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Incidence of KPC (Klebsiella Pneumoniae Carbapenemase) in adults admitted to hospitals in the regions of Brazil from 2006 to 2016: literature review

Incidencia de KPC (Klebsiella Pneumoniae Carbapenemase) en adultos ingresados en hospitales de las regiones de Brasil de 2006 a 2016: revisión de la literatura

Incidência de KPC (Klebsiella Pneumoniae Carbapenemase) em adultos internados em hospitais nas regiões do Brasil de 2006 a 2016: revisão bibliográfica

ABSTRACT
Klebsiella pneumoniae carbapenemase (KPC), known as "superbug", plays an important role in relation to nosocomial infections. Objectives: To identify the incidence of Klebsiella pneumoniae with resistance factor KPC in adults in hospitals in the Midwest, Southeast and South regions of Brazil between the years 2006 and 2016, also observing the profile of resistance to antimicrobials. Method: Retrospective research with descriptive and qualitative basis, being a systematic literary literature review carried out through the databases: SciELO, Medline, LILACS and Pubmed. Results: 95 articles were found, of which 58 were included. The South region obtained the highest prevalence for KPC isolates in hospitals, being Klebsiella pneumoniae. Regarding antimicrobials, Ertapenem had almost 100% resistance in all states. Conclusion: It is necessary to implement precautions and control the spread of this type of resistance mechanism.
DESCRIPTORS: Bacterial resistance; Enterobacteria; Epidemiology.

RESUMEN
Klebsiella pneumoniae carbapenemase (KPC), conocida como "superbacteria", juega un papel importante en relación con las infecciones nosocomiales. Objetivos: Identificar la incidencia de Klebsiella pneumoniae con factor de resistencia KPC en adultos en hospitales de las regiones Medio Oeste, Sudeste y Sur de Brasil entre los años 2006 y 2016, observando también el perfil de resistencia a los antimicrobianos. Método: Investigación retrospectiva con base descriptiva y cualitativa, siendo una revisión sistemática de la literatura literaria realizada a través de las bases de datos: SciELO, Medline, LILACS y Pubmed. Resultados: se encontraron 95 artículos, de los cuales se incluyeron 58. La región Sur obtuvo la mayor prevalencia de aislamientos de KPC en hospitales, siendo Klebsiella pneumoniae. Con respecto a los antimicrobianos, Ertapenem tenía casi el 100% de resistencia en todos los estados. Conclusión: Es necesario implementar precauciones y controlar la propagación de este tipo de mecanismo de resistencia.
DESCRIPTORES: Resistencia bacteriana; Enterobacterias; Epidemiología.

RESUMO
A Klebsiella pneumoniae carbapenemase (KPC), conhecida como "superbactéria", desempenha um papel importante em relação às infecções hospitalares. Objetivos: Identificar a incidência de Klebsiella pneumoniae com fator de resistência KPC em adultos nos hospitais das regiões Centro-Oeste, Sudeste e Sul do Brasil entre os anos de 2006 e 2016, observando também, o perfil de resistência aos antimicrobianos. Método: Pesquisa retrospectiva com base descritiva e qualitativa, sendo uma revisão bibliográfica literária sistemática realizada por meio das bases de dados: SciELO, Medline, LILACS e Pubmed. Resultados: Localizou-se 95 artigos, dos quais 58 foram incluídos. A região Sul obteve a maior prevalência para isolados KPC nos hospitais, sendo a Klebsiella pneumoniae. Em relação aos antimicrobianos o Ertapenem teve quase 100% de resistência em todos os estados. Conclusão: É necessário que sejam implementadas precauções e o controle da disseminação desse tipo de mecanismo de resistência.
DESCRITORES: Resistência bacteriana; Enterobactérias; Epidemiologia.

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INTRODUCTION

The enzyme KPC (Klebsiella pneumoniae carbapenemase), became known as "super bacterium", after having undergone a genetic mutation, which gave it resistance to multiple antimicrobials and other bacteria. This enzyme was first identified in the United States in 1996, found for the first time in the Klebsiella Pneumoniae bacterium, hence the name received. [1]

The enzyme quickly spread to several countries, Colombia in 2006 was the first South American country to record the occurrence of cases of KPC-2 in isolates of Klebsiella pneumoniae. [1-2] Although the first Brazilian registration occurred in 2005, it was only in 2011 that more serious outbreaks began to be observed regarding KPC-producing bacteria. The first outbreak of nosocomial infection occurred in 2009, but was only recorded in 2011. [1]

KPC is an enzyme produced by gram-negative bacteria (enterobacteria), restricted to the hospital environment, which provides resistance to carbapenemic antimicrobials, widely used in the treatment of infections involving Enterobacteriaceae, such as: Meropenen, Ertapenen, Imipenen, in addition to inactivating other Beta agents-lactam: cephalosporins, penicillins and monobactamics. [3-7]

In other bacteria, such as: Enterobacter cloacae, Citrobacter freundii, Salmonella spp., E. coli and Pseudomonas spp.[8] The K. pneumoniae it is a bacterium with great capacity to transfer its genetic material, due to its plasmidial location and consequently, the resistance genes. [9-11]

The easy dissemination makes it difficult to control epidemics, and worries health professionals, as the treatment of these infections is extremely difficult, increasing mortality rates. Several factors are involved in the spread of these multi-resistant pathogens, including the abuse of antibiotics, invasive procedures, inadequate technique or lack of hand hygiene and the lack of routine in disinfecting surfaces. [8,12-13]

The use of antibiotics helped to contain infections and its success generated great optimism regarding the prevention and treatment of infectious processes. However, the indiscriminate practice of antibiotic therapy has led to the development of common resistance mechanisms, resulting in a continued decline in the effectiveness of most antimicrobials over the past few decades. [8,14] Between 2000 and 2010 the use of antibiotics increased by 36% in 71 countries, Brazil, Russia, India, China and South Africa accounted for 76% of this increase. [14]

The problem surrounding hospital infections is still a major public health challenge worldwide.[8] Some publications report mortality rates between 40% to 50% for carbapenema-producing enterobacteria. [15] Prevention is the main weapon in the fight against bacteria producing carbapenemase, since treatment is difficult due to its high resistance to antimicrobials. Thus, all care must be meticulous regarding infections caused by these multi-resistant bacteria, as they represent a serious public health problem and a major therapeutic challenge. [14,16-17]

In this perspective, considering the importance of the theme, the objective of this study was to conduct a survey of the epidemiological incidence of these bacteria in hospitals in the Midwest, Southeast and South regions of Brazil, through a bibliographic review to observe their dissemination and resistance to antimicrobials.

METHOD

Retrospective study with descriptive and qualitative basis, carried out through the databases: SciELO, Medline, LILACS and Pubmed being a systematic literary literature review in Spanish, English and Portuguese. The theme was based on the incidence of KPC-producing bacteria in hospital environments, in adults, in the Midwest, Southeast and South regions of Brazil in the years 2006 to 2016 for a collection of epidemiological data and a perspective of bacterial resistance due to indiscriminate use of antibiotic therapy.

The data were analyzed and treated according to the number of KPC isolates in the regions and their respective states; bacteria most frequently, this being Kblebsiella Pneumoniae Carbapenemase; most affected gender; and insulation source more often. The total number of articles added up to 95, of which 37 were excluded and 58 included for the study. The exclusion criteria were based on articles of which they did not understand the established year; the age of the patients; the bacterial resistance factor; the pre-established regions and the objective for an epidemiological survey. The adult audience was a criterion for inclusion; incidence of KPC in hospital environments between the years 2006 and 2016; the established regions; with the most current articles possible and relevant data for a regional and national epidemiological survey.

Epidemiological data were collected from articles from the three regions of Brazil, taking into account the prevalence of KPC for each region of Brazil analyzed and the number of positive bacterial isolates for Kblebsiella Pneumoniae Carbapenemase; prevalence and number of bacteria most frequently in KPC isolates; genre; average age; source of isolates; year and the resistance of carbapenem antibiotics.

RESULTS

Each region and its states were analyzed separately, between the years 2006 to 2016. In the three regions, the KPC prevailed at the age of 53 years (median of 56,3). There was a predominance of males (51%). Few studies have shown the female audience (7%) and some did not specify the gender (42%), due to the fact that it does not influence the susceptibility to infections.

The source of isolation of bacteria with KPC factor in the three regions, predominated for urine samples (35%), followed by rectal swab (17%), blood culture (16%), tracheal secretions (5%), amputation fragments (3%) and venous catheter (1%). The high number of unspecified sources (23%) stood out.

Among all regions, there were 6,184 KPC positive isolates, with K. pneumoniae, the bacterium with the highest frequency in these isolates, comprising 3,703 the total number (Table 1).

Table 1- Prevalence of positive KPC isolates in hospitals in the Midwest, Southeast and South of Brazil.

Regiões Estados	N° de isolados KPC	Bactéria com maior frequência	Isolados com maior frequência	Gênero	Fonte de Isolamento com maior prevalência
Centro Oeste					
Distrito Federal	1.320	K. pneumoniae	770	masculino	Urina
Goiás	160	K. pneumoniae	105	masculino	Urina
Mato Grosso	4	K. pneumoniae	2	masculino	Aspirado Traqueal
TOTAL	1.484	K. pneumoniae	877	masculino	Urina
Sudeste					
Minas Gerais	391	K. pneumoniae	123	masculino	Hemocultura
Espírito Santo	37	K. pneumoniae	20	masculino	Urina
Rio de Janeiro	276	K. pneumoniae	115	masculino	Urina
São Paulo	156	K. pneumoniae	145	masculino	Urina
TOTAL	860	K. pneumoniae	403	masculino	Urina
Sul					
Rio Grande do Sul	831	K. pneumoniae	433	masculino	Urina
Santa Catarina	1.325	K. pneumoniae	1.210	masculino	Urina
Paraná	1.644	K. pneumoniae	780	masculino	Swab retal
TOTAL	3.840	K. pneumoniae	2.423	masculino	Urina
TOTAL REGIÕES	6.184	K. pneumoniae	3.703	masculino	Urina

Source: Author (2020).

The bacterium K. pneumoniae was the most frequent in the study, making up 84%, Acinetobacter baumannii (2%), E. aerogenes (1%) and E. cloacae (1%), with a considerable number of bacteria not specified for the KPC factor with 12%.

It can be seen that in the state of Paraná (PR), in the southern region of Brazil, between the years 2009 and 2015, there was an increasing increase in KPC isolates, totaling 1.644 samples. In this same region between the years 2006 and 2016, the state of Santa Catarina (SC) had a high incidence for K. pneumoniae with a resistance factor for KPC-producing bacteria compared to the other states. In the Midwest region between 2006 and 2013, specifically in the Federal District (DF), there was a marked rate for the KPC factor, comprising 1,320 isolates. In general, the prevalence of KPC-producing bacteria in Brazil was observed, with the South region having the highest incidence followed by the Southeast and Midwest regions, respectively, between the years 2006 and 2016 (Graph 1).

In the Midwest region, the states of Distrito Federal (DF), Goiás (GO) and Mato Grosso (MT), 11 studies reported a lower prevalence for the number of KPC isolates, compared to the others. DF was the state with the highest prevalence of numbers of KPC isolates in 1.320 out of a total of 1.484, with K. pneumoniae being the most frequent bacterium, with 770 isolates out of 877, resulting in 75%. Of these, urine (39%), blood culture (17%), tracheal aspirate (6%) rectal (5%) and unspecified (33%) prevailed as isolation sources, with 50% being the most affected, where 44% were not specified and only 6% were female.

In the Southeast region, 16 studies were investigated. This was the intermediate region in relation to the prevalence of KPC isolates, when compared to the others. The states that were part of this research comprise a total of four states, namely: Minas Gerais (MG), Espírito Santo (ES), Rio de Janeiro (RJ) and São Paulo (SP). A total of 860 isolates were presented, the bacterium K. pneumoniae being the most frequent, with a number of 303 isolates, resulting in 63% of the samples.

The state with the highest number of isolates was MG, totaling 391 for the KPC factor and 123 with K. pneumoniae prevalence. Of the total isolates from this region, the majority came from a source of urine isolation (38%), followed by blood culture (24%), rectal swab (14%), tracheal secretions (3%) and unspecified (24%) . Males were the most affected with 45% in relation to females, still 48% for unspecified genders.

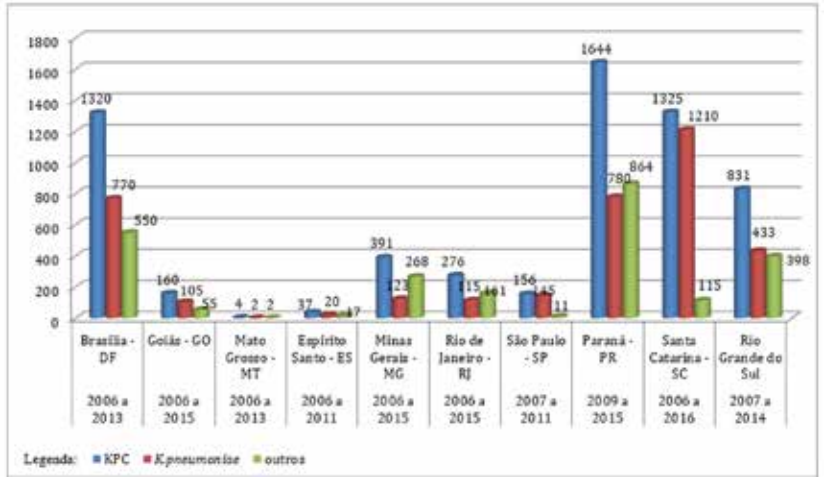
The South region, on the other hand, was the most prevalent in terms of analyzed papers, totaling 23 articles. This region had the highest prevalence for KPC isolates, totaling 3,064 positive KPC isolates with an incidence of K. pneumoniae in 2.423 findings, of which resulted in 92% of samples. The states that were part of this research were: Rio Grande do Sul (RS), Santa Catarina (SC) and Paraná (PR).

PR had the highest prevalence with 1.644 KPC isolates, with K. pneumoniae also being the most common bacterium in the findings, however, it was in the state of SC that K. pneumoniae had the highest frequency, with a total of 1.210 isolates, but the number of total KPCs in the state was less than the state of PR. The source of greatest isolation was urine with 31%, followed by rectal swab (27%), unspecified (18%), blood culture (9%), fragment of amputation and tracheal secretions (6%) and venous catheter (3%). Male gender was also the most prevalent with 58% of the findings.

Regarding antimicrobials, 16 authors were selected to survey the resistance and sensitivity of bacterial isolates with KPC factor, whose K. pneumoniae had the highest prevalence in all regions and states under study.

In the Midwest region, between 2006 and 2013, Ertapenem had a higher prevalence as an antimicrobial with greater resistance in all states, GO and MT with 100% and DF with 9,8%, followed by Meropenem as the second with greater resistance, DF (92,5%), GO (90%) and MT (50%). The lowest resistance was found in Gentamicin with 57% in DF and GO, with no prevalence for MT. The antibiotic with greater sensitivity was

Graph 1- Epidemiological survey according to the selected states, for the incidence of KPC factor, K. pneumoniae and other bacteria from 2006 to 2016.



Source: Author (2020).

Amikacin in DF, with 96% and in GO with 92,2%, there was also no prevalence for the mean in MT.

In the Southeast region, from 2006 to 2015, Ertapenem had 100% resistance in three states, ES, MG and RJ, already in SP, did not present studies for greater resistance. Meropenem was the second antibiotic with the highest resistance, with ES being the state with the highest prevalence of 94,55%. Gentamicin was the least resistant antibiotic in all states, comprising 12% in SP and 31% in ES. The highest mean for sensitivity was also Gentamicin with 95,6% in MG, followed by Amikacin with 95,6% in RJ and 94,7% in SP.

In the South region, from 2006 to 2014, SC had 100% resistance to Ertapenem and RS with 97,2%. However, in 2011, in the state of PR, Ertapenem also had greater resistance, but with only 40%. The second with greater resistance was Meropenem, as in the other regions, comprising 94,55% in SC and 91,4% in RS, also showing a decrease in the state of PR, with 32%. The least resistance was Gentamicin, with 28,2% in RS. The highest sensitivity was Fosfomycin, with 100% in RS, 92,2% in SC and in the state of PR Imipenem was the result for greater sensitivity, with 83% (Table 2).

DISCUSSION

HAIs (Healthcare-Associated Infections) caused by Gram-negative bacteria are of great concern worldwide, especially in patients admitted to hospitals in developing countries, where mortality rates and costs are extremely high and significant, especially when multidrug-resistant strains are implicated. [18-20] In a study carried out in an ICU in Juiz de Fora - MG, in 2015, the mortality rate was 73,53%, 25 deaths of the 34 patients infected with KPC. 20

In the study, patients over 18 years of age were specifically selected, with a mean age of 53 years, a similar result from other authors.[16-17,21] Regarding the most affected gender, there was a predominance of males in all regions, with a total of 50% of the samples, corroborating with other studies.[17,22] Other studies showed no significance between sex/age and the development of infections by resistant microorganisms[15], being one of the limitations found for collecting epidemiological data for the study.

Regarding carbapenem-resistant K. pneumoniae, the frequency in Brazilian hospitals is high, as reported by other authors. [21,23] These bacteria are more frequent in a hospital environment than other coliforms, including on the surface of the hands and floors and other locations can potentially be a reservoir during outbreaks.[24-25] Among the strains analyzed with the KPC factor, Klebsiella pneumoniae had the highest percentage, with 84% in a total of all regions, with the South region having the highest frequency with 92%. In the study by Dienstmann et al., (2010) 8, there was also a prevalence of the same bacteria with a total of 70%, as well as in the study by Amorim et al, (2014). [26]

Thus, the early detection of patients infected or colonized by KPC is of great importance, since these microorganisms can cause serious infections and there is a shortage of therapeutic options. In addition, it is necessary to im-

Table 2: Prevalence of beta-lactam antibiotics with greater resistance and sensitivity in K. pneumoniae producing KPC.

Região Estado	Ano	Média da Maior Resistência (%)	Média de menor Resistência (%)	Média de Maior Sensibilidade (%)
Centro-Oeste				
Distrito Federal	2006 - 2013	Ertapenem 92,8	Gentamicina 57	Amicacina 96
Goiás	2006 - 2010	Ertapenem 100	Gentamicina 57	Fosfomicina 92,2
Mato Grosso	2011 - 2013	Ertapenem 100	-	-
Sudeste				
Espírito Santo	**2006 - 2010**	**Ertapenem 100**	**Gentamicina 31,15**	**Fosfomicina 92,2**
Minas Gerais	2006 - 2013	Ertapenem 100	Gentamicina 23,3	Gentamicina 95,6
São Paulo	2007 - 2009	-	Gentamicina 12	Amicacina 94,7
Rio de Janeiro	2006 - 2015	Ertapenem 100	Gentamicina 24,7	Amicacina 95,7
Sul				
Paraná	2009 - 2011	Ertapenem 40	-	Imipenem 83
Santa Catarina	**2006 - 2010**	**Ertapenem 100**	**Gentamicina 31,15**	**Fosfomicina 92,2**
Rio Grande do Sul	2007 - 2014	Ertapenem 97,2	Gentamicina 28,2	Fosfomicina 100

Source: Author (2020)

plement contact precautions protocols in addition to hand hygiene training, thus providing adequate treatment for patients and controlling the dissemination of this type of resistance mechanism in Brazil and worldwide. [27-29]

In developing countries like Brazil, the density of antibiotic use is higher, particularly in intensive care units. [30] This high consumption of antimicrobials results in the selective pressure of antibiotics, the main responsible for the urgency of resistant and multiresistant samples, which adding to the existence of dominant clones and the failure in the basic practices of infection prevention and control justify the spread of this microorganism in the hospital environment. [6,31-34] Data from Hospital Conceição - Uberlândia, show very high rates of bacteria resistant to antibiotics [35], particularly related to their high consumption. [30,36-37]

The absence of susceptibility to Ertapenem was already expected, considering that it is a marker of resistance to carbapenems, and may be directly related to the KPC enzyme or to other mechanisms that decrease susceptibility to this antimicrobial in a specific way. [38] Our review study showed 100% resistance to Ertapenem in most states, with PR, in the South, the only one with a low percentage of only 40% between 2009 and 2011.

The CIM related to the antimicrobial Imipenem may be related to the decrease in permeability of the outer membrane due to loss of porin, associated with the production of beta-lactamase. [38] On the other hand, data from MYSTIC [39] point to an increase in the susceptibility of K. pneumoniae in recent years, in the USA, due to the practice of controlling the dissemination of resistant samples. Unlike the results found in our study, in which Meropenem was the second antibiotic with the highest resistance, being in the state of PR where it had a better result with only 32% resistance compared to the others.

Like the study by ALMEIDA (2013)[40] these results presented K. pneumoniae as the microorganism with greater resistance to carbapenems. An increasing prevalence of these microorganisms increased the dependence on the use of carbapenems, antimicrobials considered as the option for the treatment of infections with multidrug-resistant Gram-negative bacilli. [27] The crucial fact resulting from the emergence of samples of K. pneumoniae with resistance to carbapenems in the few treatment alternatives, which include Colistin and Tigecycline, which present problems in terms of toxicity and efficacy, respectively. [27] Currently, the choice of drugs is very restricted, and treatment is carried out with the combination of three antibiotics: Polymyxin B, Tigecycline and Amikacin, or together with aminoglycosides.

The absence of susceptibility to Ertapenem was already expected, considering that it is a marker of resistance to carbapenems, and may be directly related to the KPC enzyme or to other mechanisms that decrease susceptibility to this antimicrobial in a specific way.

According to a study carried out in Porto Alegre[22], presented sensitivity equal to or above 70% for K. pneumoniae, Gentamicin 70%, Tigecycline 79.4%, highlighting Amikacin with sensitivity of 97,5%, as well as our study in which Amikacin had higher percentages of 92% in the Midwest and Southeast, with Fosfomycin being the highlight for the South with 100% sensitivity for the state of RS. In another similar study[41] 100% sensitivity to gentamicin was observed among KPC-producing isolates of K. pneumoniae, as well as in our study in which the state of MG showed a similar result with 95,6% sensitivity. Bearing in mind that none of these antimicrobials has an adequate relationship in serious systemic infections, the association of one or more antibiotics to combat these infections is indicated, if possible.

In the study by Seibert et al. (2014) 23 presented 83% resistance to Meropenem and 91,5% to Ertapenem, since Ertapenem has a carbapenem resistance marker, which may be directly related to the KPC enzyme or other mechanisms, which reduce the sensitivity to this antimicrobial in a specific way , such as the production of other beta-lactamases and loss of porins. [40,42] In a study involving 62 KPC-producing isolates of K. pneumoniae, resistance to carbapenems Imipenem, Meropenem and Ertapenem was 98%, 96% and 100%, respectively. [43] In this study, the authors concluded that resistance to Er-

tapenem represented the most sensitive clinical test for detecting KPC production. [29,44-45] All of these results being compatible with that of our study.

There are few studies on epidemiology involving risk factors in patients infected with K. pneumoniae in our country. On the other hand, there are several published articles characterizing the association between risk factors and KPC-producing Gram-negative bacteria. [46]

The National Health Surveillance Agency (ANVISA) approved in 2018 the first specific antibiotic to fight resistant bacteria, including KPC. [47] The drug is a combination of the antibiotic ceftazidime and avibactam, being effective against two other bacteria considered critical for public health: Pseudomonas aeruginosa and broad-spectrum beta-lactamase-producing Enterobacteria. [48]

KPC has a high potential for dissemination as a global health issue. K. pneumoniae had the highest percentage for KPC-producing bacteria, due to its plasmidial location, which facilitates the transfer of the interspecies gene and has been of concern in hospitals and health institutions worldwide. [23]

Regarding bacterial multiresistance, the indiscriminate use of antimicrobials is the main responsible for this problem. The greatest concern refers to the hospital environment and, mainly, to seriously ill and immunosuppressed patients. On the other hand, another contributing factor to the resistance is the carelessness of health professionals with the patient severely colonized or infected by microorganisms, such as non-adherence and precaution of adequate contact and non-use of PPE's.

There are few studies on epidemiology involving risk factors in patients infected with K. pneumoniae in our country. On the other hand, there are several published articles characterizing the association between risk factors and KPC-producing Gram-negative bacteria.

The South region had a higher prevalence of KPC isolates more specifically in the state of Paraná, followed by the Midwest Region, with the Federal District standing out. Santa Catarina was the most worrying state in relation to the high rate of isolates for K. pneumoniae with KPC factor, which is a multi-resistant bacterium of great concern worldwide. States with a higher rate of development have greater access to treatment with antibiotics and their indiscriminate use is also a worrying factor for the spread of bacteria.

Ertapenem proved to be the best indicator of resistance to carbapenems, and may or may not be related to the production of the enzyme Klebsiella pneumoniae carbapenemase. Aminoglycosides and Tigecycline showed a good percentage of sensitivity, showing a reasonable therapeutic option in the treatment of carbobenemic-resistant enterobacteria and its association with one or more antimicrobials is recommended. [23]

CONCLUSION

KPC is an important hospital pathogen and is spreading worldwide. The lack of preventive measures can be the main factor for the spread of these pathogens. Because of this, it is important and necessary the rapid laboratory detection of the resistance mechanisms of these microorganisms, as well as the adoption of rigorous and immediate measures for prevention and control of dissemination, such as the implementation of contact precautions and appropriate treatment. ■

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