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Prevalence and antimicrobial susceptibility profile of ESKAPE pathogens from the Federal District, Brazil

Prevalência e perfil de suscetibilidade aos antimicrobianos de bactérias do grupo ESKAPE no Distrito Federal, Brasil

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ABSTRACT

Introduction: The leading cause of hospital-acquired infections are the pathogens named by the acronym ESKAPE, which are the initials for the following bacterial: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa* and *Enterobacter* spp., which have high resistance rates by escaping the action of the antimicrobial. **Objective:** To trace the antimicrobial susceptibility profile of the ESKAPE pathogens in a primary public hospital in the Federal District, Brazil. **Methods:** A cross-sectional, retrospective and descriptive study was conducted by analyzing the corresponding data from January 2010 to December 2015 of samples considered positive to ESKAPE pathogens in order to generate an antimicrobial susceptibility profile. **Results:** Analyzing the Gram-positive bacteria, almost 80% of *E. faecium* strains were vancomycin-resistant *enterococci* (VRE) and almost 40% of *S. aureus* strains were methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA). It was observed that gram-negative strains (the ESKAPE group) examined in this study have a higher resistance rate to carbapenems than in other studies. In the molecular analysis, four *Klebsiella pneumoniae* strains were positive to bla_{KPC} gene, three strains to bla_{NDM} and one *Acinetobacter baumanni* strain was positive to bla_{OXA-23} gene. **Conclusion:** Studies such as this should be performed periodically in order to evaluate the bacterial susceptibility profile. They demonstrate the importance of implementing strategies to prevent hospital-acquired infections, as well as greater antibiotic prescribing control.

Key words: microbial sensitivity tests; genes; bacteria.

INTRODUCTION

Bacteria may be intrinsically resistant to an antimicrobial, when it is an inherent characteristic of a species, related to chromosomal genes. Furthermore, they may acquire resistance to certain antimicrobials through chromosomal mutations or horizontal gene transfer by three mechanisms: 1) bacteriophage-mediated transduction; 2) transformation by chromatin incorporation of chromosomes, plasmids and deoxyribonucleic acid (DNA) from dead organisms; and 3) conjugation through plasmids and conjugative transposons[1, 2]. These transfers may occur in water, soil, food, and the digestive system of animals and humans[3].

These resistances hindering patients' treatment, since the use of broad spectrum antimicrobials is required, but the development and approval of new drugs grow at a much slower rate than the emergence of bacterial resistance. Bacterial resistance mechanisms usually occur two or three years after the introduction of a new antimicrobial into therapy[4] and a drug of this type can take 12 to 22 years to be available in the market[5]. This reduces the effectiveness of the antimicrobial treatment, making it difficult and costly, which can increase the length of hospital stay of infected patients and often leading to their death[6-8]. Bacteria from the ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa* and *Enterobacter* spp.) are the main causes of hospital-acquired infections in the United States and they are able to escape from the antimicrobial actions due to the resistance profile[9].

It is necessary that studies trace periodically the bacterial resistance profile, to contribute for both local and global epidemiological data. These data assist in therapeutic management, since they consider the prevalence of resistance

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locally, adding it to the clinical effectiveness and cost of the antimicrobial. The present study aims to evaluate the susceptibility profile of ESKAPE pathogens in a primary hospital of the public network of the Federal District, Brazil.

METHODS

Characterization of the study

The present study is considered cross-sectional, retrospective and descriptive, in which were analyzed the data from antimicrobial susceptibility tests performed in the microbiology sector of the clinical analysis laboratory of a hospital in the public network of Brasília, Brazil, in the period from January 2010 to December 2015. The hospital analyzed is a primary hospital, and does not have an intensive care unit. This study was approved by the Research Ethics Committee of the Faculty of Health Sciences of the Universidade de Brasília (UnB) CAAE: 38856114.0.0000.0030.

Data analysis

Using WHONET 5.6 software, 2,527 samples were analyzed, among which 577 were positive to the ESKAPE group pathogens. Data such as age, sex and type of sample were considered. The minimum inhibitory concentration (MIC) used to trace the susceptibility profile was interpreted from the cut-off points determined by the Clinical & Laboratory Standards Institute (CLSI) 2015.

WHONET is a program developed for the analysis and monitoring of microbiological data, especially for antimicrobial susceptibility test. It was developed in 1989 by the Collaborating Center for Surveillance of Antimicrobial Resistance of the World Health Organization (WHO), helping to understand epidemiological data for antimicrobial choice and outbreak detection[10]. It is a free program, used in more than 90 countries, and available in more than 20 languages, including Portuguese.

Bacterial isolates

The resistance genes were investigated in eight samples that were sent to the Central Public Health Laboratory of the Federal District [Laboratório Central de Saúde Pública do Distrito Federal (LACEN/DF)] for genetic identification, of which seven *Klebsiella pneumoniae* strains and one *Acinetobacter baumannii*. The criterion for sending the strains of these enterobacteria used by the laboratory of clinical analyzes of the public health network was the carbapenem-resistance profile and also the modified Hodge test or enzymatic blockade test with positive ethylenediamine tetraacetic acid (EDTA)[11, 12].

Molecular detection of genes by polymerase chain reaction (PCR)

For molecular confirmation, the genes: bla_{KPC}, bla_{NDM}, bla_{IMP} e $bla_{VIM,}$ were investigated, since they were the most prevalent in carbapenem-resistant enterobacteria, and the $bla_{OXA-23,}$ gene in carbapenem-resistant *Acinetobacter baumannii* in Brazil[13, 14]. For this purpose, we used the primers indicated in **Table 1**.

TABLE 1 – Primers used

Primers	Sequence	Amplicon size (PB)
NDM F	5' GGTTTGGCGATCTGGTTTTC	512
NDM R	5' GGCCTTGCTGTCCTTGATC	
KPC F	5' TGTCACTGTATCGCCGTC	1011
KPC R	5' CTCAGTGCTCTACAGAAAACC	
VIM F	5' GATGGTGTTTGGTCGCATATC	332
VIM R	5' CTCGATGAGAGTCCTTCTAGAG	
IMP F	5'AACACGGTTTGGTGGTTCTT	440
IMP R	5'GGACTTTGGCCAAGCTTCTA	
OXA-23 F	5'GATCGGATTGGAGAACCAGA	501
OXA-23 R	5' ATTTCTGACCGCATTTCCAT	

NDM: New Delhi metalo-betalactamase; F: forward; R: reverse; KPC: Klebsiella pneumoniae *carbapenemase; OXA: oxacilinase.*
Source: Faria Junior et al. *(2016)[15] and Woodford N* et al. *(2006)[16].*

The reactions were subjected to the temperature cycles programming of 2 minutes at 94ºC, followed by 40 cycles, denaturation at 94ºC for 45 seconds, annealing at 58ºC for 45 seconds and extension at 72ºC for 1 minute. The PCR was concluded with the extension cycle at 72ºC for 2 minutes. The PCR products, 15 µl, were visualized on 2% agarose gel electrophoresis, prepared in 1× tris-acetate-EDTA (TAE) buffer, followed by gel staining in ethidium bromide solution; the amplified fragments were observed by ultraviolet light (UV) transilluminator using KODAK Gel Logic 200 Imaging System (Eastman Kodak Company).

RESULTS

When analyzing the samples regarding age and gender, it was observed that 52% of the patients are male and 48.2% correspond to the age group of 60 years or older (**Table 2**).

From 577 samples, the most prevalent microorganism was *Klebsiella pneumoniae* (41%), followed by *Staphylococcus aureus* (22%), *Pseudomonas aeruginosa* (14%), *Enterobacter spp.* (11%),

TABLE 2 – Age group by sex of positive samples between 2010 and 2015

Age group (years)	Total	%	Female	%	Male	%
0-9	40	6.9	20	7.2	20	6.7
10-19	16	2.8	16	5.8	0	0
20-59	206	35.7	103	37.1	103	34.4
≥ 60	278	48.2	124	44.6	154	51.5
Not reported	37	6.4	15	5.4	22	7.4
Total	577	100	278	100	299	100

Acinetobacter baumannii (8%) and *Enterococcus faecium* (4%). The isolates analyzed were obtained mainly from urine (46%), retal swab (19%), nasal swab (11%) and blood (8%). In urine and rectal swab, the microorganism most commonly found *Klebsiella pneumoniae*, and in nasal swab and blood, was *Staphylococcus aureus* (**Table 3**).

When analyzing gram-positive bacteria, about 80% of the *Enterococcus faecium* strains were resistant to vancomycin – vancomycin-resistant enterococci (VRE) –, and also had a higher resistance to erythromycin (95.8%), followed by ciprofloxacin (91.7%), ampicillin (91.7%) and penicillin G (91.7%), and increased sensitivity to linezolid (87.5%) and daptomycin (83.3%) (**Figure**).

TABLE 3 – Microorganisms by sample type between 2010 and 2015

Microorganism	Urine	Rectal swab	Nasal swab	Blood	Other*	Total
Enterococcos faecium	3	20	-	1	-	24
Staphylococcus aureus	17	-	63	29	19	128
Klebsiella pneumoniae	165	54	-	5	10	234
Acinetobacter baumannii	8	16	1	5	15	45
Pseudomonas aeruginosa	30	9	-	3	39	81
Enterobacter spp.	46	9	-	2	8	65
Total	269	108	64	45	91	577

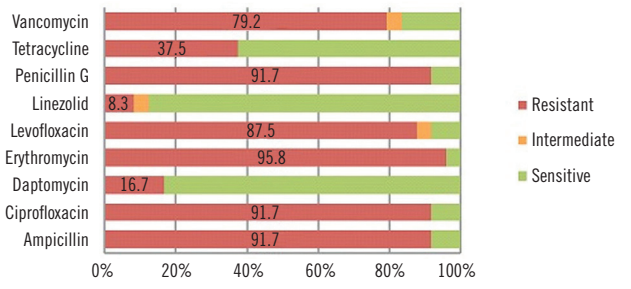

FIGURE – *Susceptibility profile of* Enterococcus faecium

The red bar represents the percentage of antimicrobial resistance, the orange bar indicates the intermediate profile and the green bar represents the percentage of sensitivity.

From the *Staphylococcus aureus*, 40% strains presented resistance to oxacillin (MRSA), 96.9% were resistant to penicillin G, 75.8% to erythromycin and 63.3% to ciproflxacin and levoflxacin. *S. aureus* strains resistant to linezolid (3.9%), daptomycin (4.7%) and vancomycin (2.3%) were also found.

When analyzing the susceptibility profile for *Klebsiella pneumoniae*, it was possible to observe that this strain presented the highest resistance rates to the following antimicrobials: aztreonam, cefepime and cefotaxime (75.2%) and ertapenem (69.7%); and the lowest rate of resistance was 2.6% to amikacin.

Acinetobacter baumannii presented the most worrying susceptibility profile, presenting a resistance frequency of 100% to imipenem; 91.1% to ciprofloxacin, ceftazidime and cefotaxime; 88.8% to cefepime; 86% to meropenem and 82.2% to levofloxacin.

The highest resistance rates to *Pseudomonas aeruginosa* were 54.3% to ciprofloxacin, 53.1% to levofloxacin and imipenem, and 47% to norfloxacin. While that to *Enterobacter* spp. 96% were resistant to cephalothin; 87.5% to amoxicillin/clavulanic acid; 79.2% to cefoxitin; 78.5% to ampicillin; and 73.9% to cefotaxime.

In molecular analysis, the bla_{KPC} gene was found in four *Klebsiella pneumonieae* strains, which were one in rectal swab specimens and three in urine samples; the bla_{NDM} gene was found in three *Klebsiella pneumonieae* positive retal swab samples, while the bla_{OXA-23} gene was found in one *Acinetobacter baumannii* strain isolated from a tissue fragment culture.

DISCUSSION

The incidence of VRE among the *E. faecium* is worrisome, since these strains have become a worldwide problem due to infections caused in association with hospital morbidity and mortality[17], as well as *S. aureus* strain resistant to linezolid and daptomycin, these antimicrobials are considered as the final option for the treatment of infections caused by MRSA[18].

Compared to a study conducted in Latin America (Argentina, Brazil, Chile and Mexico) from 2008 to 2010, the susceptibility profile analyzed in this study showed a greater resistance to imipenem and meropenem, while in Latin America they showed resistance around 6% to these antimicrobials and 36% to cefepime. However, in this study the resistance found to amikacin and gentamicin was lower than that found in Latin America, 7.8% and 33%, respectively[19]. When comparing the results obtained

with a study conducted in 2011 in a university hospital in Londrina, Paraná, Brazil, the profile found in the present study demonstrated a higher frequency of resistance compared to the following antimicrobials: ertapenem (40%) and cefotaxime, cefepime and aztreonam (60%)[20].

Acinetobacter baumannii showed the most worrying susceptibility profile, since this bacterium are easy to develop resistance. In the 1990s, most strains were sensitive to quinolones and carbapenems, and several outbreaks of multidrug resistant strains have been reported in recent years[21]. The decrease in susceptibility to carbapenems can be observed when comparing two studies conducted by the Sentry Antimicrobial Surveillance Program in Brazil in 2001 and 2010, especially imipenem, which reduced from 97.8% to 27%, and to meropenem, which previously was 96.7% and today is 27.3%[19, 22]. In a study that analyzed only the Gram-negative pathogens of the ESKAPE group in the Latin American countries *A. baumanni* was the pathogen with the highest resistance rate to amikacin, cefepime, ceftazidime, imipenem and levofloxacin[23].

When comparing *Pseudomonas aeruginosa* with a study carried out in Bahia, by Assis *et al*. (2012)[24], 66% of the strains were resistant to levofloxacin and 51%, to amikacin, that is, they showed greater resistance. However, this study showed less resistance to meropenem (34%)[24]. Comparing the results obtained with another study conducted in Latin America (Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Panama, Peru and Venezuela), it was possible to observe a greater resistance to imipenem (44.9%) and to levofloxacine (38.2%), and a similar resistance rate to meropenem (38.4%) and Amikacin (20.5%)[25].

Regarding *Enterobacter spp*., this study presented a greater resistance to amoxicillin/clavulanic acid than the study carried out in Rondônia, Brazil, in which the resistance rate was 66.7%[6].

Klebsiella pneumoniae carbapenemase (KPC) strain, New Delhi metalo-betalactamase (NDM-1) and oxacilinase-23 (OXA-23) are carbapenemases. KPC belongs to Amber class A and NDM-1, to Amber class B [metalo-β-lactamase (MBL)[26, 27]]. Class A hydrolyzes penicillins, cephalosporins, carbapenems and aztreonam, but this hydrolysis is inhibited *in vitro* by the clavulanic acid and tazobactam. However, class B hydrolyzes all beta-lactams mentioned above, with the exception of aztreonam, and does not have its activity inhibited by beta-lactam inhibitors, since its hydrolysis depends on the interaction of betalactam with zinc ions at its catalytic site; its activity is inhibited *in vitro* by EDTA[14]. Oxacillinases are class D, and in Brazil OXA-23 stands out[13, 28].

These genes have already been described in Brazil, and the first report of the presence of KPC in brazil was in 2009, after the discovery of the gene in strains isolated from a patient in an intensive care unit at a tertiary hospital in Recife, Brazil[29]. The first strain containing NDM-encoding gene in Brazil was isolated in Rio Grande do Sul and later a strain with this gene was also found in the Federal District[15, 30]. The first description of OXA-23 in Brazil was established from *A. baumannii* isolates found in 1999 in two tertiary hospitals in Curitiba, Paraná, Brazil[31].

It is important to emphasize that the hospital studied is considered small and, although only few strains with resistance profile have been found, this is still worrying. This resistance is not specific to this hospital, since most of the patients come from other hospitals in the public health network of the Federal District, which arrive already colonized or infected by multidrug resistant (MDR) microorganisms.

CONCLUSION

Brazil took an important step towards the control of multi-drug resistant strains by prohibiting the sale of antimicrobials without prescription through the RDC 44/2010, which was replaced by the RDC 20/2011 of the National Sanitary Surveillance Agency [Agência Nacional de Vigilância Sanitária (Anvisa)], reducing its irrational use. However, many practitioners still prescribe antimicrobials without any need, or prescribe broad spectrum antimicrobials when the first-choice antimicrobials are effective. Thus, this work demonstrates important data that reflect an increase in the prevalence of MDR strains in hospitalized patients of the Federal District, Brazil.

RESUMO

Introdução: *Os principais patógenos causadores de infecções nosocomiais foram resumidos pela sigla ESKAPE, que são as iniciais das seguintes bactérias:* Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanni, Pseudomonas aeruginosa *e* Enterobacter *spp., as quais possuem altas taxas de resistência por conseguirem escapar das ações dos antimicrobianos.* ***Objetivo:*** *Traçar o perfil de suscetibilidade antimicrobiana do grupo ESKAPE em um hospital primário da rede pública do Distrito Federal, Brasil.* ***Métodos:*** *Foi realizado um estudo transversal, retrospectivo e descritivo, analisando os dados correspondentes de janeiro de 2010 a dezembro de 2015 para as amostras consideradas positivas para o grupo ESKAPE, com o intuito de gerar um perfil de sensibilidade aos antimicrobianos.* ***Resultados:*** *Ao analisar bactérias Gram positivas, quase 80% das cepas de* Enterococcus faecium *foram resistentes à vancomicina (VRE) e cerca de 40% das cepas de* Staphylococcus aureus*, resistentes à oxacilina (MRSA). Nas bactérias do grupo ESKAPE, observaram-se cepas com uma taxa de resistência maior aos carbapenens do que em outros estudos. Ao realizar uma análise molecular, quatro cepas de* Klebsiella pneumoniae *foram positivas para o gene* bla_{KPC} *e três, para o* bla_{NDM}*; uma de* Acinetobacter baumanni *foi positiva para o gene* bla_{OXA-23}*.* ***Conclusão:*** *Estudos como este devem ser realizados periodicamente de modo a avaliar o perfil de suscetibilidade das bactérias. Eles demonstram a importância do uso de estratégias para evitar infecções nosocomiais, bem como um maior controle na prescrição de antimicrobianos.*

Unitermos: *testes de sensibilidade microbiana; genes; bactérias.*

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