



# Infection by Carbapenemase-Producing *Klebsiella pneumoniae* in Renal Transplant Recipients

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 [https://doi.org/10.53855/bjt.v25i3.436\\_in](https://doi.org/10.53855/bjt.v25i3.436_in)

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Section Editor  
Edna Frasson S Montero

Received  
Jun. 6, 2021

Approved  
Jun. 8, 2022

Conflict of interest  
Nothing to declare.

How to Cite

Como Citar:  
Campos Júnior SA, Foresto RD, Viana  
LA, Requião-Moura LR, Tedesco-  
Silva Junior H, Medina-Pestana J.  
Infection by Carbapenemase-Producing  
*Klebsiella pneumoniae* in Renal Transplant  
Recipients. BJT. 2022.25(03):e0522.  
[https://doi.org/10.53855/bjt.v25i3.436\\_in](https://doi.org/10.53855/bjt.v25i3.436_in)

eISSN  
2764-1589



**Abstract:** There is a tendency to increase the number of cases of infection by multidrug-resistant bacteria, in view of the indiscriminate and sometimes excessive use of broad-spectrum antibiotics in the hospital environment. These infections have generated great impact, especially in immunosuppressed patients undergoing solid organ transplantation. National data revealed a significant increase in the rates of infections by multidrug-resistant bacteria. The present study aimed to evaluate the incidence and demographics of health care-related infections by carbapenemase-producing *K. pneumoniae* (KPC). This is an observational, retrospective, descriptive study conducted at a single center (Kidney Hospital) with evaluation of the outcomes of kidney transplant recipients with KPC infection between November 2009 and December 2015. In our center, KPC bloodstream infection had the highest prevalence, followed by urinary tract infection. The overall 30-day mortality was 36%, similar to that found in the international literature. Infection with multidrug-resistant bacteria is a serious clinical condition in transplant patients and poses a therapeutic challenge.

**Descriptors:** Kidney Transplantation; *Klebsiella* Infections; Hospital Infection; Beta-Lactam resistance.

## INTRODUCTION

Infections by multiresistant bacteria have become a worldwide public health problem in recent years, with a need even for new terms to classify these bacteria, such as multidrug-resistant, extended resistance spectrum, and pandrug-resistance.<sup>1</sup> The causes of the development and spread of these bacteria are multifactorial, based on the indiscriminate use of antimicrobials to treat infections in humans for prolonged periods, as well as through contact with contaminated healthcare workers or medical equipment.<sup>2</sup>

In 2017, the Center for Disease Control and Prevention (CDC) published a document that evaluated the severity of the global scenario and the prospects for the evolution of multidrug-resistant organisms in the United States. Based on the clinical and economic impact, incidence, transmissibility, availability of effective antibiotics, and barriers to prevention, the CDC has classified these microorganisms as a serious public health threat. Enterobacteriaceae resistant to carbapenems, *Staphylococcus aureus* resistant to methicillin, vancomycin-resistant enterococci, and some gram-negative bacilli have major implication for infectious control that has not yet been resolved.<sup>3</sup> *Neisseria gonorrhoeae* resistant to cefuroxime, ceftriaxone, azithromycin and tetracycline, and *Clostridium difficile* need attention and immediate and aggressive action for their control.<sup>2</sup>

Brazilian data revealed a significant increase in infection rates by multidrug-resistant bacteria reported to the Coordenadoria de Vigilância em Saúde (Covisa), a municipal agency that answers to the federal agency of the Ministry of Health. In 2011, 14% of *Klebsiella pneumoniae* isolated in bloodstream infections in São Paulo hospitals were identified as resistant to carbapenems. In 2016, this proportion increased to 53%.<sup>4</sup>

In the current scenario, we observe that infection by multidrug-resistant bacteria is a much discussed and studied subject among health professionals, but it is also being spread to the nonspecialized public. Several publications in the nonspecialized press have described for the general population the current concern about these infections and explained about them. *Veja* magazine published an article in 2016 entitled “The postantibiotic era,” warning of a possible scenario in which antibiotics will no longer be effective and reinforcing the scarcity of investment in new drugs.<sup>5</sup> The American magazine *The Economist*, also in 2016, released the article “When the drugs don’t work: How to combat the dangerous rise of antibiotic resistance,” warning the population about the risk of infections that will no longer be treated and that resistance is widespread.<sup>6</sup> The American magazine *Time*, in 2017, published the article “Why bacteria are more threatening than ever” making a mention of the indiscriminate use of antibiotics and, consequently, the increase in bacterial resistance.<sup>7</sup> The BBC, also in 2017, published a report entitled “Superbacteria advance in Brazil and prompt health authorities to race against time,” reporting that 43.3% of hospital infections are associated with carbapenem-resistant *K. pneumoniae*.<sup>8</sup> These publications demonstrate the concern that multidrug-resistant bacteria infections have brought in recent years.

Infection by resistant bacteria generates great impact especially in patients subject to solid organ transplantation. Sites of infection vary in the literature, with the most common being urinary tract and surgical site infection.<sup>9,10</sup> An additional risk factor found was the performance of multiple organ transplantation, considering that in these patients the surgical procedure is complex, with the need for additional invasive devices and a longer hospital stay. Another risk factor was the use of a ureteral catheter, with a greater predisposition to urinary tract infection. The incidence of carbapenemase-producing *K. pneumoniae* infection is 3-10% in the literature, and 30-day mortality can be as high as 42%.<sup>9</sup>

The objective of this study was to describe the incidence and demographics of healthcare-associated infections at the Kidney Hospital (São Paulo, SP, Brazil) by *K. pneumoniae* producer of carbapenemases (KPC) and the main control and prevention measures introduced during this period.

## MATERIAL AND METHODS

### *Study design*

A retrospective, descriptive study was carried out to present the demographic data and incidence densities of health care-related infections at the Kidney Hospital—Oswaldo Ramos Foundation—associated to the Escola Paulista de Medicina, Federal University of São Paulo, which specializes in kidney transplantation, having performed about 900 transplants in recent years. The hospital has 151 beds, 16 of which are intensive care and 9 day-hospital basis.

Data collection took place from November 2009 to December 2015. Data were collected from patients’ medical records and anonymized for analysis. According to hospital protocol, surveillance cultures are routinely collected in asymptomatic patients on admission and at discharge from the intensive care unit (ICU), weekly, both in the ward and ICU sectors, and in patients admitted for kidney and/or pancreatic transplantation. These surveillance cultures were not taken into account in the analysis. Central venous catheter-associated bloodstream infections, urinary tract infections 30 days after transplantation, ventilator-associated lung infection, ICU bladder catheter-associated urinary tract infections, and surgical site infection were evaluated. Resistance mechanisms were identified by Hodge test and by polymerase chain reaction (PCR). All patients with culture positive for Enterobacteriaceae resistant to carbapenems by production of the KPC enzyme, proven by PCR or phenotypic test, who filled criteria for health care-related infection according to CDC criteria were evaluated. The incidence densities of infection by this microorganism in the period and the main control measures introduced were analyzed.

### *Statistical analysis*

Numerical variables were summarized by means of the mean or median and interquartile ranges (IQRs), depending on their distribution, and categorical variables, in the form of absolute frequency and percentage. Only descriptive analyses were performed.

Incidence was calculated by the number of patients infected in the period in question, as well as the estimated number of transplant patients in the study data collection period being followed up at the Kidney Hospital transplant service.

## RESULTS

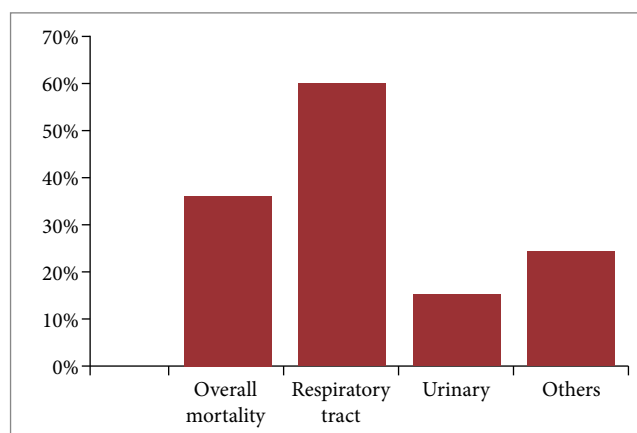
From November 2009 to December 2015, 86 cases of infections by *K. pneumoniae* resistant to carbapenems were identified, and 3 patients had more than one episode of infection, so there were 86 infections in 82 patients. What we observed were two moments with higher incidence density of infections by *K. pneumoniae* resistant to carbapenems in the fourth quarter of 2013 and the first quarter of 2015.

Of these infections, 74 occurred in kidney transplant patients, 12 in pancreas/kidney transplant patients. About 65% were men, and the major cause of chronic kidney disease was glomerulonephritis, followed by kidney disease associated with diabetes (Table 1). The median age of these patients was 50 years (IQR 14-73 years), and the most frequent site was bloodstream infection, followed by urinary tract infection, surgical site infection, and lower respiratory tract infection. All were on corticoids, with tacrolimus being the second most used drug (86%). The overall 30-day mortality was 36%, respiratory tract infection had the highest mortality rate, with 60%, and urinary tract infection, the lowest mortality, 15.38% (Fig. 1). Table 1 shows the main demographic data of the 82 patients evaluated.

**Table 1.** Demographic, clinical, and transplant-related data.

Demographic	
Age (median) – years (interquartile range)	50 (14–73)
Female gender – number (%)	27 (32.92%)
Male gender – number (%)	55 (67.08%)
Ethnicity – number (%)	
Caucasian	44 (53.66%)
Black	20 (24.39%)
Brown	17 (20.73%)
Other	1 (1.22%)
Clinical	
Etiology of kidney disease – number (%)	
Glomerulonephritis	50 (60.97%)
Diabetes mellitus	24 (29.27%)
Hypertensive nephropathy	4 (4.88%)
Others	4 (4.88%)
Transplant	
Type of donor – number (%)	
Living donor	33 (40.24%)
Deceased donor	49 (59.76%)
HLA mismatches – number	
Mismatches HLA 0	66
Mismatches HLA 1	94
Mismatches HLA 2	59
Performed dialysis before transplantation – number	81
Time on dialysis in years – mean, median, standard deviation	4, 3, 3.96
Time of cold ischemia – number (%)	
< 10 hours	13 (15.85%)
11–15 hours	8 (9.76%)
16–25 hours	40 (48.78%)
> 26 hours	15 (18.29%)
Not determined	6 (7.32%)
Immunosuppression therapy – number (%)	
Tacrolimus	71 (86.58%)
Everolimus	2 (2.43%)
Azathioprine	28 (34.14%)
Corticosteroid	82 (100%)

HLA: human leucocyte antigen.



**Figure 1.** Overall mortality and according to site of infection.

## DISCUSSION

Infections by KPC have an important clinical and epidemiological impact on health care-related infections. Most of these infections are associated with patients hospitalized for prolonged periods, with the need for the use of devices and antibiotics.<sup>11</sup> To assess the spread of Enterobacteriaceae resistant to carbapenems in the world, we chose to search the review articles, described below.

According to the 2011 CDC publication “Global spread of carbapenemase: Producing Enterobacteriaceae,” cases of infection with carbapenemase-resistant Enterobacteriaceae by KPC production have been identified in the following countries: United States, Puerto Rico, Brazil, Argentina, Colombia, Israel, Israel, China, Greece, Italy, Hungary, Switzerland, Poland, Germany, Finland, Sweden, Norway, Denmark, Netherlands, Belgium, United Kingdom, Ireland, France, Spain and Portugal.<sup>12</sup>

A 2013 Lancet Infectious Diseases publication entitled “Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases” describes the spread of *K. pneumoniae* in the world, citing Canada, Argentina, Brazil, Scotland, Ireland, Spain, France, Italy, Poland, Greece, Israel, India, China, Australia, and New Zealand.<sup>13</sup>

More recent articles have shown infections detected also in Australia, Malaysia, Venezuela, Lebanon, Nepal, Russia, and provinces in southern Africa.<sup>14-19</sup> They were identified in the global publication “Dissemination of carbapenemase-producing *Klebsiella pneumoniae*: Epidemiology, genetic context, treatment options, and detection methods,” 2016, from the journal *Frontiers in Microbiology*, KPC infections in 44 countries.<sup>20</sup> Another article, published in 2016 in the *Mediterranean Journal of Hematology and Infectious Diseases*, identified KPC infections in countries located in the Mediterranean.<sup>21</sup> Therefore, by integrating these articles with the review articles analyzed, we were able to map at least 59 countries that described infections by this resistant bacterium in their regions.<sup>12-22</sup>

Infections by bacteria resistant to carbapenems have been spreading across countries and continents for at least 25 years, since their first record, in the United States, in 1996.<sup>13</sup> In the review conducted, we identified publications of infections caused by bacteria with this resistance mechanism in different countries, detected in all continents.<sup>12-22</sup> In 2013, a review article was published in which less than 10 cases were described in Australia and New Zealand of infection by KPC-producing bacteria, which were associated with tourism and patient immigration from other countries, even though the countries have a strong infection prevention control system for multidrug-resistant bacteria.<sup>13</sup>

In order to evaluate the epidemiological data of the infections by KPC in the websites related to the health administration bodies in the states of Brazil, the following pages were searched: portal of the Ministry of Health, portal of the Oswaldo Cruz Foundation (Fiocruz), portal of the National Health Surveillance Agency (Anvisa), and the Department of Informatics of the Unified Health System (Datusus). They, to date, had no publicly released data on KPC infections, except Covisa, which makes available biannual data on ICU bloodstream infections, in which *K. pneumoniae* resistant to carbapenems are evaluated, but without distinguishing the mechanism of resistance.

Information on infections and colonization by KPC enzyme-producing Enterobacteriaceae was therefore searched for based on published articles. Articles with molecular studies, that did not describe the infections, and that could not identify the origin of the evaluated strains were excluded. The articles were obtained using the keywords “KPC” and “Brazil” from databases such as PubMed, Scientific Electronic Library Online (SciELO) and Virtual Health Library (VHL). As a result, we were able to raise a

total of 62 articles, among them 24 pertinent to the study, and these encompassed 17 of the 26 Brazilian states that have already presented data on infection/colonization by bacteria that produce the KPC enzyme.<sup>12,23-44</sup>

To evaluate the hospitals that presented cases of infection/colonization by bacteria producing the KPC enzyme in the state of São Paulo, a survey was conducted in the search portal for scientific articles PubMed and SciELO with the following keywords: “KPC,” “resistant,” “Enterobacteriaceae” and “São Paulo,” generating the result of 68 articles. Of these, 57 were excluded because they did not fit the research question, resulting in 11 articles. The exclusion criteria were: articles that did not identify the hospital of origin of the infection; articles published by hospitals in São Paulo, but referring to patients from other states; molecular studies that evaluate resistance mechanism, but do not describe the origin of the strains; and articles that did not identify the carbapenemase KPC or did not identify enterobacteria. Thus, a total of 12 articles were pertinent to this study, in which we identified two hospitals in cities in the state of São Paulo and eight in the state capital.

In the state of São Paulo, the Hospital Municipal Dr. José de Carvalho Florence, of the city of São José dos Campos,<sup>45</sup> and the Hospital das Clínicas of the city of Ribeirão Preto<sup>9,23,46-54</sup> describe infections by enterobacteria producing the KPC carbapenemase. In the city of São Paulo, the following hospitals were identified: the Heart Hospital and the São Paulo Hospital,<sup>47</sup> the Clinics Hospital,<sup>9,45</sup> the Cancer Institute of the State of São Paulo,<sup>45,48</sup> the Dante Pazzanese Cardiology Hospital,<sup>49-51</sup> the Heliópolis Hospital,<sup>52</sup> the Brigadeiro Hospital<sup>53</sup> and the M’boi Mirim Hospital.<sup>54</sup>

In Brazil, as in many other countries, there is no surveillance program for all infections caused by multidrug-resistant bacteria. This scarcity of data also reflects the lack of specialized laboratories to identify the resistance mechanisms of these bacteria. Therefore, the number of cases described here probably does not reveal the current epidemiological situation. Based on this survey, we can see that the country still does not have a well-established surveillance structure for these infections.

The state of São Paulo is one of the main hubs of academic production in the country, in addition to its economic strength and being the most populous city in Brazil. This makes it easier to understand that it contains large hospitals and a larger pool of epidemiological data and samples available, as demonstrated in this study. After several data surveys in search engines such as PubMed and SciELO, it was possible to see that most of the publications in the state are related to the city of São Paulo.

The hospital that performs the most kidney transplants in the world is the Kidney Hospital. Approximately 900 kidney transplants and 20 pancreas transplants are performed there each year, and the hospital maintains outpatient follow-up care for approximately 7,000 kidney transplant recipients.<sup>55</sup> There were data that evaluated health care-associated infections in kidney transplant patients. We observed high mortality rate, especially in relation to ventilator-associated infections, and it cannot be ruled out that the status of severity of these patients contributed to this result, because the severity score was not raised. In 2013, we had a major increase in the number of cases worldwide, and with the implementation of a package of local measures, a decrease in incidence densities was observed.

In this first moment, infection prevention measures related to multidrug-resistant bacteria were intensified, with surveillance culture collection from the entire hospital weekly, training of the multidisciplinary team, feedback of new cases to the teams in daily meetings, and review of all cleaning and disinfection processes. In the second moment, prevention measures were reinforced again through training for multiprofessional staff, and measures related to bloodstream infection were also reinforced, as they had the highest infection densities, and the ICU surveillance culture collections were maintained.

The sites of infection most commonly found in our study were in the bloodstream, urinary tract, and surgical site, while in the international literature the urinary tract is the site of highest incidence. The mortality found (36%) was similar to what other studies report, and can be as high as 42%.

Since this is a descriptive epidemiological study, we were not able to infer the real reasons for the increased rate of infections in that period. No data were collected at a second point in time nor were the antibiotic treatment regimens taken by the patients after the surveillance measures were implemented.

## CONCLUSION

Control measures must be strongly followed and monitored to decrease the risk of spreading these infections. We increased the frequency of surveillance collection during patients’ hospitalization, especially in the intensive care sector, and reinforced training with the multidisciplinary team on hospital hygiene measures. In this Brazilian study, there was agreement on the site of infection affected, as well as on the overall mortality.

## AUTHORS' CONTRIBUTION

**Substantive scientific and intellectual contributions to the study:** Foresto RD, Requião-Moura LR, Tedesco-Silva Junior H and Medina-Pestana J; **Conception and design:** Campos Júnior SA and Foresto RD; **Data collection, analysis and interpretation:** Foresto RD, Viana LA and Tedesco-Silva Junior H; **Article writing:** Campos Júnior SA, Foresto RD and Viana LA; **Critical review:** Requião-Moura LR, Tedesco-Silva Junior H and Medina-Pestana J; **Final approval:** Campos Júnior SA.

## AVAILABILITY OF RESEARCH DATA

All data were generated or analyzed in the present study.

## FUNDING

Not applicable.

## ACKNOWLEDGEMENTS

We thank the entire team at the Teaching and Research Center of the Kidney Hospital for enabling and encouraging scientific research.

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