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# Prevalence of β-lactamases and carbapenemases in cultures of kidney recipients treated at a university hospital in Ceará

**Antonia Carolaynne LIMA[1], Andreza de Araujo ANDRADE[1], Thaynara Carvalho de FREITAS[1], Fernando de Castro PEDROZA[1], Ana Beatriz RODRIGUES[1], Glaydiane Alves de SOUSA[1], Lizandra Máximo de OLIVEIRA[1], Denis Farias de CASTRO[2], Henry Campos REIS[1], Alene Barros de OLIVEIRA[1], Alexsandra Nunes PINHEIRO[1]**

[1]Hospital Universitário Walter Cantídio, Ceará. [2] Universidade Federal do Rio Grande do Norte, Rio Grande do Norte.

Corresponding author: Lima AC, acarolaynne@gmail.com

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## Abstract

**Objective:** The present study aimed to identify the prevalence of β-lactamases and carbapenemases in cultures of kidney recipients treated at a university hospital in Fortaleza, Ceará. **Methods**: This is a descriptive and retrospective study, carried out between January 2017 and December 2020 at a university hospital in Fortaleza, Ceará. Patients were included in the study, admitted to the renal transplant ward (12 beds), monitored by pharmacists from the *"Antimicrobial Stewardship Program"* (ASP) and using antimicrobials standardized in the institution as a therapeutic reserve for at least minimum 48 hours. **Results:** Male patients prevailed (53.2%), clinical outcome of discharge and death in the total of both sexes was 96.5% and 3.5% respectively. A total of 684 cultures were analyzed, but only 166 had growth of microorganisms, being 9 of fungal nature, 34 gram-positive bacteria and 123 gram-negative bacteria. Among the isolates, the highest prevalence was of *Klebsiella pneumoniae* 39.0% (n=47), with 54.3% (n=19) bacteria producing extended spectrum beta-lactamases (ESBL) and 88.2% (n= 15) carbapenem-resistant enterobacteriaceae (ERC) and regarding the types of culture, a greater number of urine cultures were observed (57.7%). **Conclusions:** A high prevalence of *Klebsiella pneumoniae* was observed, and it was also the most frequent microorganism in ESBL and ERC. Infections after kidney transplantation are causes of significant morbidity and mortality, and often difficult to diagnose in immunosuppressed patients, it is interesting that the rational use of antimicrobials is well established, considering that the more exposure to the use of these drugs, the favoring of the selection of multidrug-resistant strains.

**Keywords:** kidney transplantation; bacterial infections; bacterial resistance to multiple drugs.

# Prevalência de β-lactamases e carbapenemases em culturas de receptores de rim atendidos em um hospital universitário do Ceará

## Resumo

**Objetivo:** O presente trabalho teve por objetivo identificar a prevalência de β-lactamases e carbapenemases em culturas de receptores de rim atendidos em um hospital universitário de Fortaleza, Ceará. **Métodos:** Trata-se de um estudo descritivo e retrospectivo, realizado entre janeiro de 2017 a dezembro de 2020 em um hospital universitário de Fortaleza,Ceará. Foram incluídos no estudo pacientes internados na enfermaria de transplante renal (12 leitos), acompanhados pelos farmacêuticos do "*Antimicrobial Stewardship Program"* (ASP) e em uso de antimicrobianos padronizados na instituição como de reserva terapêutica por no mínimo 48 horas. **Resultados:** Prevaleceram pacientes do sexo masculino (53,2%), desfecho clínico de alta e óbito no total de ambos os sexos foi 96,5% e 3,5% respectivamente. Foram analisadas 684 culturas, porém apenas 166 tiveram crescimento de microrganismos, sendo 9 de natureza fúngica, 34 bactérias gram-positivas e 123 bactérias gram-negativas. Dentre os isolados a maior prevalência foi de *Klebsiella pneumoniae* 39,0% (n=47), sendo 54,3% (n=19) bactérias produtoras de beta-lactamases de espectro estendido (ESBL) e 88,2% (n=15) enterobactérias resistentes aos carbapenêmicos (ERC) e quanto aos tipos de cultura, observou-se em maior número urocultura (57,7%). **Conclusões:** Uma alta prevalência de *Klebsiella pneumoniae* foi observada, e também foi o microorganismo mais frequente em ESBL e ERC. Infecções após o transplante renal são causas de morbidade e mortabilidade significativas, e muitas vezes de difícil diagnóstico em pacientes imunossuprimidos, é interessante que o uso racional de antimicrobianos esteja bastante estabelecido, tendo vista que quanto mais exposição ao uso destes medicamentos, ocorre o favorecimento da seleção de cepas multirresistentes.

**Palavras-chave:** transplante renal; infecções bacterianas; resistência bacteriana a múltiplas drogas.

## Introduction

Solid organ transplantation is considered a complex surgery, given its peculiarities in relation to the technique itself and its long-term care needs. Kidney transplantation is the treatment of choice for individuals with end-stage Chronic Kidney Disease (CKD) of irreversible nature, provided they do not have any contraindications to undergoing surgery[1].

The high susceptibility to infections, due to the use of immunosuppressive medications and to exposure to the hospital environment, becomes an important morbidity and mortality factor for kidney transplant recipients[2]. Bacterial infections represent more than 70% of the postoperative infections, among which urinary, surgical site and pulmonary are the most common[3]. In addition to that, for presenting similar signs to those of infections such as fever in graft rejection processes, their diagnosis can be further delayed[4].

The incidence of microorganisms resistant to different classes of antimicrobials represents a problem at a global level, making frequent monitoring of therapeutic regimens essential for the treatment of patients with infections, a fact of extreme relevance for transplanted individuals[5]. It is estimated that 14% of the renal graft recipients have a post-transplant infection by multidrug-resistant microorganisms, including *Enterococcus spp, Staphylococcus aureus* and Enterobacteriaceae, which may result in a negative outcome for the person[5].

Considering the main in-hospital etiologic agents, Gram-negative bacteria stand out. These, in turn, are capable of developing strong resistance mechanisms, most likely as a result of excessive use of antibiotics such as cephalosporins and fluoroquinolones and, thus, they delay treatment of the installed infectious process[6]. According to the World Health Organization (WHO), Gram-negative microorganisms such as *A. baumanni, P. aeruginosa, K. pneumoniae and E. coli* are a priority in the critical resistance ranking[7].

It is known that transplant recipients present several consolidated risk factors that favor colonization and subsequent infection by resistant microorganisms, such as recurrent exposure to broad-spectrum antimicrobials, extensive contact with health care environments and exposure to the intensive care unit[8,9].

On a global scale, Brazil and Latin America present alarming antimicrobial resistance levels when compared to the United States, with bacteria producing Extended Spectrum Beta-Lactamases (ESBLs) and even carbapenemases made evident[10,11]. And for these latter, in the population of solid organ transplant recipients, the incidence of infection by carbapenemase-producing enterobacteriaceae is from 3% to 10%, with a mortality rate that reaches 30%[12]. In view of this, the major concern with this problem becomes evident, as an alert of a global threat.

A tool capable of clinically monitoring individuals with infections is the "Antimicrobial Stewardship Program" (ASP), in Brazil called *Programa de Gerenciamento em Terapia Antimicrobiana* (PGTA), which allows minimizing the negative outcomes by guaranteeing the pharmaco-therapeutic effect and adverse events, in addition to preventing selective pressure of the microorganisms with sensitization about rational use of antimicrobials[13]. The current study aimed at identifying the prevalence of β-lactamases and carbapenemases in cultures of kidney recipients treated at a university hospital in Fortaleza, Ceará.

## Methods

This is a descriptive and retrospective study conducted between January 2017 and December 2020 in a university hospital from Fortaleza, Ceará. The health care complexity of the hospital where the study was carried out is classified as tertiary-level and is integrated into the Unified Health System (*Sistema Único de Saúde*, SUS), which is a reference in the North and Northeast regions in Solid Organ and Bone Marrow Transplants. The hospital's pharmacy service has a clinical pharmacy unit, where, among other activities, monitoring of the treatment time with antimicrobials is carried out.

The data were informed from available information. ASP form used by the clinical pharmacy. The instrument is by the institution and used by the drugs clinicians who work or in solid unit transplantation for monitoring the treatment with antimicrobials of reserve or strategic. The variables included in the study were sex (male and female), age, time of nation and female hospital institution, clinical outcome (discharge or death), types of microbiological culture (urine, blood, tracheal aspirate, catheter, agent, agents advertised, used and operated), agent isolated etiology and antimicrobial resistance profile.

The study included patients, hospitalized in the renal transplant ward (12 beds), monitored by the ASP pharmacists, and using antimicrobials standardized at the institution as therapeutic reserve and/or strategic for at least 48 hours. For the microbiological analysis, positive Gram-negative bacterial cultures were included, as well as the corresponding Antimicrobial Susceptibility Test (AST). Patients whose cultures had not been requested were excluded, as well as those with biological sample infeasibility or absence of information for the research.

According to the National Guideline for the Elaboration of Antimicrobial Use Management in Health Services (2017) of the National Health Surveillance Agency (*Agência Nacional de Vigilância em Saúde*, ANVISA), therapeutic reserve antimicrobials are those with a broader spectrum, tending to induce greater microbial resistance, and thus considered as the last therapeutic choice for patients who have not responded to previous treatments, and the strategic ones are those that allow simplifying the patient's therapy and dehospitalization, due to their oral bioavailability greater than 80%.

Based on this, the therapeutic reserve antimicrobials were defined in the study, according to the institution's standardization, namely: liposomal amphotericin B, lipid complex amphotericin B, anidulafungin, micafungin, daptomycin, ertapenem, piperacillin/tazobactam, polymyxin B, polymyxin E, imipenem + cilastatin, meropenem, voriconazole, tigecycline, teicoplanin, aztreonam, and ceftazidime + avibactam. In turn, the strategic antimicrobials selected were the following: levofloxacin, ciprofloxacin, fluconazole, voriconazole, clindamycin, metronidazole and linezolid.

In the study hospital, the Identification (ID) and Antimicrobial Susceptibility Test (AST) of the biological samples were performed using the *Vitek-2®* method interpreted from the recommendation of the Clinical and Laboratory Standards Institute (CLSI) and the Brazilian Committee on Antimicrobial Susceptibility (Br Cast).

The data obtained from the clinical and laboratory monitoring of the patients included in the study were audited and entered into the institutional ASP database, designed in *Microsoft Excel®* 2016. Subsequently, these data were analyzed and the results were stratified to better visualize the microbiological profile found in the institution's kidney transplant unit.

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The study met the ethical requirements as per Resolution No. 466/2012 of the National Health Council (*Conselho Nacional de Saúde*, CNS). It was approved by the Research Ethics Committee of the Walter Cantídio University Hospital of the Federal University of Ceará (*Hospital Universitário Walter Cantídio/Universidade Federal do Ceará*, HUWC/UFC) under number 3,697,674 (CAAE: 21510719.8.0000.5045).

## Results

In total, 201 patients with a minimum age of 12 and a maximum of 79 years; most of them were men (n=107; 53.2%) with a mean age of 52.5 ± 14 years old, while the women (n=94; 46.7%) had a mean age of 43.2 ±14.8 years old, with medians of 54 and 44 years old, respectively. The mean hospitalization time was 25 days, with 194 discharges and 7 deaths as clinical outcomes (Table 1).

**Table 1.** Clinical and demographic characterization of the study patients from January 2017 to December 2020 in a university hospital from Fortaleza, Ceará.

| Variables<br>Total (n=201) | N(%)/Mean/Standard Deviation |
|---|---|
| Gender | |
| Male | 107 (53.2%) |
| Female | 94 (46.8%) |
| Age | |
| Male | 52.5 ± 14.0 |
| Female | 43.2 ± 14.8 |
| Hospitalization time (days) | 25.1 ± 21.0 |
| Outcome | |
| Discharge | 194 (96.5%) |
| Death | 7 (3.5%) |

A total of 684 culture results were requested from the study patients, although only 166 presented growth of microorganisms, with 9 of a fungal nature, 34 Gram-positive bacteria and 123 Gram-negative bacteria. Among the Gram-negative bacteria isolates (Table 2), there was growth of *Klebsiella pneumoniae* (n=48; 39%), *Escherichia coli* (n=45; 36.6%), *Pseudomonas aeruginosa* (n=13; 10.6%), *Enterobacter cloacae* (n=5; 4%) *Burkholderia cepacia* (n=4; 3.25%), *Proteus mirabilis* (n=3; 2.4%), *Acinetobacter baumanni* (n=1; 0.8%) and other etiological agents (n=4; 3.25%). 35 (28.4%) were classified as Extended-Spectrum Beta-Lactamases (ESBLs) and 17 (13.8%) as Carbapenem-Resistant Enterobacteria (CRE).

Regarding the types of culture (Table 2), the most frequently observed were urine cultures (n=71; 57.7%), followed by blood cultures (n=25; 20.3%). Among the bacteria classified as ESBLs (Table 3), there was prevalence of *K. pneumoniae* (n=19; 54.3%), *E. coli* (n=15; 42.8%) *and P. aeruginosa* (n=1; 2.8%); in turn, for the microorganisms classified as CRE, *K. pneumoniae* (n=15; 88.2%), *E. coli* (n=1; 5.9%), and *E. cloacae* (n=1; 5.9%) were found.

In relation to the prevalence of infections by bacteria that produce Extended-Spectrum Beta-Lactamases (ESBLs) and Carbapenem-Resistant Enterobacteria (CRE) and their respective topographies (Table 4), higher frequency of ESBL infections can be observed in the urine cultures (n=26; 74.3%), followed by the blood cultures (n=5; 14.3%). In turn, for infections by CRE, positive samples of rectal swabs were the most frequent (n=9; 52.9%), followed by urine cultures (n=5; 29.4%) and blood cultures (n=2; 11.8%).

## Discussion

The resistance profile of the Gram-negative bacteria analyzed consisted mainly of Extended-Spectrum Beta-Lactamases (ESBLs), followed by Carbapenem-Resistant Enterobacteriaceae (CRE). In addition to that, the *Klebsiella pneumoniae* microorganism was more prevalent, followed by *Escherichia coli*, both in infections and regarding presence of antimicrobial resistance.

As a patient can receive more than one kidney transplant, some demographic data may differ significantly between the studies, particularly with regard to age. Among the population under study regarding the gender and age, it was observed that 53.2% were male with a mean age of 52.5±14 years old, similarly to a

**Table 2.** Characterization of Gram-negative specimens associated with the types of cultures isolated from January 2017 to December 2020 in a university hospital from Fortaleza, Ceará.

| Type of culture | *A. baumanni* | *B. cepacia* | *E. cloacae* | *E. coli* | *K. pneumoniae* | *P. aeruginosa* | *P. mirabilis* | Others[b] |
|---|---|---|---|---|---|---|---|---|
| Urine culture | - | 1 | 2 | 32 | 27 | 4 | 2 | 3 |
| Blood culture | - | 3 | 1 | 10 | 6 | 4 | - | 1 |
| Rectal swab | - | - | - | - | 10 | - | - | - |
| Catheter tip | - | | 1 | | 2 | 1 | 1 | - |
| Tracheal aspirate | 1 | - | - | - | 1 | - | - | - |
| Surgical wound | - | - | - | - | 1 | - | - | - |
| Bronchoalveolar lavage | - | - | - | - | 1 | - | - | - |
| Others[a] | - | - | 1 | 3 | - | 4 | - | - |
| Total | 123 | | | | | | | |

[a]Renal graft, bone marrow, heart valve. [b]*Stenotrophomonas maltophilia* and *Enterobacter sp.*

**Table 3.** Multidrug resistance profile of the specimens isolated from the study patients between January 2017 and December 2020.

| Multidrug resistance | Total (n=52) | *K. pneumoniae* | *E. coli* | *P. aeruginosa* | *E. cloacae* |
|---|---|---|---|---|---|
| ESBLs[a] | 35 | 19 (54.3%) | 15 (42.8%) | 1 (2.8%) | - |
| CRE[b] | 17 | 15 (88.2%) | 1 (5.9) | - | 1 (5.9%) |

[a]Extended Spectrum Beta-Lactamases. [b]Carbapenem-Resistant Enterobacteria.

**Table 4.** Prevalence of Extended Spectrum Beta-Lactamases and Carbapenem-Resistant Enterobacteria in the respective types of culture.

| Type of culture | Resistance profile | |
|---|---|---|
| | ESBLs[a] N (%) | ESBLs[a] N (%) |
| Tracheal aspirate | - | - |
| Surgical wound | - | 1 (5.9%) |
| Blood culture | 5 (14.3%) | 2 (11.8%) |
| Bronchoalveolar lavage | - | - |
| Urine culture | 26 (74.3%) | 5 (29.4%) |
| Catheter tip | 1 (2.8%) | - |
| Rectal swab | - | 9 (52.9%) |
| Others[c] | 3 (8.6%) | - |
| Total | 35 (100%) | 17 (100%) |

[a]Extended Spectrum Beta-Lactamases. [b]Carbapenem-Resistant Enterobacteria. Renal graft, bone marrow, heart valve.

retrospective study carried out between 2003 and 2008 with 83 kidney transplant recipients where it was observed that the patients' mean age was 42.0±14.5 years old and that 68.9% were male[14]. In this study it was not possible to correlate the death and discharge outcomes with the respective resistance values or with the reason for hospitalization and infections in patients.

As for the types of cultures, a higher number of urine cultures was observed, 57.7% with a positive result, followed by blood cultures with 20.3%, which corroborates a study found in a university hospital in southeastern Brazil, in 2016, carried out in kidney transplant recipients, where the frequency of Urinary Tract Infections (UTIs) was 46.58%[15].

Colonization by microorganisms in the urinary tract among these patients is favored for several reasons, such as presence of urethral catheters in the first weeks after transplantation and displacement of the urinary tract at the time of the surgery, in addition to vesicourethral reflux and prostatic abnormalities[16].

In another study carried out in São Paulo at two reference hospitals in transplants, of the 588 UTI episodes, etiology was mostly attributed to *Eschericia coli* (37%), *Enterobacter sp* (19%), *Klebsiella pneumoniae* (11%) and *Pseudomonas aeruginosa* (6%)[17], similarly to this study, in which *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Enterobacter cloacae* were more frequent.

As for the multidrug resistance profile of isolated specimens, a study carried out in 2008 in a clinical microbiology laboratory, with the Gram-negative bacilli analyzed, noticed predominance of bacteria of genus *Klebsiella sp*. (35%) and *Escherichia coli* (22%) producing extended-spectrum beta-lactamases[18] and, with regard to carbapenem-resistant enterobacteriaceae, in a study conducted in 2014 at the Mulago Hospital in Uganda, among 56 positive isolates, *Klebsiella pneumoniae* was the most frequent specimen (52.2%)[19].

In another study carried out in 2012 with solid organ transplant recipients in Italy, among the 185 Gram-negative bacteria isolates, 49 (26.5%) were resistant to carbapenems, with *Klebsiella sp.* (49.1%) being particularly prevalent[20] and, in this same study, *E. coli* presented 1.9% frequency, which can favor the data from our study, where *K. pneumoniae* (54.3%) and *E. coli* (42.8%) were the most prevalent ESBLs and CRE, with 88.2% and 5.9% respectively.

In another study conducted with 45 transplanted patients, 277 samples were positive for carbapenemase-producing *K. pnemoniae*. The isolates found were in urine cultures (62%), blood cultures (25%), surgical wound (9%) and tracheal aspirate (4%); these results contribute to our study[21]. In a study conducted in Iraq from January to November 2018, 26 (8.67%) of 300 biological samples analyzed from kidney transplant patients were Gram-negative bacteria. *E. coli* was the most frequent Gram-negative bacterium with 21 (7%), of which 16 (76.2%) were ESBLs[22].

In another study, conducted from January 2019 to January 2020, the incidence of urinary tract infections in kidney transplant recipients was verified: from 200 samples, 8 (4%) were *E. coli* and 1 (0.5%) corresponded to *K. pneumoniae.* However, the difference between the numbers and the isolated microorganisms compared to our study may be due to the different conditions of each hospital, cities or between countries.[23]

In relation to the type of culture and the multidrug resistance profile, in a study conducted with 84 kidney transplant recipients[24], there were 215 UTI episodes, 37% of which were ESBL infections, differing from our study, where 74.3% prevalence of positive urine cultures for extended-spectrum beta-lactamases was found. This is probably due to the history of antimicrobial therapies used, which can vary across health institutions, leading them to have different microbiota in the hospital environment. Regarding the infections by carbapenem-resistant enterobacteriaceae, in a study carried out between 2010 and 2015 in public hospitals from Singapore, among the 430 CRE isolates, the colonization site with the highest number was rectal swab (62.1%)[25], which contributes to the data of this study where rectal swab (52.9%) was more frequent.

In terms of urine and blood cultures by CRE, in another study conducted at a university hospital in China between 2013 and 2020, among the 153 solid organ transplant patients, the most common CRE infection was in the urinary tract (31.4%), followed by bacteremia (19.6%)[26], which corroborates the data of the current study where urine (29.4%) and blood (11.8%) cultures presented similar results.

As a result of the facts analyzed, it becomes necessary to engage in strategies capable of mitigating bacterial resistance, such as reducing the prescription of unnecessary antibiotics in the patient's clinical treatment, investing in laboratory technologies in order to obtain more reliable results on the samples analyzed, and implementing continuing education in the hospital institutions, as well as in the communities, in order to reach maximum awareness of the population about this problem[27,28].

## Conclusion

This study established the profile of the Gram-negative bacteria isolated and their bacterial resistance from January 2017 to December 2020 in kidney transplant patients treated at the institution. The findings indicated that the most prevalent infectious complications were urinary tract infections, followed by those of the bloodstream. Regarding multidrug resistance, bacteria *Klebsiella pneumoniae* and *Eschericia coli* were found in greater numbers, both in terms of extended-spectrum beta-lactamases and carbapenem-resistant enterobacteriaceae.

Infections after kidney transplantation are a cause of significant morbidity and mortality; therefore, careful monitoring of these patients is necessary in order to achieve a positive clinical outcome. In addition to that, rational use of antimicrobials should be well-established to avoid selection of multidrug resistant strains.

Considering the study limitations, it was not possible to correlate the following: the death outcome and the treatment used by the patient for the respective resistance profiles; the reason for hospitalization (if a transplant was performed or if it was due to a complication) and the analysis of infections per patient.

In summary, the results can contribute as a basis for future epidemiological studies.

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**Collaborators**

Authors ACL, AAA, TCF, HCR, ANP and ABO took part in elaboration of the project and in critical review of the intellectual content; ACL, AAA, ABR BFR and LMO contributed to data analysis and interpretation; and FCP, DFC and GAS participated in writing of the article.

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**Conflict of interest statement**

The authors declare that there are no conflicts of interest in relation to this article.

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