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Occurrence and resistance profile of bacteria belonging to the ESKAPE group in hemodialysis patients

Ocorrência e perfil de resistência de bactérias pertencentes ao grupo ESKAPE em pacientes hemodialíticos

Perfil de ocurrencia y resistencia de bacterias pertenecientes al grupo ESKAPE en pacientes en hemodiálisis

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ABSTRACT

Introduction: Hemodialysis is the main treatment for patients with Chronic Renal Insufficiency and one of the main complications resulting from it is the occurrence of infections caused by opportunistic microorganisms belonging to the "ESKAPE" group. **Aim:** to determine the frequency of isolation of pathogens from the ESKAPE group and evaluate their respective antimicrobial resistance profiles in hemodialysis patients in a medium and high complexity hospital located in the Amazon. **Outlining:** Retrospective study carried out with collection of data available in the medical records of 167 patients diagnosed with Chronic Renal Insufficiency, undergoing hemodialysis or peritoneal dialysis from 2015 to 2019 in a regional hospital in the Southeast of Pará. **Results**: Of the 174 bacteriological cultures analyzed, 70.1% were positive and, of these, 57.4% were positive for bacteria belonging to the ESKAPE group. The most frequent microorganism belonging to the ESKAPE group was *Staphylococcus aureus* (47.1%); as to the resistance levels, 50% of *Acinetobacter baumannii* were resistant to carbapenems. **Implications:** The phenotypic profile of multidrug resistance to antimicrobials in strains of *Acinetobacter baumannii* was identified, highlighting the importance of knowledge about the profile of sensitivity to antimicrobials for a more assertive treatment and better prognosis.

DESCRIPTORS

Renal Insufficiency; Drug Resistance, Multiple; Cross Infection; Renal Dialysis.

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INTRODUCTION

The Chronic Renal Insufficiency (CRI) consists in the degradation of the kidney function in a progressive manner, the mechanisms that maintain homeostasis fail, causing uremia and requiring appropriate treatment for the maintenance of life. It can be caused by chronic glomerulonephritis, pyelonephritis, uncontrolled hypertension, infection, amongst other.[1]

In accordance with Brazilian Society of Nephrology (SBN)[2], the estimated number of people with chronic kidney disease in the world approaches 850 million people. The mortality rate is increasing, approximately 2.4 million deaths occur per year.[2] A census carried out in 2014 showed that the total number of dialysis patients was approximately 112 thousand, presenting higher incidence and prevalence rates in the Southeast region (49%) and lower in the North region (4%).[3]

The main treatment for CRI is the hemodialysis, which consists of replacing the renal function of blood filtration by artificial equipment, based on the diffusion processes between membranes, to remove excess of water, solutes, and toxins. Therefore, this procedure provides the maintenance of homeostasis, which is primordial to gain time until the renal transplantation is possible. In addition, to carry out this process, venous accesses are made, which may be catheters, arteriovenous fistulas, or arteriovenous grafts.[1]

Thus, the main complication resulting from the treatment is the occurrence of infections by opportunistic microorganisms due to greater immunological fragility and greater exposure associated with the breakdown of the integrity of the primary barriers, resulting in a higher frequency of hospital occurrences due to Healthcare-Associated Infections (HAIs).[4] These infections are the main causes of morbidity and mortality among immunosuppressed patients who undergo invasive clinical procedures that frequently occur in hemodialysis patients, such as punctures, insertion of catheters and prostheses.[4]

Amongst the main microorganisms associated with HAI there is a group called "ESKAPE", which is composed of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp*.[5] These bacteria have the capacity for rapid replication, high transmissibility, high rates of antimicrobial resistance and high pathogenicity. They can display resistance to several antimicrobials, including drugs of last therapeutical choice, through the production of enzymes, change in membrane permeability, efflux pumps, and modification of the antibiotic target site.[6-9] Thus, it is necessary to emphasize that these bacteria are priority and critical for research and development of new therapeutic options.[9]

Therefore, considering the greater susceptibility of hemodialysis patients to infections caused by bacteria belonging to the ESKAPE group and the scarcity of research on this topic in the region, the knowledge about the clinical-epidemiological profile of these microorganisms and their phenotypic characteristics of antimicrobial resistance is of great value, enabling the mitigation of damages inherent to health, in addition to bringing economic benefits to the health service.

Thus, the present study aimed to determine the frequency of bacterial isolation of pathogens of ESKAPE group and evaluate their respective profiles of antimicrobial resistance in hemodialysis patients from a hospital of medium and high complexity located in the Amazon.

METHOD

METHOD

This is a cross-sectional study with a quantitative approach carried out at the Regional Hospital that provides medium and high complexity services to patients in 15 municipalities in the

Southeast of the State of Pará, Brazil. These fifteen municipalities belong to the 12th Regional Center of Health. The hospital is located at a distance of 1,018 km from the capital, Belém, currently has 98 beds and several specialties, with emphasis to the department of nephology with transplant service implemented in 2012. In addition, it has a renal replacement therapy service with 32 hemodialysis machines and the capacity to serve 180 patients.

Upon approval by the Research Ethics Committee of the Faculty of Higher Education of the Gathered Amazon with the Certificate of Presentation for Ethical Appreciation (CAAE): 30736820.2.0000.8104 and opinion: 4.126.561, meeting the Resolution 466/12 from the National Health Council, the data collection period began. In order to select the participants, inclusion and exclusion criteria were applied. There were included patients diagnosed with CRI, of both sexes, undergoing hemodialysis or peritoneal dialysis, who had cases of infections or colonization in the 2015 to 2019 period, over 18 years, and who agreed partaking the study. The medical records of patients who did not meet the inclusion criteria and who had incomplete information were excluded.

The study was carried out through the analysis of reports using hospital's own electronic medical records system, duly released. 174 bacterial cultures from 167 patients diagnosed with CRI were analyzed. Data collection took place between July and August 2020. Data was collected from medical records referring to clinical specimens, isolated microorganisms, and their respective profiles of antimicrobial resistance, which were previously obtained using identification and sensibility tests to antimicrobials in a semi-automatic device (MicroScan 4 Siemens®). The recommendations of the National Health Surveillance Agency (ANVISA) were used for the technical procedure of microbiological analysis of the samples and the recommendations of the Clinical and Laboratory Standards Institute (in force for each year) to determine the susceptibility profile against antimicrobials.

For sociodemographic characterization the variables race, educational attainment, home (rural/urban), municipality of origin, age range and comorbidities were analyzed. After collection, data were tabulated in Excel spreadsheets (Microsoft 2016®) and consolidated according to the appropriate coding for each of the variables studied. Statistical analysis was performed using absolute and percentage distributions.

RESULTS

During the period covered in the study (2015 to 2019), the hospital treated an average of 139 patients per year. It is important to point out that patients are followed up for prolonged periods, with no frequent insertion of new patients. Over this period, 174 bacteriological cultures were requested from 167 patients, of which 70.1% (122/174) were positive and, of these, 57.4% (70/122) were positive for bacteria belonging to the ESKAPE group.

Of the total number of patients cared by the nephrology service during the study period, 38/167 had positive cultures for bacteria from the ESKAPE group, of which 47.7% (18/38) were male and 52.6% (20/38) were female. In addition, 55,3% (21/38) were aged over 30 and 42.1% (16/38) were over 60.

Regarding housing, 14.3% lived in rural areas and 85.7% lived in urban areas, mainly distributed among the municipalities of Redenção (40%), Xinguara (17.4%), São Felix do Xingu (17.2 %). It was observed that the year with the highest number of positive cultures was 2019, with 34.3% (24/70), followed by 2018, with 27.1% (19/70), and 2015, with 17.4% (12/70).

As to the diagnosis of chronic diseases, most of the patients presented Systemic Arterial Hypertension 84.2% (32/38), followed by Diabetes Mellitus 42.1% (16/38) and Glomerulonephritis 10.5% (4/38), worth noting that some patients were

simultaneously diagnosed with Systemic Arterial Hypertension and Diabetes Mellitus 47.36% (18/38).

A higher frequency of positive results was observed in blood culture (28.6%), surveillance cultures (17.1%) and swab test at catheter insertion point (15.7%), followed by catheter tip (14.3%), urine (8.6%), surgical wound exudate (5.7%), among others.

Regarding the etiology of colonization/infections, the most frequently detected microorganism belonging to the ESKAPE group was S. aureus (47.1%), followed by P. aeruginosa (11.4%) and K. pneumoniae (11.4%) (Table 1).

Table 1 – Distribution of bacterial species belonging to the ESKAPE group detected in infections/colonization in hemodialysis patients, Pará, Brazil, 2015 to 2019.

Biological Samples	**Microorganisms (%)**				
	***A. baumannii* (n= 4)**	***S. aureus* (n=35)**	***K. pneumoniae* (n=8)**	***Enterobacter* spp. (n= 6)**	***P. aeruginosa* (n= 17)**
Tracheal aspirate (n=2)	-	2.9	-	-	5.9
Blood (blood culture) (n=20)	-	42.8	25.0	66.6	-
Bronchioalveolar lavage fluid (n=1)	-	-	-	-	5.9
Peritoneal fluid (n=1)	-	-	-	-	5.9
Catheter insertion point (n=11)	25.0	11.4	-	16.6	29.4
Catheter tip (n=10)	25.0	11.4	12.5	-	23.5
Surgical wound (n= 4)	25.0	5.7	-	-	5.9
Foot wound Swab (n=3)	-	8.6	-	-	-
Surveillance Swab (n=12)	25.0	11.4	50.0	-	17.6
Urine (n=6)	-	5.7	12.5	16.8	5.9

Source: Research authors. (%) Numerical data shown in percentage, represents the frequency of positivity for bacteria of the ESKAPE group among clinical specimens. – Numerical data equal to 0.

Regarding the susceptibility profile, it was observed that Gram-negative microorganisms showed low sensitivity to amoxicillin/clavulanate (37%). Whereas in relation to imipenem and meropenem, the strains showed high sensitivity. It is noteworthy that A. baumannii showed high levels of resistance to carbapenems (50%, on average), with a phenotypic profile of multidrug resistance.

For the classes of quinolones and cephalosporins, variable sensitivity rates were observed depending on the drug used. Gram-positive bacteria were highly sensitive to vancomycin in the quantitative method, which was not observed for the group of penicillin, which showed low efficacy for the strains under study (Table 2).

Table 2 – Table 2. Resistance profile of bacterial isolates from colonization/infections in hemodialysis patients, Pará, Brazil, 2014 to 2019.

Microorganisms (n)	Antimicrobial resistance (%) (Semi-automatic device and broth microdilution)																	
	AMI	AMC	ATM	CPM	CFO	CAZ	CRO	CIP	GEN	IMP	MER	SUT	TET	ERI	AZT	RIF	OXA	VAN*
A. baumannii (4)	100	100	100	100	100	100	100	75	50	50	50	100	100	-	-	-	-	-
S. aureus (34)	53	72.7	3	3	18	-	-	-	24.2	-	-	11.7	26.4	73.5	64.7	3	17.6	3
P. aeruginosa (17)	41	-	23.5	29.4	94	41	17	17	29.4	29.4	29.4	100	88.2	-	-	-	-	-
Enterobacter spp. (7)	14	14	14	28	14	14	42	14	0	28	0	0	14	-	-	-	-	-
K. pneumoniae (8)	12.5	75	62.5	62.5	37.5	0	75	37.5	25	0	0	62.5	75	-	-	-	-	-

Source: Research authors. (%) Numerical data shown in percentage, represents the frequency of resistance of the isolates against antimicrobials. – Representation of untested antimicrobials. AMP: Ampicillin; AMI: Amikacin; CPM: Cefepime; TET: Tetracycline; CRO: Ceftriaxone; AMC: Amoxicillin+Clavulanate; SUT: Sulfamethoxazole+Trimethoprim; CIP: Ciprofloxacin; CFZ: Cefazolin; ATM: Aztreonam; PIT: Piperacillin/Tazobactam; CFO: Cefoxitin; CAZ: Ceftazidime; IPM: Imipenem; MPM: Meropenem; GEN: Gentamicin; AZT: Azithromycin; ERI: Erythromycin; RIF: Rifampicin; VAN*: Vancomycin, carried out by microdilution; OXA: Oxacillin;

DISCUSSION

Patients with CFK can be 26 times more affected by infections than the general population, and 100 to 200 times more prone to acquire opportunistic microorganisms.[10] The high rates of infections caused by bacteria belonging to the ESKAPE group detected in this study corroborate this fact. Furthermore, the high positivity in blood cultures shows that bacteremia in dialysis patients represents one of the main causes of morbidity and mortality, as well as increases in hospitalizations and hospitalization costs.[10]

This greater susceptibility is due to the immunological weakness that occurs in these patients, which may be related to the neutrophilic dysfunction associated with uremia, as well as primary diseases such as diabetes and hypertension. Thus, it is possible to comprehend the clinical profile for the individuals included, with 50% presenting associated hypertension and diabetes. Additionally, the failures in the hemodialysis proceeding, such as water contamination, lack of familiarity with the use of the dialyzer, and repetitive breakdown of skin integrity, are important factors.[11-12]

Thereby, it is evident that the continuous carrying out of surveillance bacterial cultures is able to define the epidemiology of the infections in those patients, contribute to the early detection of colonization and thus stop the progression to systemic infections. In this sense, it should be noted that catheter tip and ostium cultures as well as surveillance cultures were also positive, similar to what was found in a study in which most bloodstream infections were related to vascular access (catheter) (76,0%).[13]

Therefore, in addition to the possibility of mitigating the rates of colonization and infections, screening with microbiological tests makes it possible to analyze the virulence and pathogenicity of the etiological agents. As demonstrated in a study on the etiology of nosocomial infections, revealing that of the total of 53 isolated pathogens, the main microorganism involved was Methicillin-Resistant *S. aureus* (MRSA) (16,1%), corroborating the findings of this research.[14] It should be noted that this phenotypic profile of resistance is often associated with changes in the site of action of antimicrobials.

Despite the robust recommendations on good care practices, an evaluation in outpatient hemodialysis units found that the indication and duration of the prophylaxis are not consistent with the guidelines in 20% of the cases, which can worsen the scenario associated with bacterial resistance and prognoses for the patients. [20-21] In addition, it is

necessary to consider that outpatient dialysis facilities are favorable environments for the spread of multidrug-resistant organisms, reinforcing the need to identify and investigate similar strains between patients and the environment, evidencing the occurrence of cross-transmission.[22-23]

Corroborating this fact, a cohort study carried out in a dialysis sector revealed that the acquisition of one or more multidrug-resistant bacteria was frequent, occurring in 40% of patients. Of these occurrences, 13% and 15% acquired MRSA or vancomycin-resistant Enterococcus (VRE), respectively.[22-23] The detection of multidrug-resistant Gram-negative bacteria was even more common 69%, evidencing the problem associated with the transmission of interspecies genes in this group. [22-23]

Another fact that must be considered is that the attempt to decolonize patients, dialysis facilities and hydraulic routes of hemodialysis machines, can facilitate the selection of strains capable of expressing their resistance mechanisms, and may also influence the selection of strains containing genes resistance to disinfectants and antiseptics.[24]

Some strategies, such as the continuous practice of hand hygiene, carrying out surveillance cultures, appropriate catheter care, adequate use of antiseptic agents, rational use of antimicrobials and continued education for the team, can mitigate preventable infections, morbidity, and mortality in this population. [20,25]

It is also necessary to consider the associated external factors, such as the interventions used to increase the outcomes of the agricultural areas and of and animal husbandry carried out in livestock. The use of antimicrobials, which sometimes occurs continuously and indiscriminately, can favor the selection of multi-resistant bacteria from animal and environmental sources and their dissemination to humans, reinforcing the need to adopt One Health precepts.[26]

Finally, about limitations, a retrospective design makes the study vulnerable to possible inaccuracies in data collection. Therefore, to carry new studies to establish the local prevalence correlated with clinical outcomes is of great value.

CONCLUSION

The detection of bacteria belonging to the ESKAPE group among CRI patients and the detection of the observed phenotypic profile of multi-resistance to antimicrobials reinforce the importance of monitoring the sensitivity profile before the antimicrobials through the performing of microbiological tests. Furthermore, greater investment in the prevention and control of the spread of microorganisms among these patients is of great value, especially in those with multidrug resistance, which are associated with higher morbidity and mortality in this population.

RESUMO

Introdução: A hemodiálise é o principal tratamento para pacientes com Insuficiência Renal Crônica e uma das principais complicações decorrentes dela é a ocorrência de infecções causadas por microrganismos oportunistas pertencentes ao grupo "ESKAPE". **Objetivo:** Determinar a frequência de isolamento de patógenos do grupo ESKAPE e avaliar seus respectivos perfis de resistência aos antimicrobianos em pacientes hemodialíticos em um hospital de média e alta complexidade localizado na Amazônia. **Delineamento:** Estudo retrospectivo realizado com levantamento de dados disponíveis em prontuários de 167 pacientes diagnosticados com Insuficiência Renal Crônica, submetidos à hemodiálise ou diálise peritoneal no período de 2015 a 2019 em um hospital regional no Sudeste do Pará. **Resultados**: Das 174 culturas bacteriológicas analisadas 70,1% foram positivas e destas, 57,4% foram positivas para bactérias pertencentes ao grupo ESKAPE. O microrganismo pertencente ao grupo ESKAPE mais frequente foi *Staphylococcus aureus* (47,1%); em relação aos níveis de resistência 50% dos *Acinetobacter baumannii foram* resistentes aos carbapenêmicos. **Implicações:** Identificou-se o perfil fenotípico de multirresistência aos antimicrobianos em cepas de *Acinetobacter baumannii*, ressaltando a importância do conhecimento acerca do perfil de sensibilidade frente aos antimicrobianos para um tratamento mais assertivo e melhor prognóstico.

DESCRITORES

Insuficiência Renal; Resistência a Múltiplos Medicamentos; Infecção Hospitalar; Diálise Renal.

RESUMEN

Introducción: La hemodiálisis es el principal tratamiento de los pacientes con Insuficiencia Renal Crónica y una de las principales complicaciones derivadas de ella es la aparición de infecciones causadas por microorganismos oportunistas pertenecientes al grupo "ESKAPE". **Objetivo:** Determinar la frecuencia de aislamiento de patógenos del grupo ESKAPE y evaluar sus respectivos perfiles de resistencia antimicrobiana en pacientes en hemodiálisis en un hospital de mediana y alta complejidad ubicado en la Amazonía. **Delineación:** Estudio retrospectivo realizado con recolección de datos disponibles en las historias clínicas de 167 pacientes con diagnóstico de Insuficiencia Renal Crónica, sometidos a hemodiálisis o diálisis peritoneal de 2015 a 2019 en un hospital regional del Sudeste de Pará. **Resultados:** De los 174 cultivos bacteriológicos analizados, el 70,1% fueron positivos y de estos el 57,4% fueron positivos para bacterias pertenecientes al grupo ESKAPE. El microorganismo más frecuente perteneciente al grupo ESKAPE fue *Staphylococcus aureus* (47,1%); en cuanto a los niveles de resistencia, el 50% de *Acinetobacter baumannii* fueron resistentes a los carbapenémicos. **Implicaciones:** Se identificó el perfil fenotípico de multirresistencia antimicrobiana en cepas de *Acinetobacter baumannii*, destacando la importancia del conocimiento sobre el perfil de sensibilidad antimicrobiana para un tratamiento más asertivo y mejor pronóstico.

DESCRIPTORES

Insuficiencia renal; Resistencia a Múltiples Medicamentos; Infección Hospitalaria; Diálisis Renal.

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COLLABORATIONS

ERA: substantial contributions in the conception and planning of the research project, obtaining or analysis/interpretation of the data, writing and critical review. KKSA: substantial contributions in the conception and planning of the research project, obtaining or analysis/interpretation of the data. JAGA: substantial contributions in obtaining or analysis/interpretation of the data, and in writing and critical review of the article. **All authors agree and are responsible for the content of this version of the manuscript to be published.**

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AVAILABILITY OF DATA

The data used in this research are available in full in the electronic medical records of the Public Regional Hospital of the Araguaia, located in Redenção, Pará.

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CONFLICTS OF INTEREST

There are no conflicts of interest to declare.