM) carbapenemases confer resistance to last-line antibiotics, compromising treatment and worsening clinical outcomes. This retrospective and descriptive study aimed to analyze the frequency of multidrug-resistant bacteria in cultures from patients admitted to a reference hospital in Piauí, Brazil, and their correlation with patient outcomes, including affected hospital sectors, clinical progression, and length of stay. **Methods:** Conducted in a reference tertiary hospital and through data analysis covering the period from January 2021 to December 2022, it highlights the prevalence and resistance mechanisms of bacterial species, with an emphasis on the KPC and NDM genes. **Results:** KPC was predominantly found in *Pseudomonas aeruginosa* and *K. pneumoniae*, whereas NDM was mainly detected in *K. pneumoniae* and *Serratia marcescens*. Some species, particularly *K. pneumoniae*, exhibited dual resistance genes. The study revealed higher mortality rates when both KPC and NDM genes were present: 45.83% for KPC, 43.75% for NDM, and 65.71% for infections with both genes. It also explored hospital stay lengths, showing KPC infections averaged 58.9 days, NDM infections 69 days, and dual gene infections 49 days. **Conclusion:** This research provides critical insights into the challenges of antibiotic-resistant organisms in hospitals, underscoring the need for effective patient management and resource allocation strategies. To the best of our knowledge, this study uncovers the first documented cases of NDM gene infections in Piauí.

Keywords: *Antibiotic resistance. Resistance genes. Klebsiella pneumoniae. Outcome Assessment. Health Care.*

RESUMO

Justificativa e Objetivos: As carbapenemases *Klebsiella pneumoniae* carbapenemase (KPC) e metalo-beta-lactamase de Nova Delhi (NDM) conferem resistência a antibióticos de última linha, comprometendo o tratamento e agravando os desfechos clínicos. Este estudo retrospectivo e descritivo teve como objetivo analisar a frequência de bactérias multirresistentes em culturas de pacientes internados em um hospital de referência no Piauí, Brasil, e sua correlação com os desfechos dos pacientes, incluindo setores afetados, evolução clínica e tempo de internação. **Métodos:** Realizado em um hospital terciário de referência e por meio de análise de dados do período de janeiro de 2021 a dezembro de 2022, o estudo destaca a prevalência e os mecanismos de resistência das espécies bacterianas, com ênfase nos genes KPC e NDM. **Resultados:** O mecanismo de resistência KPC foi predominantemente encontrado em *Pseudomonas aeruginosa* e *K. pneumoniae*, enquanto o NDM foi identificado principalmente em *K. pneumoniae* e *Serratia marcescens*. Algumas espécies, particularmente *K. pneumoniae*, exibiram genes de resistência dupla. O estudo revelou taxas de mortalidade mais altas quando ambos os genes KPC e NDM estavam presentes: 45,83% para KPC, 43,75% para NDM e 65,71% para infecções com ambos os genes. A pesquisa também explorou a duração das internações hospitalares, mostrando que infecções por KPC tiveram uma média de 58,9 dias, infecções por NDM 69 dias e infecções com genes duplos 49 dias. **Conclusão:** Esta pesquisa fornece insights críticos sobre os desafios dos organismos resistentes a antibióticos em hospitais, sublinhando a necessidade de estratégias eficazes de gerenciamento de pacientes e alocação de recursos. Até onde sabemos, este estudo revela os primeiros casos documentados de infecções pelo gene NDM no Piauí.

Descritores*: Resistência a antibióticos. Genes de resistência. Klebsiella pneumoniae. Avaliação de Resultados em Cuidados de Saúde. Atenção à Saúde.*

RESUMEN

Justificación e Objetivos: Las carbapenemasas *Klebsiella pneumoniae* carbapenemasa (KPC) y metalo-beta-lactamasa de Nueva Delhi (NDM) confieren resistencia a los antibióticos de última línea, lo que compromete el tratamiento y empeora los resultados clínicos**.** Este estudio retrospectivo y descriptivo tuvo como objetivo analizar la frecuencia de bacterias multirresistentes en cultivos de pacientes ingresados en un hospital de referencia en Piauí, Brasil, y su correlación con los desenlaces de los pacientes, incluyendo los sectores afectados, la evolución clínica y el tiempo de estancia. **Métodos:** Realizado en un hospital terciario de referencia y mediante análisis de datos del período de enero de 2021 a diciembre de 2022, el estudio destaca la prevalencia y los mecanismos de resistencia de las especies bacterianas, con énfasis en los genes KPC y NDM. **Resultados:** KPC se encontró predominantemente en *Pseudomonas aeruginosa* y *K. pneumoniae*, mientras que NDM se identificó principalmente en *K. pneumoniae* y *Serratia marcescens*. Algunas especies, particularmente *K. pneumoniae*, exhibieron genes de resistencia dual. El estudio reveló tasas de mortalidad más altas cuando estaban presentes ambos genes KPC y NDM: 45,83% para KPC, 43,75% para NDM y 65,71% para infecciones con ambos genes. También se exploraron las duraciones de las estancias hospitalarias, mostrando que las infecciones por KPC tuvieron un promedio de 58,9 días, las infecciones por NDM 69 días y las infecciones con genes duales 49 días. **Conclusión:** Esta investigación proporciona información crítica sobre los desafíos de los organismos resistentes a antibióticos en hospitales, subrayando la necesidad de estrategias efectivas de manejo de pacientes y asignación de recursos. Hasta donde sabemos, este estudio revela los primeros casos documentados de infecciones por el gen NDM en Piauí.

Palabras Clave: *Resistencia a antibióticos. Genes de resistencia. Klebsiella pneumoniae. Evaluación de Resultado en la Atención de Salud. Atención a la Salud.*

INTRODUCTION

Multidrug-resistant organisms are defined as species with acquired insensitivity to at least one agent in 3 or more different classes of antimicrobials, responsible for an increasing number of hospital- and community-acquired infections.[1] In this context, there is an impact on mortality rates, leading to increased treatment costs, hospitalisation, diagnostic tests, and therapeutic challenges. It is estimated that approximately 20% to 30% of hospital-acquired infections in developing countries are associated with bacteria resistant to multiple classes of antimicrobials, which directly impacts mortality rates and increases the costs of treatment, hospitalization, diagnostic testing, and therapeutic challenges.[1]

These infections are treated with antimicrobials; however, the excessive, inappropriate, and unnecessary use of these agents has contributed to high bacterial resistance rates, progressively rendering treatments ineffective.[2,3] A significant milestone was the spread of the pandemic caused by SARS-CoV-2, where the widespread use of antimicrobial therapies as part of the clinical care package was observed, increasing resistance rates.[4-7]

In Brazil, Gram-negative bacilli producing the NDM-1 enzyme have been detected with alarming frequency since 2013, with 81 clinical isolates reported across nine states and 11 bacterial species—all confirmed as multidrug-resistant.[8] Colistin and amikacin remain among the few antibiotics with activity against these strains, highlighting the scarcity of effective therapeutic options.

Monitoring and early intervention with appropriate treatment in healthcare units are fundamental strategies to prevent and control the spread of these bacteria.[9] Thus, epidemiological surveillance and mandatory reporting of suspected cases of healthcare-associated infections become essential mechanisms for the control of Healthcare-Associated Infections (HAIs) enabling the investigation of outbreak causes, the identification of locations with higher occurrences of these infections, and the prevention of new cases.[10-12]

In light of the above, the present study aimed to analyze the frequency of multidrug-resistant bacteria in cultures from patients at a reference hospital in Piauí, Brazil, and their correlation with patient outcomes, including affected hospital sectors, clinical progression, and length of stay.

Given the above, this study aimed to describe the frequency of multidrug-resistant bacteria isolated from clinical cultures of patients admitted to a referral hospital in the state of

Piauí, Brazil, and to examine their correlation with patient outcomes, including affected hospital sectors, clinical evolution, and length of hospital stay.

METHODS

Study Design

This was a retrospective descriptive study conducted over 2 years, based on records from January 2021 to December 2022. The primary objective of this investigation was to elucidate the frequency of multidrug-resistant bacteria in the mentioned healthcare unit, analyse the hospitalisation time of diagnosed patients, and identify the most affected sectors.

Study Setting

The research was conducted at the University Hospital of the Federal University of Piauí, covering the pharmacy and microbiology laboratory sectors. It is noteworthy that this hospital is a tertiary referral centre in the state, offering both outpatient and inpatient services, with a total of 190 beds, incorporating clinical and surgical care in regular and intensive care units. The institution is structurally organized into four inpatient nursing stations, an outpatient care area, and an Intensive Care Unit (ICU). Nursing Station 1 is dedicated to orthopedic and neurosurgical patients; Nursing Station 2 focuses on oncology patients; Nursing Station 3 serves internal medicine (clinical) patients and Nursing Station 4 accommodates surgical patients. Additionally, during the Covid-19 pandemic, a separate ICU was established for patients with SARS-CoV-2 infection.

The study covered all inpatient units (including wards and ICUs) where cultures were routinely collected and processed by the microbiology laboratory.

Study Population

All hospitalized patients from whom microbiological cultures were collected and who had confirmed hospital-acquired infections caused by multidrug-resistant bacteria were eligible for inclusion regardless of age or sex, as long as they met the criteria for nosocomial infection (i.e., culture collected ≥48 hours after admission).

Inclusion Criteria

Patients admitted to HU-UFPI between January 2021 and December 2022 who had a positive culture for multidrug-resistant bacteria, with microorganisms identified as hospital-acquired (cultures collected ≥48 hours after admission).

Exclusion Criteria

Community-acquired infections, defined as positive cultures obtained within the first 48 hours of admission; duplicate isolates, considering only the first isolate of each species per patient; and cultures with insufficient data for analysis, such as missing information on clinical evolution or sector of admission. No sampling strategy was applied, as all eligible cases during the study period were included, and no patient-identifiable information was used at any stage of data collection.

Data Collection

Microbiological data are routinely collected from patient records, laboratory test results, and local surveillance systems. Samples are collected and sent to the microbiology laboratory, where it is inoculated into culture media and analysed by the VITEK® 2 COMPACT, an automated system for routine microbial identification and antibiogram testing, standardised according to BrCAST based on the identified species.[13] These data are linked to the patient's history, resulting in a spreadsheet with diagnostic information that will be manually entered into the hospital's IT system. The investigation of resistance genes is carried out for five types: KPC (*Klebsiella pneumoniae* carbapenemase), NDM (New Delhi metallo-beta-lactamase), OXA-48 (OXA-48 beta-lactamase), IMP (Imipenemase), and VIM (Verona imipenemase) through immunochromatographic testing (VITEK®2 COMPACT - bioMérieux, France). Although the detection of resistance genes included KPC, NDM, OXA-48, IMP, and VIM, only KPC- and NDM-producing isolates were identified during the study period. No samples tested positive for OXA-48, IMP, or VIM. Therefore, while all carbapenemases were considered eligible for inclusion, the final dataset contained only cases involving KPC and NDM.

Data such as admission location, identified microorganism, case outcome, culture site, among others, were processed to generate overall secondary indicators, including: i) prevalence of microorganisms in the hospital, ii) outcomes of patients with the clinical condition of multidrug-resistant infection, iii) number of hospitalisation days when an infection is diagnosed, iv) mortality rate, and v) sector with the highest number of identified cases.

To avoid data duplication, only the first isolate per species per patient was considered. Secondary infections or subsequent isolates from the same hospitalization were excluded.

Data Analysis

Data analysis was exclusively descriptive. Data were extracted from tables provided by the hospital's microbiology department and manually compiled into Microsoft Excel® 2019 spreadsheets. Categorical variables, such as bacterial species, presence of resistance genes, hospitalization unit, and patient clinical outcomes, were analyzed using simple sums and expressed as absolute and relative frequencies (n and %). Confidence intervals for proportions were calculated using the Agresti–Coull method. No hypothesis testing was performed, as the study was not inferential in nature.

The data processing was carried out using the R programming language.

Ethical Considerations and Other Information

The project was duly reviewed and approved by the Ethics Committee of HU-PI under authorisation number 66872123.6.0000.8050. During the preparation of this work the authors used ChatGPT-3.5 as a writing assistance tool. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

RESULTS

The study assessed the prevalence of resistant bacterial infections and the distribution of resistant species among 187 patients admitted to the hospital from January 2021 to December 2022. Among the 187 samples that received such a diagnosis, urine culture yielded 62 positive results, while blood culture recorded 57, being the collection sites with the highest number of diagnoses (Table 1). In 2021, a higher prevalence is evident with 113 cases compared to 2022, which had only 74 identified cases (Figure 1).

Table 1. Type of isolated culture and number of bacterial samples with any type of resistance gene.

Bacteria found in the type of culture	Number of cases found
Urine culture	62
Blood culture	57
Wound secretion	31
Tracheal aspirate	6
Rectal swab	6

Stool culture	5
Catheter tip	4
Cerebrospinal fluid (CSF)	3
Ascitic fluid	1
Bacteriological	1
Abdominal collection	1
Tendon	1
Pleural effusion	1
Bronchoalveolar lavage (BAL)	1
Tissue biopsy	1

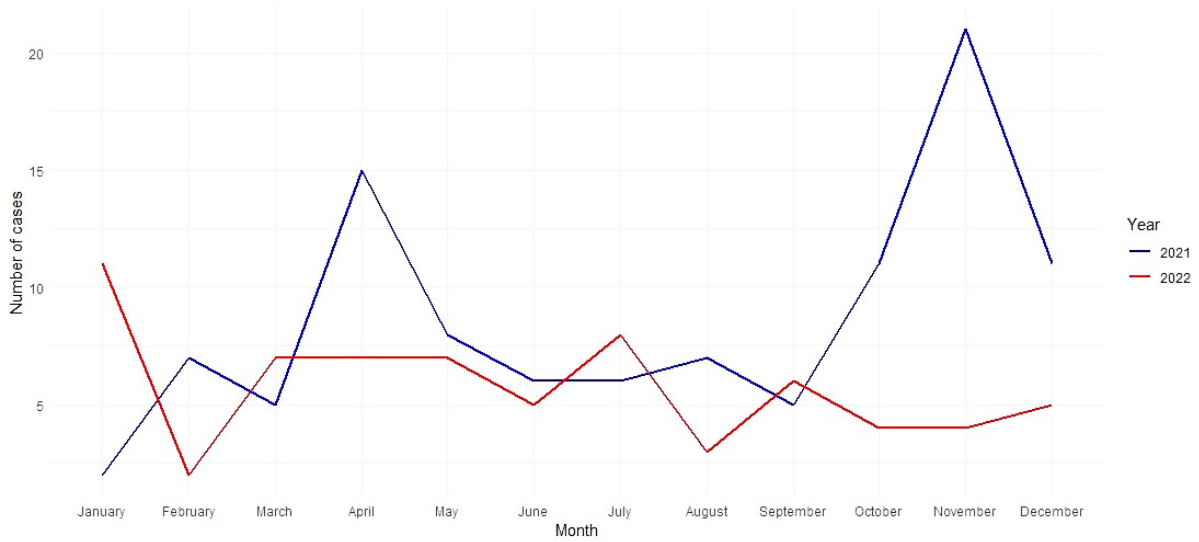

Figure 1. Number of Identified Cases of Multidrug-Resistant Bacteria. Monthly distribution of identified cases of multidrug-resistant bacteria at the Piauí University Hospital in 2021 and 2022.

Nursing Station 3 allocates patients from the medical clinic, and among all stations, it is the one that yielded the highest number of positive results for multidrug-resistant infections, totaling 59 identified patients. The ICU, on the other hand, is the location with the highest prevalence of this clinical condition, registering 61 cases in the investigated years, highlighting the need for specific measures for prevention and control, particularly in environments with critically ill patients.

The categorisation of bacterial species into different resistance mechanisms demonstrated that the KPC gene was present in the following species: *Pseudomonas aeruginosa* with a total of 24 cases, along with *K. pneumoniae* with a total of 20 cases, making the two species the most prevalent, followed by the species *Serratia marcescens* (2 cases), *Proteus hauseri* (1 case), *Escherichia coli* (1 case) and *Citrobacter koseri* (1 case) with a

lower prevalence of this resistance enzyme (Figure 2). The NDM gene was found in the following species: *K. pneumoniae* with a total of 79 cases , being the most prevalent, followed by *S. marcescens with of 7 cases*, and the species *Enterococcus faecium* (1 case), *Enterococcus spp.* (2 cases), *Enterobacter cloacae* (2 cases) and *K. ozaenae* (1 case) also found with the gene but in smaller quantities (Figure 2). Importantly, a single patient could harbour isolates carrying more than one resistance gene, meaning that cases are not mutually exclusive across resistance mechanisms.

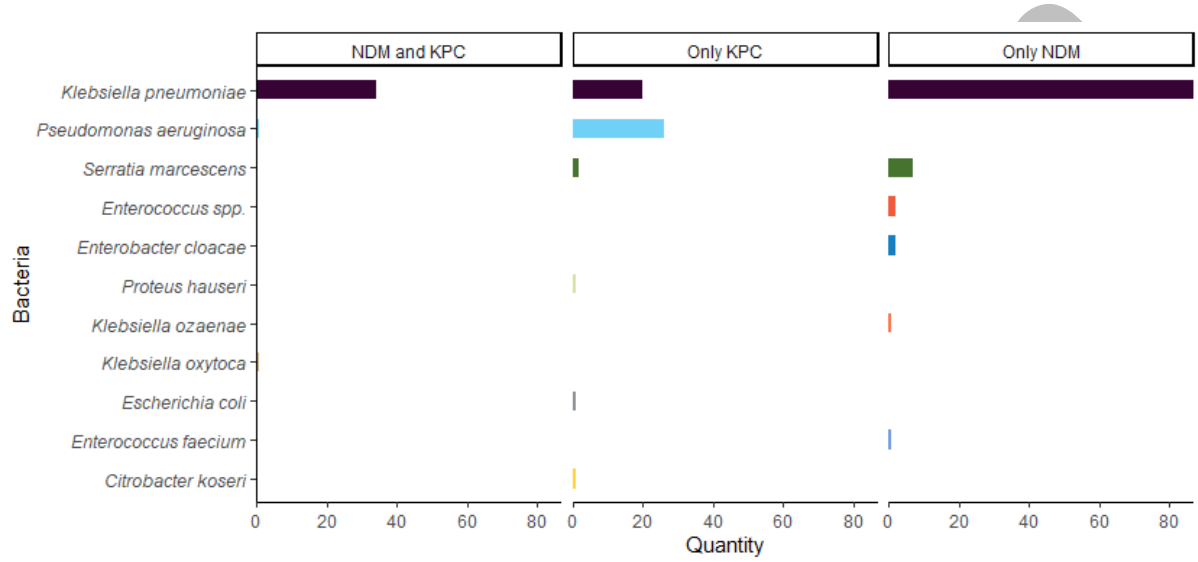

Figure 2. Prevalence of bacteria by type of resistance gene. Quantity of bacterial species found separated by type of resistance mechanism, being with only KPC (enzyme that confers resistance to carbapenems), only with NDM (enzyme belonging to the class of metallo-beta-lactamases that confers resistance to various antimicrobials, including carbapenems), and microorganisms that have both types of genes together.

In the studied samples, it was possible to verify that some species contain both resistance genes, conferring a high degree of resistance. The most prevalent species with both resistance genes was *K. pneumoniae* with a total of 20 cases, followed by *P. aeruginosa* and *K. oxytoca*, with at least one case of each species (Figure 2).

The progression of patients according to the resistance gene was also investigated. Analysing the investigated cases, the mortality rate was observed, where, upon acquiring KPC, the mortality rate was 45.83% [32.6% - 59.7%]. Among cases with the NDM gene, the mortality rate was 43.75% [34.3% - 53.7%]. When analysing cases where both resistance genes were present in the same infection, the chance of progressing to death increased to 65.71% [49.1% - 79.2%], highlighting a higher mortality rate and worse outcome for this type of infection (Figure 3).

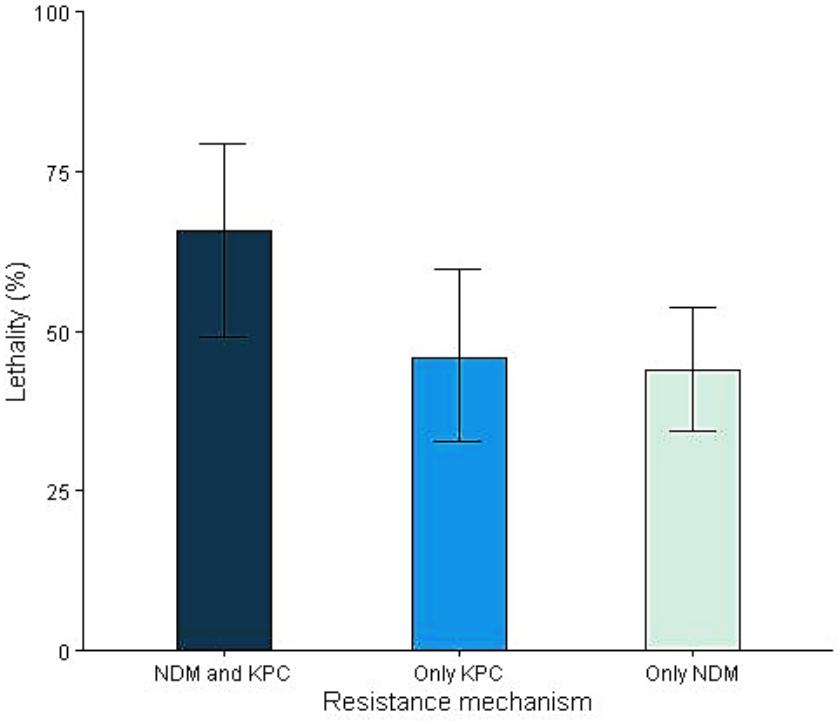

Figure 3. Mortality Rates by Resistance Gene. Lethality (%) among hospitalized patients, according to the type of investigated resistance gene.

Additionally, it was possible to analyse the length of hospital stay according to the type of acquired infection (Figure 4). KPC exhibited the highest number of cases with an average hospitalisation period of 59 days [34.5 - 73], when the condition progressed to hospital discharge and 51 days [29.5 - 75] for cases that evolved to death. In the case of NDM, the average length of hospitalisation varies according to the patient's prognosis; when linked to hospital discharge, the average time is 69 days [36 - 85.25], while for cases resulting in hospital death, the average is 46 days [30.25 - 54]. On the other hand, when investigating infections with both resistance genes, the average length of hospital stay was 49 days [24.75 - 78] for cases that were discharged and 50 days [21.5 - 85] for those that resulted in death (Figure 4).

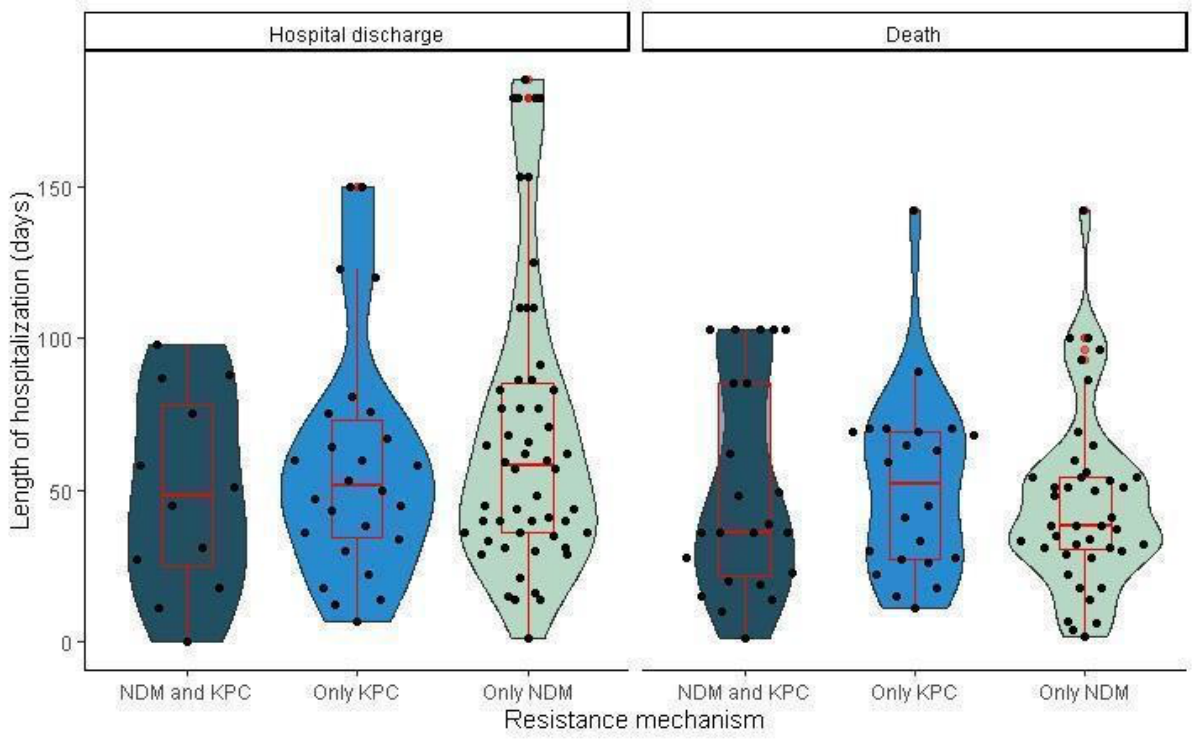

Figure 4. Average Length of Hospital Stay. Average number of days patients were hospitalized based on the type of resistance gene and patient outcome (discharge or death).

DISCUSSION

In this study, it was possible to identify a higher chance of death when a species acquires both KPC and NDM strains, which may be related to the restriction that the patient faces regarding treatment alternatives for the condition. Furthermore, we had a greater number of cases reported in 2021, with a high prevalence of *K. pneumoniae*, containing the KPC resistance gene and an average number of days of hospitalisation reaching 58.9 days.

The diagnosis of an infectious condition is based on clinical, epidemiological, and laboratory results. Among these epidemiological characteristics, both the most prevalent bacteria and the sensitivity profile of the hospital's microorganisms significantly contribute to the formulation of empirical treatment protocols when the patient's health status cannot afford the wait for culture test results.[14] This underscores the fundamental importance of establishing a comprehensive database with the hospital's or region's historical clinical data. Our data play a crucial role in helping to develop effective empirical treatment protocols.

It is worth highlighting the high influence of hospital infections on management costs, as they drastically impact the period of hospitalisation. For example, the average length of stay researched within the hospital varies according to the type of infection, reaching, in some cases, such as bacteria with the NDM gene, around 69 days. During this period, considering the length

of stay, the consumption of antibiotics, the duration of isolation, laboratory tests, and human resources, these are all costs generated by this clinical condition. Reducing infection rates can play a fundamental role in mitigating the economic challenges faced by public hospitals, in addition to benefiting the reduction of the patient's hospitalisation time, increasing bed turnover rates, and the availability of places in ICUs.

Since the 1980s, pharmaceutical companies have gradually shifted focus from antimicrobial research to concentrate on drug therapy for chronic non-communicable diseases.[15] Carbapenems, such as meropenem and imipenem, are a class of beta-lactam antibiotics with a broad spectrum of action, being effective against many gram-positive and gram-negative bacteria and generally reserved for the treatment of severe infections.[16,14] Due to increasing resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides, carbapenems have progressively established themselves as the main option for potentially fatal infections by multidrug-resistant *E. coli*.[16] As carbapenems become an increasingly common therapeutic choice, it is crucial to establish monitoring programmes to prevent the emergence and spread of resistance to these drugs, especially as the emergence of new antibiotics has been increasingly scarce.

Both KPC and NDM genes are carbapenem resistance genes; they encode an enzyme capable of hydrolysing beta-lactam antibiotics, including carbapenems. KPC-like enzymes are capable of hydrolysing all β-lactams, and strains harbouring this gene often acquire resistance to fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole, creating multidrug-resistant organisms.[17] On the other hand, bacteria carrying the NDM enzyme are highly transmissible and, due to their dissemination through environmental sources in community settings in low-income countries, they are currently considered endemic worldwide. Treatment becomes a challenge due to the limited availability of effective antimicrobials for these clinical conditions, sometimes requiring a combination of antimicrobials to obtain an efficient result.[15] However, this increases the risk of side effects and the possibility of selecting new resistant strains.[18] Therefore, the presence of both strains increases the patient's morbidity and mortality.

Regarding prevalence, the results found showed a high prevalence of *K. pneumoniae* in the three investigated forms of resistance. This is the most common species found in hospital infections, especially in intensive care units and in patients with compromised immune systems. This is partly due to its ability to colonise hospital surfaces and survive in these environments for long periods.[19] Infections occur due to an imbalance between the host's immune defences and the pathogen, which, upon invading the patient, trigger local reactions

that initiate the infectious process. In patients hospitalised in the ICU, the risk of this imbalance is much higher due to underlying conditions, compromised immunity, extensive use of antibiotics, and exposure to invasive devices. The invasive procedures often used for treatment, such as tracheal intubation, mechanical ventilation, and intravascular catheters, become susceptible surfaces for the colonisation of enterobacteria, justifying this increased vulnerability to nosocomial infections in ICU patients.[20] Examples of this include bloodstream infections by bacteria and urinary infections, which are commonly related to catheter use. [20]

In addition to the ICU, Nursing Station 3, responsible for medical clinic patients, also had a notably high prevalence of multidrug-resistant infections, with 59 cases identified during the study period. This station is the only one equipped with isolation beds, which likely contributes to the higher absolute number of cases, as these beds are designated for patients with known or suspected resistant infections. The high number of infections can also be attributed to the profile of patients admitted to this unit: frequently polymorbid, elderly, or immunosuppressed, with longer hospital stays and greater exposure to antibiotics—well-known risk factors for colonization and infection by resistant pathogens. [1] This reinforces the importance of infection control protocols in clinical wards.

Another data point studied was that, when comparing the years 2021 and 2022, a significant reduction in the number of cases presented with multidrug-resistant infection was suggested, going from 113 patients to 74 patients in 2022. In this last year, Brazil began its vaccination campaign against Covid-19 in the second half of January 2021, increasing the vaccination rate in the country.[21] As already reported in other studies, individuals who were not fully vaccinated or who did not receive any vaccine against Covid-19 had an excess risk of hospitalisation and death from the disease.[22] In this context, the introduction of the vaccine triggered a significant transformation in the patterns of hospital admissions, resulting in a notable reduction in the number of infections, justifying this reduction in cases.[23]

This study provides unprecedented data on the epidemiology of multidrug-resistant bacteria in the state of Piauí, Brazil, filling an important gap in national surveillance. To our knowledge, existing research on the distribution of NDM-1-producing Gram-negative bacteria in the Brazilian clinical setting did not include data from the state of Piauí. [24]

Our study has some limitations. First, the hospital only evaluates specific resistance genes—NDM, KPC, OXA-48, IMP, and VIM—and restricts its analysis to bacteria, disregarding other resistant microorganisms. Furthermore, it was not possible to identify any readmissions of patients to other healthcare institutions after their initial hospitalization. The high prevalence of *K. pneumoniae* and the identification of resistance genes such as NDM,

KPC, and dual combinations highlight a critical scenario for infection control and antimicrobial stewardship. The findings reveal a worrying association between the presence of these genes and adverse clinical outcomes, including high mortality rates and reduced hospital stays resulting from death. The detection of combined resistance genes further highlights the need for targeted interventions, given their clinical impact.

Although the analysis was limited to bacterial isolates, the data reinforce the urgent need for continued molecular surveillance, expanded rapid diagnostic capabilities, and strengthened regional health monitoring systems. Furthermore, the limited scope of genotypic testing in the hospital setting highlights the importance of expanding molecular diagnostics to encompass other emerging determinants of resistance and neglected microbial species.

This contribution is crucial to filling existing gaps in understanding the spread of these resistant strains in the Brazilian clinical setting. This information may be useful for research aimed at improving antimicrobial stewardship and developing effective strategies to control the spread of resistant bacteria.

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Ruana Stephany Macedo Santos contributed to the literature review, writing of the abstract, introduction, methodology, discussion, interpretation and description of the results, preparation of tables, conclusions, revision, and statistical analysis. **Eduardo Lima de Sousa** contributed to project administration, literature review, writing of the abstract, introduction, methodology, discussion, interpretation and description of the results, conclusions, revision, and statistical analysis. **Thallyta Maria Tavares Antunes** contributed to writing of the abstract, revision, and statistical analysis. **José Felipe Pinheiro do Nascimento Vieira** contributed to writing of the abstract, revision, and statistical analysis. **Samara Belchior Gaído** contributed to writing of the abstract, revision, and statistical analysis. **Bruno Guedes Alcoforado Aguiar** contributed to project administration, literature review, writing of the abstract, introduction, methodology, discussion, interpretation and description of the results, conclusions, revision, and statistical analysis.

All authors approved the final version to be published and are accountable for all aspects of the work, including ensuring its accuracy and integrity.