




Epidemiological profile of healthcare-associated infections caused by Carbapenemase-producing Enterobacteriaceae*

Perfil epidemiológico das infecções relacionadas à assistência à saúde causadas por Enterobactérias produtoras de Carbapenemase

Perfil epidemiológico de las infecciones relacionadas con la asistencia sanitaria causadas por Enterobacterias productoras de Carbapenemasa

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ABSTRACT

Objective: To study the epidemiological profile of Healthcare-associated Infections caused by Enterobacteria which carry the *Klebsiella pneumoniae* Carbapenemase gene (blaKPC) in the hospital environment. **Method:** A descriptive study was conducted in a private hospital in Belo Horizonte, MG, Brazil, which included all patients with infections caused by Enterobacteriaceae which carry the *Klebsiella pneumoniae* Carbapenemase gene. The data were collected by the Automated System of Hospital Infection Control and analyzed by descriptive statistics by the *Epi Info 7* program. **Results:** Eighty-two (82) patients participated in the study. *Klebsiella pneumoniae* was the most frequent species (68%) isolated in blood (30%), bronchoalveolar lavage (22%) and urine (18%), while catheter-associated bloodstream infection (30%) predominated regarding topography. A case fatality rate of 62% is highlighted in evaluating the outcome. **Conclusion:** The resistance genes spread rapidly, limiting the antimicrobial options for treating infectious diseases. The epidemiological profile of Healthcare-Associated Infections found in this study can be prevented by prevention and infection control programs.

DESCRIPTORS

Enterobacteriaceae; Cross Infection; Drug Resistance; Microbial; Infection Control.

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INTRODUCTION

“Healthcare-Associated Infections (HAIs) represent a serious global public health problem, as they lead to longer hospitalization, higher healthcare costs and increased morbidity and mortality in health services⁽¹⁾. It is estimated that the incidence in Europe is 4 million inpatients per year. In the United States, approximately 1.7 million HAIs are reported annually, with records higher than 90,000 deaths. In Brazil, it is known that the last national study showed a HAI prevalence of 15% in hospitals”⁽¹⁻³⁾.

Antibiotics (ATB) have revolutionized the treatment of HAIs, representing a major breakthrough for modern medicine. However, the empirical, indiscriminate and irrational use of these substances has become an exponentially dangerous factor for the development of antimicrobial resistance⁽⁴⁻⁶⁾.

Carbapenemase-producing Enterobacteriaceae which carry the blaKPC gene (CPE-KPC) stand out among bacteria of epidemiological importance which present unrestrained growth in its resistance profile. These microorganisms spread rapidly and end up being associated with a high mortality rate by limiting the therapeutic options for infected patients^(5,7-8).

Although international studies are well advanced in relation to the subject, especially in those aspects which concern the rapid genotypic laboratory detection of the microorganism in the hospital environment, the World Health Organization (WHO) affirms that there are still gaps in research that should be better investigated. In addition, data in Brazil are limited in relation to the epidemiological aspects of the blaKPC gene among enterobacteria⁽⁸⁻¹¹⁾.

It is believed that the data will serve as subsidies for broad discussions related to planning actions which reduce the chance of infection in Health Care Facilities. Therefore, this study aimed to raise the epidemiological profile of HAIs caused by Carbapenemase-producing Enterobacteriaceae which carry the blaKPC gene (CPE-KPC) in the hospital environment.

METHOD

STUDY DESIGN

This is an epidemiological and descriptive study.

SCENARIO

This study was conducted in a general private hospital of Belo Horizonte, MG, Brazil. The institution has 167 inpatient beds and 30 Intensive Care beds, with an average of 1,130 patients hospitalized per month and performs approximately 7,389 surgeries per year.

Notification of HAIs is performed through an active prospective search by the nurses of the Infection Control Service. In this case the National Healthcare Safety Network (NHSN) system of the Center for Disease Control and Prevention (CDC) is used with the support of a Hospital Infection Control software⁽¹²⁾. The NHSN methodology has been incorporated by the study hospital for HAI diagnosis since 2002, justifying the choice of the CDC criteria for HAI reporting.

STUDY POPULATION

The potential study population was comprised of 82 (100%) patients who acquired HAI caused by CPE-KPC between 2013 and 2017. All patients diagnosed with the blaKPC gene had phenotypic confirmation by the hospital laboratory of this study and genotype by the Public Health Central Laboratory of Minas Gerais⁽¹³⁾.

SELECTION CRITERIA

The inclusion criteria were being 18 years of age or older and having 3 days or more of hospital stay. According to the CDC, an infection is considered HAI when the occurrence date occurs during the third day of admission or after this period^(12,14).

The period delimitation (2013 to 2017) was due to the fact that the electronic medical record in the study hospital was totally installed in June/2012, in addition to having undergone a major structural reform in the three Intensive Care Units during the same period, which could have contributed to a change in the local microbiological profile.

DATA COLLECTION

Data collection was performed between January and May 2017 by the researcher through a search in the Automated Hospital Infection Control System (*SACIH – Sistema Automatizado de Controle de Infecção Hospitalar*) and the patient's electronic medical record. *SACIH* was created and validated in 1993 by physicians, statisticians and system analysts using the adapted methodology of the National Nosocomial Infections Surveillance (NNIS) of the United States^(2,12).

The collection instrument was composed of sociodemographic data (age, gender, skin color, education and marital status) and epidemiological data (microorganism, specimen, HAI topography, minimal inhibitory concentration of antimicrobials which follow the standards of the Clinical & Laboratory Standards Institute, and the patient outcome)⁽¹⁴⁾.

DATA ANALYSIS AND PROCESSING

After compiling the information, the results were aggregated into a spreadsheet generated by *Microsoft Excel 2013*[®].

For processing the data, descriptive statistical analysis was performed by the Epi Info[®] version 7 program for presenting absolute values, percentages, 95% confidence intervals (CI 95%), mean and standard deviation.

ETHICAL ASPECTS

The project was approved by the Research Ethics Committee under protocol number 1.887.637 (2017) in compliance with Resolution 466/2012 of the National Health Council, which refers to the Guidelines and Norms Regulating Human Research⁽¹⁵⁾.

RESULTS

The study sample consisted of 82 (100%) patients with a mean age of 71 years (sd ± 13.6), with a minimum age of 30 and a maximum of 93 years. The socio-demographic

profile (Table 1) showed a prevalence of males (66%), married (57%), white (66%) and high school graduates (49%).

Table 1 – Sociodemographic profile of patients with HAIs caused by Enterobacteria carrying the gene – Belo Horizonte, MG, Brazil, 2017.

Variables	n	%	CI95%
Gender			
Female	28	34	25-39
Male	54	66	61-75
Civil status			
Married	47	57	46-68
Separated/Others	23	28	19-39
Single	12	15	8-24
Skin color			
White	54	66	55-76
Black	18	22	14-32
Brown	10	12	6-21
Education			
Elementary	15	18	11-28
High school	40	49	38-60
Undergraduate	26	32	22-43
Postgraduate	1	1	0-7

Note: (n=82).

Most of the HAIs caused by CPEC-KPC occurred by *Klebsiella pneumoniae* (68%) and were isolated in blood (30%), bronchoalveolar lavage (22%) and urine (18%). In relation to topography, there was a prevalence of catheter-associated bloodstream infection (BSI) (30%). In the outcome evaluation, a case fatality rate of 62% of the patients was highlighted (Table 2).

Table 2 – HAI profile caused by Enterobacteria carrying the blaKPC gene – Belo Horizonte, MG, Brazil, 2017.

Variables	n	%	CI 95%
Bacteria			
<i>Klebsiella pneumoniae</i>	56	68	57-78
<i>Serratia marcescens</i>	19	23	15-34
<i>Enterobacter cloacae</i>	7	9	4-17
Specimen			
Blood	25	30	21-42
Bronchoalveolar lavage	22	27	16-35
Urine	18	22	14-32
Tissue fragment	7	9	3-15
Abdominal fluid	7	9	3-15
Catheter tip	3	4	1-10
Topography			
Catheter-associated bloodstream infection	25	30	21-42
Catheter-associated urinary tract infection	18	22	14-32
Infection of the lower respiratory tract, except pneumonia	16	20	12-30
Surgical site infection	14	17	10-27
Ventilator-associated pneumonia	6	7	3-15
Cardiovascular system infection	3	4	1-10
Outcome			
Discharge/Transfer	31	38	27-49
Death	51	62	51-73

Note: (n=82).

Microbial susceptibility profile to antimicrobials tested by Minimum Inhibitory Concentration (MIC) showed resistance to carbapenems meropenem, imipenem and ertapenem among *Klebsiella pneumoniae*, *Serratia marcescens* and *Enterobacter cloacae* (Table 3).

Table 3 – Descriptive analysis of the sensitivity profile between Carbapenemase-producing Enterobacteriaceae carrying the blaKPC gene – Belo Horizonte, MG, Brazil, 2017.

Antimicrobials	<i>Klebsiella pneumoniae</i> * (n=56)		<i>Serratia marcescens</i> ** (n=19)		<i>Enterobacter cloacae</i> *** (n=7)	
	n	%	n	%	n	%
Nalidixic acid	1	2	5	26	1	14
Amikacin	44	79	5	26	3	43
Amoxicillin/Clavulanic acid	1	2	2	11	2	29
Ampicillin	2	4	2	11	1	14
Ampicillin/Sulbactam	0	0	2	11	1	14
Cefepima	6	11	1	5	0	0
Cefoxitin	1	2	8	42	2	29
Ceftazidime	0	0	1	5	0	0
Ceftriaxone	1	2	0	0	0	0
Cefuroxime	0	0	3	16	2	29
Cefuroxime axetil	2	4	5	26	2	29
Ciprofloxacin	19	34	14	74	5	71
Colistin	47	84	1	5	7	100
Ertapenem	0	0	0	0	0	0
Gentamicin	29	52	15	79	5	71
Imipenem	0	0	0	0	0	0
Meropenem	0	0	0	0	0	0
Piperacillin/Tazobactam	1	2	5	26	3	43
Tigecycline	30	54	17	89	3	43
Trimethoprim/Sulfamethoxazole	13	23	8	42	5	71

Note: No. of specimens tested by microorganisms: [**Klebsiella pneumoniae* (n=56) subdivided in: blood (n=17), urine (n=17), tracheal aspirate (n=12), tissue fragment (n=6), abdominal fluid (n=3) and BAL (n=1)]; [***Serratia marcescens* (n=19) subdivided in: blood (n=8), tracheal aspirate (n=6), catheter tip (n=3), abdominal fluid (n=1) and urine (n=1)]; [****Enterobacter cloacae* (n=7) subdivided in: tracheal aspirate (n=4), abdominal fluid (n=2) and tissue fragment (n=1)]. (n=82).

DISCUSSION

The mean age of the study groups was 71 years, well above the data in the literature, which ranged from 49 to 64 years⁽¹⁶⁻¹⁸⁾. In this case, the high age was mainly attributed to the profile of patients attended at the institution: chronic, with the need for semi-intensive care and who remained hospitalized for a longer time. However, the prevalence of males, marital status, skin color and education did not obtain a specific explanation in the literature regarding infectious events^(16,19).

Klebsiella pneumoniae was the most frequent species, mainly in BSI, respiratory tract infections and urinary tract infection. Studies have shown the prevalence of this microorganism in BSI and have highlighted the importance of the etiological agent for the current epidemiological context. Primary bloodstream infections are generally associated with the use of vascular catheters because such devices have direct binding to blood vessels, and such invasiveness can be considered a gateway for microorganisms^(18,20).

The presence of enterobacteria in bronchoalveolar lavage samples was also highlighted. A systematic review showed that the lung was the most common infection site related to *Klebsiella pneumoniae*⁽²¹⁾. Another study found similar findings in tracheal secretions⁽¹⁹⁾.

Regarding the outcome of patients, it was highlighted that the high lethality of 62% observed in this study was similar to other studies which presented rates above 50%. It is inferred that the HAI topography, as well as the limitation to the antimicrobial treatments received during the hospitalization period have a strong impact on the evolution of the patient's death. In addition, aspects related to the complexity of the microorganism, the severity of the patient, as well as their comorbidities influence the high lethality rate^(16-18,22).

Enterobacteria carrying the blaKPC gene contribute to spreading the phenomenon of antimicrobial resistance, which has been surpassing continental barriers and becoming a problem which directly affects the current treatments^(4,23). Changes in the sensitivity profile of microorganisms have been promoting therapeutic limitations and generating concern about what has been done worldwide to combat resistance^(5,23).

This study showed that the antimicrobials of the carbapenem group had a very low sensitivity profile, according to the parameters described in Technical Note 01/2013 of ANVISA (*Agência Nacional de Vigilância Sanitária* – Brazilian Health Regulatory Agency) and the Facility Guidance for Control of Carbapenem-resistant Enterobacteriaceae of the Atlanta CDC^(5,13). A study has reported that the sensitivity profile of microorganisms to antimicrobials can range from 0% to 4% when tested on *Klebsiella pneumoniae*⁽²⁴⁾. Similar data were also found in the *Serratia marcescens* and *Enterobacter cloacae* species⁽²⁵⁻²⁶⁾. It is important to emphasize the fact that the therapeutic limitation is a problem due to the rapid dissemination of resistance genes among the community, negatively impacting the outcome of hospitalized patients⁽²⁴⁾.

There was a low sensitivity of the microorganisms to cefepime, ceftazidime and ceftriaxone in the cephalosporin group. Gentamicin, belonging to the aminoglycoside group, was considered a good therapeutic option, and the sensitivity could vary between 52% and 79%. Tigecycline also proved to be a good indication for treatment. Colistin was effective in combating *Klebsiella pneumoniae* (84%) and *Enterobacter cloacae* (100%), but it did not obtain the same sensitivity for *Serratia marcescens* (5%). This can be attributed to the already intrinsic resistance of the microorganism to the colistin antimicrobial among the last species⁽²⁷⁾. However, despite the availability of some drugs for treating HAIs, there is still a restriction for using these options, with the use of combination therapy and/or dose optimization being indicated to decrease mortality⁽²⁸⁻²⁹⁾.

In this sense, it is worth emphasizing that the pharmaceutical industries have reduced investments for new discoveries of antibiotics at the present time. The approval of new antimicrobials by the US Food and Drug Administration (FDA) has reduced by 56% in the last 20 years, warning of the importance of creating measures which encourage and facilitate the development of new substances, especially for the fight against infections caused by resistant microorganisms⁽³⁰⁾.

This study had some limitations that should be recognized. The data collection occurred retrospectively and therefore problems were noted in the data in the electronic medical records. It was also observed that there were only three microorganism species confirmed for the blaKPC gene, showing that the epidemiological and microbiological profile only represented the reality of the study hospital.

CONCLUSION

In this study it was possible to reaffirm the importance of Carbapenemase-producing Enterobacteriaceae, in particular carriers of the blaKPC gene for the current epidemiological context. Resistance genes spread rapidly in the hospital setting, and end up negatively impacting the patient's life by limiting the antimicrobial options for treating HAIs due to the more severe complications, which can lead to death.

It is important to conclude that the multidisciplinary team should be more involved in preventing and controlling infections. This will reduce the length of hospital stay, morbidity and mortality, and care costs related to infectious diseases.

The epidemiological profile of HAIs found in this study can be prevented by infection prevention and control programs to reduce infectious diseases caused by enterobacteria which carry the blaKPC gene. It is hoped that the data found in this study may contribute to new research perspectives for HAIs, however new research is still fundamental and imperative to be carried out to enrich and understand this theme.

RESUMO

Objetivo: Levantar o perfil epidemiológico das Infecções relacionadas à Assistência à Saúde causadas por Enterobactérias que carregam o gene *Klebsiella pneumoniae* Carbapenemase (blaKPC) no ambiente hospitalar. **Método:** Estudo descritivo, realizado em um hospital privado de Belo Horizonte, MG, Brasil que incluiu todos os pacientes com infecções causadas por Enterobactérias que carregam o gene *Klebsiella pneumoniae* Carbapenemase. Os dados foram coletados pelo Sistema Automatizado de Controle de Infecção Hospitalar e analisados por estatística descritiva pelo programa *Epi Info 7*. **Resultados:** Participaram do estudo 82 pacientes. A *Klebsiella pneumoniae* foi a espécie mais frequente (68%) isolada no sangue (30%), lavado broncoalveolar (22%) e urina (18%). Em relação à topografia, prevaleceu a infecção de corrente sanguínea associada a cateter (30%). Na avaliação do desfecho, destacou-se uma taxa de letalidade de 62% dos pacientes. **Conclusão:** os genes de resistência se disseminam de forma rápida, limitando as opções antimicrobianas para o tratamento dos agravos infecciosos. O perfil epidemiológico das Infecções relacionadas à Assistência à Saúde encontrado neste estudo pode ser trabalhado de forma preventiva pelos programas de prevenção e controle de infecção.

DESCRITORES

Enterobacteriaceae; Infecção Hospitalar; Resistência Microbiana a Medicamentos; Controle de Infecções.

RESUMEN

Objetivo: Inventariar el perfil epidemiológico de las Infecciones relacionadas con la Asistencia Sanitaria causadas por Enterobacterias que transfieren el gen *Klebsiella pneumoniae* Carbapenemasa (blaKPC) en el entorno hospitalario. **Método:** Estudio descriptivo, llevado a cabo en un hospital de Belo Horizonte, MG, Brasil, que incluyó a todos los pacientes con infecciones causadas por Enterobacterias que transfieren el gen *Klebsiella pneumoniae* Carbapenemasa. Los datos fueron recogidos por el Sistema Automatizado de Control de Infección Hospitalaria y analizados por estadística descriptiva por el programa *Epi Info 7*. **Resultados:** Participaron en el estudio 82 pacientes. La *Klebsiella pneumoniae* fue la especie más frecuente (68%) aislada en la sangre (30%), lavado broncoalveolar (22%) y orina (18%). Con relación a la topografía, prevaleció la infección de torrente sanguíneo asociada con catéter (30%). En la evaluación de los resultados, se destacó una tasa de letalidad del 62% de los pacientes. **Conclusión:** Los genes de resistencia se diseminan de modo rápido, limitando las opciones antimicrobianas para el tratamiento de los agravamientos infecciosos. El perfil epidemiológico de las Infecciones relacionadas con la Asistencia Sanitaria encontrado en este estudio los puede trabajar de manera preventiva los programas de prevención y control de infección.

DESCRIPTORES

Enterobacteriaceae; Infección Hospitalaria; Farmacorresistencia Microbiana; Control de Infecciones.

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