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Risk factors for Healthcare-Associated Infections caused by KPC-producing Enterobacteriaceae: a case-control study

Fatores de risco para Infecções relacionadas à Assistência à Saúde causadas por Enterobacteriaceae produtoras de Klebsiella pneumoniae carbapenemase: um estudo de caso controle

Factores de riesgo para Infecciones relacionadas con la Asistencia Sanitaria causadas por Enterobacteriaceae productoras de Klebsiella pneumoniae carbapenemase: un estudio de caso control

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ABSTRACT:

Objective: To evaluate the risk factors for healthcare-associated infections caused by *Klebsiella pneumoniae* carbapenemase producing *Enterobacteriaceae*.

Method: This is a retrospective case-control study that consisted of a sample of 82 infected patients and 164 controls, totaling 246 patients. Data collection was performed between January and May 2017 through search in the Automated Hospital Infection Control System and in the electronic patient records.

Results: Patients previously colonized with gram-negative microorganisms (OR: 10.7, 95% CI: 2-60, p=0.007), with cancer (OR: 20.8, 95% CI: 4-120, p<0.001), using a double lumen catheter (OR: 30.5, 95% CI: 2-382, p=0.008), with pressure injury (OR: 136.2, 95% CI: 11- 1623, p<0.001) and Intensive Care Unit stay (OR: 1.4, 95% CI: 1.2-1.6, p <0.001) had a greater chance of developing Healthcare-associated Infections caused by KPC-producing *Enterobacteriaceae* than the control group. The area under the ROC curve showed a good overall performance (0.99, 95% CI: 0.992-0.998) of the final logistic regression model.

Conclusion: Previous colonization, cancer, double lumen catheter use, pressure injury and ICU stay were very important risk factors for the acquisition of infections in the hospital environment.

Key words: Enterobacteriaceae; Cross Infection; Drug Resistance, Microbial.

RESUMO:

Objetivo: Avaliar os fatores de risco para infecções relacionadas à assistência à saúde causadas por Enterobactérias produtoras de *Klebsiella pneumoniae carbapenemase*.

Método: Estudo de caso-controle, retrospectivo que foi composto por uma amostra de 82 pacientes infectados e 164 controles, totalizando 246 pacientes. A coleta de dados foi realizada entre janeiro e

maio de 2017, por meio de busca no Sistema Automatizado de Controle de Infecção Hospitalar e nos prontuários eletrônicos dos pacientes.
Resultados: Pacientes previamente colonizados com microrganismos gram-negativos (OR: 10,7, IC 95%: 2-60, p=0,007), com câncer (OR: 20,8, IC 95%: 4-120, p<0,001), utilizando cateter de duplo lúmen (OR: 30,5, IC 95%: 2-382, p=0,008), com lesão por pressão (OR: 136,2, IC 95%: 11-1623, p<0,001) e internação na Unidade de Terapia Intensiva (OR: 1,4, IC 95%: 1,2-1,6, p<0,001) tiveram maior chance de desenvolver infecções relacionadas à assistência à saúde causadas por Enterobactérias produtoras de *Klebsiella pneumoniae carbapenemase* quando comparadas ao grupo controle. A área sob a curva ROC apresentou um bom desempenho geral do modelo final de regressão logística (0,99, IC95%: 0,992-0,998).
Conclusão: Colonização prévia, câncer, uso de cateter de duplo lúmen, lesão por pressão e permanência na UTI foram fatores de risco muito importantes para a aquisição de infecções no ambiente hospitalar.

Palavras-chave: Enterobacteriaceae; Infecção Hospitalar; Resistência Microbiana a Medicamentos.

RESUMEN:
Objetivo: Evaluar los factores de riesgo para infecciones relacionadas con la asistencia sanitaria causadas por *Enterobacteriaceae* productoras de carbapenemas.
Método: Este es un estudio retrospectivo de casos y controles que consistió en una muestra de 82 pacientes infectados y 164 controles, totalizando 246 pacientes. La recopilación de datos se realizó entre enero y mayo de 2017 mediante la búsqueda en el Sistema Automatizado de Control de Infecciones Hospitalarias y en los registros electrónicos de pacientes.
Resultados: Pacientes previamente colonizados con microorganismos gramnegativos (OR: 10.7, 95% CI: 2-60, p=0.007), con cáncer (OR: 20.8, 95% CI: 4-120, p<0.001), utilizando una catéter de doble luz (OR: 30.5, 95% CI: 2-382, p=0.008), con lesión por presión (OR: 136.2, 95% CI: 11- 1623, p<0.001) y permanecer en la Unidad de Cuidados Intensivos (OR: 1.4, 95% CI: 1.2-1.6, p <0.001) fueron más propensos a desarrollar infecciones causadas por *Enterobacteriaceae* productoras de carbapenemas que el grupo control. El área bajo la curva ROC mostró un buen rendimiento general (0,99; IC 95%: 0,992-0,998) del modelo de regresión logística final.
Conclusión: La colonización previa, el cáncer, el uso de catéteres de doble luz, la lesión por presión y la estadía en la UCI fueron factores de riesgo muy importantes para la adquisición de infecciones en el entorno hospitalario.

Palabras clave: Enterobacteriaceae; Infección Hospitalaria; Farmacorresistencia Microbiana.

INTRODUCTION

Healthcare-Associated Infections (HAIs) caused by *Klebsiella pneumoniae* Carbapenemase (KPC)-producing *Enterobacteriaceae* represent a serious global public health problem. In the United States, at least 140,000 infections caused by *Enterobacteriaceae* are reported annually, of which more than 9,000 are related to the production of carbapenemase, with more than 600 deaths per year. In Europe, between 2013 and 2015, all countries reported the occurrence of KPC, raising concerns due to the serious threat to patients, since there is little to no available treatment options. Since the first reports in Brazil in 2006, emerging cases have been warning the multidisciplinary team to put an effort in the reduce transmission or development of the antimicrobial resistance [1-3].

The wide spread dissemination of blaKPC genes and its resistance to most available antibiotics, in particular to carbapenems, has required preventive measures to reduce the risk of transmission of microorganisms in health services. We highlight that protocols to reduce transmission or how to reduce selective pressure need to be implemented if risk factors for the development of multiresistant organisms are identified [4,5].

Early detection of risk factors can reduce the cross transmission of microorganisms in the environment and decrease morbimortality caused by pathogens. However, there is still no consensus in the literature on which risk factors are directly associated with HAIs caused by KPC-producing *Enterobacteriaceae.*[4,6] The objective of this study was to evaluate the risk factors for healthcare-associated infections caused by KPC-producing *Enterobacteriaceae.*

METHOD

This is a retrospective case-control study that was developed in a general private hospital in Belo Horizonte, capital of Minas Gerais State, in the southeast region of Brazil. This hospital has an average of 1,130 patients hospitalized per month.

For the sample selection, a ratio of two controls was used for each case (2:1). There were 82 patients and 164 controls, totaling 246 patients. Cases were HAIs caused by KPC-producing *Enterobacteriaceae* between 2013 and 2016 and controls were no HAIs, but colonized with non-carbapenemase producing *Enterobacteriaceae*.

Patients presenting non-carbapenemase-producing *K. pneumoniae* were randomly selected for the control group, selected by sex and proportional age. All patients, cases and controls, needed to be 18 years of age or older and have three days or more of hospitalization in the hospital setting in order to be included in the study.

Data collection was performed between January and May 2017 through search in the Automated Hospital Infection Control System and in the electronic patient records. A structured instrument was used to collect data related to the risk factors for infection.

The epidemiological data in the study hospital have been raised through active prospective search by nurses of the Infection Control Service. In this case, the National Healthcare Safety Network (NHSN) methodology of the Centers for Disease Control and Prevention (CDC) was used with the support of the Infection Control software. The date of event of the NHSN site-specific infection criterion was considered after the 3rd calendar day of admission to an inpatient location where day of admission is calendar day 1.

Potential risk factors were evaluated through the patient's electronic medical record. Data obtained included medications (eg, use of immunosuppressants, use of corticoid and use previous of antibiotics), comorbidities (eg, diabetes, heart disease, chronic obstructive pulmonary disease, chronic kidney disease, cancer, hematological diseases), presence of device, hospitalization data (eg, transfer from another institution, previous hospitalization, previous colonization, current hospital stay, ICU stay, recent surgical procedure, surgical wound and pressure injury).

During the study period, the detection of a KPC-producing *Enterobacteriaceae* occurred by the Minimum Inhibitory Concentration (MIC) and the Modified Hodge Test (MHT). The bacterial suspension technique was used in sterile saline from isolated colonies on Mueller Hinton agar plate and disc diffusion test of the antibiotic imipenem in the center of the plate for incubation at 37°C for 18 to 24 hours.

After this initial detection, the isolated microorganisms were sent to the Central Public Health Laboratory for the implementation of the Polymerase Chain Reaction (PCR) *"in house*" methodology for molecular identification of the blaKPC gene. All methodologies

followed the parameters determined by the Clinical & Laboratory Standards Institute and Technical Note 01/2013 of the Brazilian National Health Surveillance Agency [7,8].

For data analysis, an exploratory and descriptive statistical analysis was made. Univariate data analysis was performed using 95% confidence intervals (95% CI) for Odds Ratio (OR). The statistical hypothesis testing was evaluated using the Chi-square test and, when necessary, the Fisher's exact test, which considered a significance level of 5% (α=0.05) for bilateral tests. Non-parametric continuous variables were evaluated by the Mann-Whitney test.

Second, multiple logistic regression was used for multivariate analysis. All variables that obtained a p-value <0.20 were included. By the backward criterion and the Wald test, the least significant variables were removed one by one for the adjustment of the final model, which represented only the variables that obtained a p-value <0.05. All analyzes were carried out in the Epi Info® version 7 program.

The Receiver Operating Characteristic (ROC) curve was used to evaluate the predictive capacity of the final multivariate analysis model. In addition to the ROC curve, calculations were performed to simulate the chance of infection based on the risk factors found in the final multivariate analysis model, both calculated by the Microsoft Excel® 2013 program. To simulate the chance of infection, the following formula was used:

$$P = \frac{\exp(-5.7 + 2.4X_1 + 3.0X_2 + 3.4X3 + 4.9X4 + 0.3X_5)}{1 + \exp(-5.7 + 2.4X_1 + 3.0X_2 + 3.4X3 + 4.9X4 + 0.3X_5)}$$

Where: P = chance of infection; X_1 = Prior colonization by microorganisms (0 or 1); X_2 = Cancer (0 or 1); X_3 = Double lumen catheter (0 or 1); X_4 = Pressure injury (0 or 1); X_5 = Days of ICU stay (days).

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais, protocol number 1.821.249 (2016). This was a retrospective database study, therefore, it was not necessary to provide written informed consent by the patient. This study was carried out in accordance with the principles of the Declaration of Helsinki.

RESULTS

The study sample consisted of 82 cases and 164 controls, in a total of 246 patients. The average age of the two groups was 71 years (SD±13.6), with a minimum age of 30 and a maximum of 93. Most patients, both in the case and in the control groups, were males, married, white and with completed high school.

Most of HAIs caused by KPC-producing *Enterobacteriaceae* occurred by *Klebsiella pneumoniae* (68%) and were diagnosed in the blood (30%). There was a high prevalence of primary bloodstream infection (BSI) associated with central venous catheter (30%). The mortality rate was 62%.

Table 1 showed the main findings of univariate and multivariate analysis related to HAIs caused by KPC-producing *Enterobacteriaceae*. Risk factors identified by the multivariate analysis were previous colonization by gram-negative microorganisms (OR: 10.7, 95% CI 2-60), cancer (OR: 20.8, 95% CI 4-120), double lumen catheter

(OR: 30.5, 95% CI 2-382), pressure injury (OR: 136.2, 95% CI 11-162) and ICU stay (OR: 1.4, 95% CI 1.2-1.6) that increased the chance of developing HAIs caused by specific microorganisms.

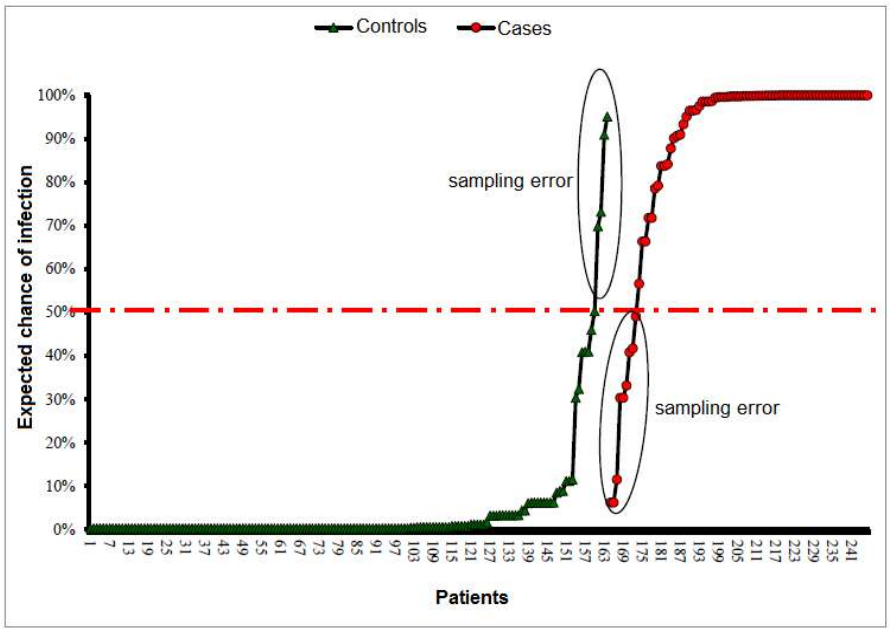
Table 1: Univariate and multivariate analysis of risk factors related to HAIs caused by KPC-producing *Enterobacteriaceae*, Brazil, 2017.

Variables	Controls (n=164)	Cases (n=82)	Univariate analysis			Multivariate analysis		
			OR	95%CI	p-Value	OR	95%CI	p-Value
Medications								
Use of immunosuppressants*	2	12	13.9	3-64	<0.001			
Use of corticoid*	2	4	4.1	1-23	0.1			
Use previous of antibiotics	39	63	10.6	6-20	<0.001			
Previous use of antibiotics (AD)**	1.7	14.1	-	-	<0.001			
Comorbidities								
Diabetes	20	21	2.5	1-5	<0.001			
Heart disease	16	19	2.8	1-6	<0.001			
Chronic pulmonary disease	8	12	3.3	1-9	<0.001			
Chronic kidney disease	14	18	3.0	1-6	<0.001			
Cancer (active disease)	14	39	9.7	5-20	<0.001	20.8	4-120	<0.001
Hematological diseases *	4	17	10.5	3-32	<0.001			
Presence of device								
Ventilator*	5	39	28.8	11-78	<0.001			
Catheter-delay bladder	20	44	8.3	4-16	<0.001			
Central venous catheter	17	60	23.6	12-47	<0.001			
Double-lumen catheter	3	11	8.3	2-31	<0.001	30.5	2-382	0.008
Hospitalization data								
Transfer from another institution	7	20	7.2	3-18	<0.001			
Previous hospitalization	28	49	7.2	4-13	<0.001			
Previous Hospitalization(AD)**	1.36	8,3	-	-	<0.001			
Previous colonization	10	45	18.7	9-41	<0.001	10.7	2-60	0.007
Current hospital stay (AD)**	8.3	60.6	-	-	<0.001			
ICU stay	45	76	33.6	14-82	<0.001			
ICU stay (AD)**	1.4	29.2	-	-	<0.001	1.4	1.2-1.6	<0.001
Recent surgical procedure	74	44	1.41	1-2	0.224			
Surgical wound	68	31	0.8	0-1	0.679			
Pressure injury *	3	38	46.3	14-157	<0.001	136.2	11-162	<0.001

Notes: *Fisher's exact test; **Mann-Whitney test. Abbreviations: AD, average days; ICU, Intensive Care Unit.
Source: Elaborated by the authors.

The area under the ROC curve evaluated the predictive capacity of the final multivariate analysis model using multiple logistic regression and showed a good overall performance (0.99, 95% CI: 0.992-0.998) in relation to sensitivity of the individual as an infectious event. The simulation of chance of infection based on the risk factors identified in the final model of multivariate analysis showed that the case-group had a predicted chance of infection concentrated between 90 and 100% because patients in this group had a greater number of risk factors (Figure 1).

Figure 1: Curve of simulation of chance of infection, per patient, between the case and control group, Belo Horizonte, Minas Gerais, Brazil, 2017.



Source: Elaborated by the authors.

DISCUSSION

The spread of blaKPC gene is a serious public health problem that directly affects clinical treatments in several health services. Since the first reports in Brazil, emerging cases have been warning about the importance of controlling these microorganisms which involves a great effort of the multidisciplinary team to reduce infections [9].

The mortality of 62% found in our study was similar to other studies that presented rates above 40%. Researchers explain that the aspects related to the complexity of the microorganism, the severity of patients, as well as their comorbidities directly influence the high mortality [4,10-12]. Although the mix case analysis is not possible, the results suggest a high mortality among patients with KPC-producing *Enterobacteriaceae*.

Early identification of risk factors is important to plan for infection prevention and control strategies. Our study showed five risk factors associated with HAIs caused by KPC-producing *Enterobacteriaceae*: 1) previous colonization, 2) ICU stay, 3) double lumen catheter, 4) pressure injury and 5) cancer (active disease). Most of these risk factors can be identified early by health professionals.

We detected that the majority of the patients who had previous colonization used antimicrobials. This can be attributed to the use of broad-spectrum antibiotics that promote selection effects under the intestinal flora, provoking resistance under the local microbiota. Studies have been emphasizing the importance of implementing the components of infection prevention and control programmes to reduce the risk of cross-transmission [11,13-15].

Severe patients, often undergoing routine invasive procedures and exposed to the use of broad spectrum antibiotics in ICU, were considered at risk for developing HAIs. Intensive Care Unit designed to assist patients selected by type of disease or

intervention, such as heart disease, neurological, surgical, among others. Therefore, ICU stay may contribute to mortality in those patients who are already infected with KPC-producing *Enterobacteriaceae* because they are more prone to the various infectious diseases [4,6,14,16].

The double lumen catheter is a type of invasive procedure commonly implanted in the ICU that had a strong association with KPC infection in our study. This device is an invasive vascular access that favors the entry of microorganisms and increases the chances of HAI [6,15-17]. Studies showed renal diseases and dialysis as a factor predisposing to infections and that may be linked to the use of the double lumen catheter [10,18].

Pressure injury was presented as a risk factor that predisposes HAIs and was found mainly in the sacral region. In addition 10.4% of KPC-producing *Enterobacteriaceae* were found in tissues of inpatients for tertiary care [17,19]. Bed restriction, prolonged hospitalization, and ineffective decubitus change are factors preventable by the care team to reduce this adverse event [20].

Our study also showed that cancer as an active disease was one of the five risk factors among the case group and corroborated with a research that showed the different types of cancers associated with bacteremia caused by *Klebsiella pneumoniae* [21]. The aggressive procedures frequently used to treat the disease as well as repeated hospitalizations for chemotherapy contribute to the acquisition of microorganisms that predispose infections in the hospital environment [11,22].

We evaluated the risk factors found in the study individually, per patient, based on the final model of the multivariate analysis. The simulation of chance of infection showed the greater the number of risk factors attributed to the patient, increases the chance of getting infections.

Calculation of the chance of infection simulation showed that the case group had a predicted chance concentrated between 90 and 100% because they had a greater number of higher risk factors than the control group that remained below 10%. Most of the risk factors have modifiable characteristics and, therefore, can be quickly recognized by the multidisciplinary team and worked early in the hospital environment.

This retrospective case-control study has some limitations that must be recognized. The data collection occurred retrospectively and for this reason, problems were noted in the data records in the electronic medical record. The use of electronic medical records presented problems of missing data and incomplete records. There were shortcomings of medical prescriptions regarding the prescribed antibiotics, generating doubts regarding the monotherapy or combined therapy and thus, the researchers chose to disregard these variables.

CONCLUSION

In this study, it was possible to evaluate the risk factors for healthcare-associated infections caused by *Klebsiella pneumoniae* carbapenemase producing *Enterobacteriaceae*. Previous colonization, cancer, double lumen catheter use, pressure injury and ICU stay were very important risk factors for the acquisition of infections in the hospital environment.

Most risk factors can be minimized when infection prevention and control programs are effectively implemented in the hospital setting. Health services should institute measures that reduce the spread of the KPC-producing *Enterobacteriaceae* to implement programs that promote the rational use of antimicrobials, as an antimicrobial stewardship and to make a constant surveillance in all the aspects that correspond to the current guidelines of prevention and control of infections.

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