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Evaluation of bacterial susceptibility to carbapenems of strains isolated from patients in an adult intensive care unit

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Abstract

Objective: To describe bacterial susceptibility to carbapenems prescribed to inpatients in the adult intensive care unit (ICU) at public hospital in São Paulo. **Methods:** This is a descriptive and retrospective study of the release reports of treatment with carbapenems and consultations to laboratory tests, including 81 reports and 129 cultures from 70 patients. Data collection was based on patients admitted to the adult intensive care unit of a Municipal Public Hospital who received carbapenem antibiotics from July to September 2021. Results: A total of eighty-one reports for carbapenem treatment in the intensive care unit were analyzed. Male sex prevailed (65.4%). The mean age of patients in the study was 63 ± 15 years. In 59 (72.8%) of the reports, meropenem was used and in the other 22 (27.2%) cases imipenem-cilastatin was prescribed. Empirical therapy was reported in most reports (57/81), 3 reports were incompleted, and 21 reports were specific therapy. In twenty-four cultures, gram-positive bacteria were identified and in forty-six cultures, gram-negative bacteria were identified. *Klebsiella pneumoniae* was the most prevalent pathogen identified in 15 samples, followed by *Pseudomonas aeruginosa* (12). Resistance to meropenem was identified in 15 gram-negative samples, while 16 gram-negative strains were resistant to imipenem. Conclusion: The results of this study indicated a high prevalence of *Klebsiella pneumoniae* followed by *Acinetobacter baumani*, and a high rate of resistance to carbapenems. Thus, it is necessary to periodically update empirical therapy protocols based on the knowledge of the nosocomial microbiota, to prevent bacterial resistance, because the development of resistance mechanisms against antimicrobial compounds is constant.

Keywords: Antibiotic therapy, bacterial resistance, rational use of antimicrobials, carbapenems, intensive care unit

Avaliação da suscetibilidade bacteriana aos carbapenêmicos por cepas isoladas de pacientes em uma unidade de terapia intensiva adulto

Resumo

Objetivo: Descrever a susceptibilidade bacteriana aos antimicrobianos da classe carbapenêmicos, prescritos aos pacientes internados em uma Unidade de Terapia Intensiva (UTI) adulto de um hospital público em São Paulo. **Metodologia:** Trata-se de um estudo descritivo e retrospectivo através dos laudos de liberação de tratamento com carbapenêmicos e consultas a exames laboratoriais, incluindo 81 laudos e 129 culturas de 70 pacientes. A coleta de dados foi baseada nos pacientes internados em UTI adulto de um Hospital Público Municipal que receberam antimicrobianos da classe carbapenêmicos, no período de julho a setembro de 2021. **Resultados:** Um total de oitenta e um laudos de liberação para tratamento com carbapenêmicos na unidade de terapia intensiva adulto foram analisados. Entre os pacientes, o sexo masculino foi predominante com 53 (65,4%). A idade média dos pacientes no estudo foi 63 ± 15 anos. Em 59 (72,8%) dos laudos foram utilizados o meropenem e nos outros 22 (27,2%) casos foram prescritos o imipenem. A terapia empírica foi relatada na maioria dos laudos (57/81), sendo que em 3 laudos não havia a informação preenchida e em 21 deles os tratamentos foram prescritos de forma específica. Em vinte e quatro culturas foram identificadas bactérias gram-positivos e em quarenta e seis culturas foram identificados gram-negativos. A *Klebsiella pneumoniae* foi o patógeno mais prevalente, sendo identificado em 15 amostras, seguido pela *Pseudomonas aeruginosa (12).* A resistência ao meropenem foi identificada em 15 amostras dos gram-negativos, já para o imipenem 16 cepas de gram-negativos foram resistentes. **Conclusão:** Os resultados deste estudo indicaram alta taxa de resistência aos carbapenêmicos para *Klebsiella pneumoniae* e *Acinetobacter baumannii.* Assim, é necessário a atualização periódica dos protocolos de terapia empírica com base no conhecimento da microbiota nosocomial, para prevenção contra a resistência bacteriana, visto que as bactérias desenvolvem constantemente novos mecanismos de resistência aos antimicrobianos.

Palavras-chaves: Antibioticoterapia, resistência bacteriana, uso racional de antimicrobianos, carbapenêmicos, unidade de terapia intensiva.

Introduction

Antibiotic therapy is one of the most prescribed treatments in healthcare, especially in hospitals. These medications are essential for the treatment of infections caused by bacteria, which may have community or nosocomial origins. Community infections are those diagnosed within 48 hours of the patient's hospitalization. If clinical signs of infection are identified after 72 hours, it will be considered a Healthcare-Associated Infection (HAI). Clinical cases involving some type of bacterial infection frequently occur in patients admitted to the Intensive Care Unit (ICU) sector[1-2].

There is high risk of acquiring a bacterial infection during the hospitalization period. Over the years, these microorganisms have acquired different ways of resisting treatments, becoming multi-resistant bacteria, which can hinder defining the most appropriate therapy. For those with recurrent hospitalization or who have already used antimicrobials for previous infections, the probability of encountering resistant bacteria becomes even greater. Another risk factor for bacterial resistance development is misuse of these medications. Antimicrobials are oftentimes prescribed for patients who do not have any infection[1,3].

Excessive consumption of antimicrobials was one of the main factors that led to bacterial resistance, becoming a serious public health problem. Over the years, new medications were developed and these microorganisms continued to evolve and acquire new resistance mechanisms. In the future, there may not be medications that are sensitive to them[3].

Care in choosing the appropriate medication is of significant importance for patient safety. This provides better recovery expectations, as well as it prevents the emergence of new multi-resistant bacteria. One of the ways to choose the correct antimicrobial is by carrying out tests such as the antimicrobial susceptibility test, known as antibiogram. It will show whether the bacteria are resistant to any of the available antimicrobials and which medications are sensitive to the bacteria identified. Some studies show how an appropriately chosen therapy can be a differentiator in the clinical case, which might save the patient's life[3-5].

Among the main treatment types for bacterial infections are empirical and specific ones. Empirical therapy is considered to be defined based on the most likely pathogen for the infection identified, when no diagnosis has yet been made. Specific treatment is the one prescribed directly for a disease that has unique characteristics[6].

To carry out the treatment, there are several classes of antimicrobials, each with its own specificity. Carbapenems are a widely used class due to their broad action spectrum. They have bactericidal action, acting by inhibiting synthesis of the bacteria's cell wall, causing their death. They are indicated for different infection sources, including gastrointestinal tract, lower respiratory tract, skin and appendages, urinary infections and septicemia. Among the main options in this class are meropenem and imipenem, which have similar structures and can resist most beta-lactamase enzymes that cause ineffectiveness of other beta-lactams.

Meropenem has greater coverage for gram-negative bacteria and is known to cause less toxicity when compared to imipenem, reason why it is considered more viable for pediatric and neurological patients. On the other hand, imipenem has greater sensitivity to some gram-positive bacteria.

Even with broad coverage, there are bacteria that have managed to acquire resistance forms to these medications; one of them is *Klebisiella Pneumoniae Carbapenemase (KPC),* which, through the production of carbapenemase enzymes, provides the bacteria with the ability to resist any beta-lactam, reducing the therapeutic options. One of the problems related to KPC is that it presents ease in sharing that resistance, through the transfer of its genes. In these cases, the morbidity and mortality rates are considered higher[7-9].

As bacterial resistance is constantly evolving, it is important to take measures to prevent it, in addition to seeking to reduce the mortality rate it causes. According to data from the World Health Organization, in 2004 infections caused 25% of all deaths worldwide. In 2020, the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária, ANVISA)* declared that bacterial resistance caused nearly 700,000 deaths per year worldwide and that, if measures are not taken, the forecast is that it could reach up to 10 million by 2050[10-11,29]. It is essential to find ways to prevent this alarming increase. Among the main prevention means are implementation of appropriate therapies, collaboration of the professionals involved and raising awareness among the population.

Therefore, the objective of the current paper was to describe bacterial susceptibility to antimicrobials from the carbapenem class, prescribed to patients admitted to the ICU for adults of a public hospital in São Paulo, given that bacterial resistance is constantly evolving and knowledge of the nosocomial microbiota location and susceptibility to the antimicrobial of choice can assist the clinical staff in their management and exert an influence on the patient's prognosis.

Methods

This is a descriptive and retrospective study using carbapenem treatment release reports and laboratory test consultations, including 81 reports and 129 cultures from 70 patients. The research was carried out in the ICU for adults sector at the Doutor Carmino Caricchio Municipal Hospital, located in the city of São Paulo/SP. The institution has 464 beds, 46 of which are ICU beds for adults.

To comply with Resolution 466/2012, the research was initiated after approval by the Ethics and Research Committee, through Certificate of Presentation of Ethical Appraisal (*Certificado de Apresentação de Apreciação Ética*, CAAE) number 57860022.4.0000.0073 and opinion No. 5,411,345. For the sample, the patients admitted to the ICU for adults from July to September 2021 were considered. The sampling group was for convenience, corresponding to the total number of patients who were hospitalized in the sector and in use of the carbapenems available at the institution, namely meropenem and imipenem, within the research period.

Data collection was carried out using a structured form with the following information: gender, age, therapy type, previous treatment, infection type, antimicrobial report, culture requests and results and their antibiograms. The data related to the patients and treatments were taken from the release reports for antimicrobial treatment, which is a hospital-specific document that, after completed by the physician, is

delivered to the pharmacy, which then forwards it to the In-hospital Infection Control Commission (*Comissão de Controle de Infecção Hospitalar, CCIH)* for them to evaluate and control in-hospital antimicrobial use. The report contains the following information: patient's name, hospital record, gender, age, hospitalization date, whether use of the antimicrobial prescribed is empirical, prophylactic or specific, whether the patient has previously used antimicrobials, information about the treatment (dosage, administration route and expected treatment time), reason for the treatment prescribed and whether a culture was requested.

The culture collection results and their respective antibiograms were carried out on the laboratory exam locus used by the hospital; the consultations were carried out within a period of 10 days prior to treatment initiation. All data were tabulated in Excel 2019®. The descriptive data analysis compared the antibiograms and sensitivity of microorganisms to the carbapenems. The quantitative variables were presented as mean +/-SD and the qualitative ones, as absolute and relative frequency (%).

Results

The sample obtained a total of 70 patients corresponding to 81 authorization reports for treatment with carbapenems (Table 1) and 129 culture samples for these patients from July to September 2021 (Table 2). For each patient, from one to two reports were completed within the data collection period, and microorganism culture samples were not performed for all patients. Males were predominant with 53 (65.4%) and 28 (34.6%) were female. The mean age of patients include in the study was 63 +/-15 years old. Meropenem was used in 59 (72.8%) of the reports and imipenem was prescribed in the other 22 (27.2%) (Table 1).

In relation to the type of use, the treatments were mostly determined as empirical in 57 (70.4%) reports, whereas specific treatments were defined in 21 (25.9%) and, this data was not filled out in 3 (3.7%) reports.

For the infection type, it was expected for Healthcare-Associated Infections (HAIs) to be prevalent, which was actually the case. In 67 (82.7%) reports, they were presumably considered as HAIs. Community infection was only classified in 3 (3.7%) of them; however, this information was not filled out in 11 (13.6%).

Previous antimicrobial use was reported in 50 (61.7%) reports, and this information was not filled out in 23 (28.4%) reports (Table 1).

Table 1. Data collection through the carbapenem treatment reports corresponding to the patients that were admitted to the ICU for adults between July and September 2021 at a public hospital in São Paulo (n=70).

N°	SEX	AGE	PREVIOUS USE OF ATB	TYPE USE	TYPE OF INFECTION	PRESCRIBED CARBAPENEMIC
1	M	57	Yes	Empirical	HAI	Imipenem
2	M	67	NP	Empirical	Community	Meropenem
3	M	36	NP	Specific	HAI	Imipenem
4	M	67	Yes	Empirical	HAI	Meropenem
5	M	67	NP	Empirical	HAI	Meropenem
6	M	68	Yes	Empirical	HAI	Meropenem
7	M	66	NP	Specific	NP	Meropenem
8	M	63	Yes	Specific	NP	Imipenem
9	M	63	Yes	Empirical	HAI	Imipenem
10	F	58	Yes	Empirical	HAI	Meropenem
11	F	65	No	Empirical	HAI	Meropenem
12	M	35	Yes	Specific	HAI	Imipenem
13	F	69	No	Empirical	HAI	Meropenem
14	M	50	Yes	Empirical	HAI	Imipenem
15	F	78	NP	Empirical	NP	Meropenem
16	M	80	Yes	Empirical	HAI	Meropenem
17	M	27	Yes	Specific	HAI	Meropenem
18	M	62	NP	Empirical	HAI	Meropenem
19	M	59	Yes	Empirical	HAI	Meropenem
20	M	50	No	Empirical	HAI	Meropenem
21	F	53	Yes	Specific	HAI	Imipenem
22	M	75	No	Empirical	HAI	Imipenem
23	M	58	NP	Specific	NP	Meropenem
24	M	64	Yes	Empirical	HAI	Meropenem
25	M	29	Yes	Empirical	HAI	Meropenem
26	M	29	Yes	Empirical	NP	Imipenem
27	M	53	Yes	Empirical	HAI	Meropenem
28	M	86	NP	Specific	HAI	Meropenem
29	M	57	No	Empirical	NP	Meropenem
30	M	70	Yes	Empirical	NP	Imipenem

Table 1. Data collection through the carbapenem treatment reports corresponding to the patients that were admitted to the ICU for adults between July and September 2021 at a public hospital in São Paulo (n=70).

N°	SEX	AGE	PREVIOUS USE OF ATB	TYPE USE	TYPE OF INFECTION	PRESCRIBED CARBAPENEMIC
31	F	86	Yes	Empirical	HAI	Meropenem
32	F	79	NP	Empirical	Community	Meropenem
33	M	61	Yes	Empirical	HAI	Meropenem
34	M	59	No	NP	HAI	Meropenem
35	M	59	Yes	Empirical	HAI	Imipenem
36	M	83	Yes	Empirical	HAI	Imipenem
37	M	37	Yes	Specific	HAI	Imipenem
38	M	62	Yes	Empirical	HAI	Meropenem
39	M	60	Yes	Empirical	HAI	Imipenem
40	M	69	Yes	Empirical	HAI	Meropenem
41	F	83	NP	Empirical	HAI	Meropenem
42	M	66	Yes	Empirical	HAI	Meropenem
43	M	81	Yes	Empirical	NP	Meropenem
44	M	56	Yes	Empirical	HAI	Imipenem
45	M	56	Yes	Empirical	HAI	Imipenem
46	M	65	NP	Specific	HAI	Meropenem
47	F	81	Yes	Empirical	HAI	Meropenem
48	F	81	Yes	Empirical	HAI	Meropenem
49	F	73	Yes	Empirical	HAI	Meropenem
50	F	73	NP	Specific	HAI	Meropenem
51	F	64	Yes	Empirical	HAI	Meropenem
52	F	65	Yes	Empirical	HAI	Meropenem
53	F	83	NP	Specific	HAI	Meropenem
54	F	51	NP	Empirical	HAI	Meropenem
55	F	51	Yes	Empirical	HAI	Meropenem
56	F	80	NP	Specific	NP	Meropenem
57	M	78	Yes	Specific	HAI	Imipenem
58	F	76	NP	Empirical	HAI	Meropenem
59	F	49	Yes	Empirical	HAI	Imipenem
60	F	81	Yes	Empirical	HAI	Meropenem
61	F	70	Yes	Empirical	HAI	Meropenem
62	M	80	NP	Specific	HAI	Imipenem
63	F	83	NP	NP	NP	Meropenem
64	F	69	Yes	Empirical	HAI	Meropenem
65	M	46	No	Empirical	HAI	Imipenem
66	M	82	Yes	Empirical	HAI	Meropenem
67	F	49	NP	Empirical	HAI	Meropenem
68	M	49	NP	Specific	HAI	Meropenem
69	M	49	Yes	Empirical	HAI	Meropenem
70	F	70	No	Empirical	Community	Meropenem
71	M	54	Yes	Empirical	HAI	Meropenem
72	M	54	Yes	Empirical	HAI	Meropenem
73	F	59	NP	Empirical	HAI	Meropenem
74	F	59	Yes	Specific	HAI	Meropenem
75	M	74	Yes	Empirical	HAI	Meropenem
76	M	74	Yes	Empirical	HAI	Meropenem
77	M	66	NP	Specific	HAI	Meropenem
78	M	18	Yes	Specific	HAI	Meropenem
79	M	71	NP	NP	NP	Meropenem
80	M	69	Yes	Specific	HAI	Imipenem
81	M	69	Yes	Specific	HAI	Imipenem

No.: Report number; M: Male; F: Female; ATM: Antimicrobial; NFO: Not Filled Out; HAI: Healthcare-Associated Infection;

Among the samples collected for culture, we found a total of 129 samples, 76 of which were positive and 53 negative. 8 different types of gram-positive bacteria, 10 types of gram-negative bacteria and 6 samples positive for fungi were found in the samples. In a total of 24 (34.3%) cultures, gram-positive microorganisms were identified, mostly *Staphylococcus epidermidis (6 samples),* followed by *Enterococcus faecalis* (5 samples), *Staphylococcus aureus* (4 samples), *Staphylococcus capitis* (3 samples), *Staphylococcus haemolyticus and Staphylococcus cohnii* (2 samples), and *Staphylococcus hominis* and *Streptococcus salivarius,* both with 1 sample only (Tables 2 and 3).

Gram-negatives were identified in 46 (65.7%) cultures. The majority corresponded to *Klebsiella pneumoniae* in 15 samples, followed by *Pseudomonas aeruginosa* (12 samples), *Escherichia coli* (5 samples), *Proteus mirabilis* (4 samples), *Serratia marcescens* and *Acinetobacter baumannii* (with 3 samples), *Morganela morganii, Stenotrophomonas maltophilia, Acinetobacter junii* and *Acinetobacter lwoffii,* all with 1 sample (Tables 2 and 3).

Table 2. Culture samples collected from patients admitted to the ICU for adults between July and September 2021, who underwent treatment with carbapenems and their respective results, including culture types, bacteria identified, and sensitivity to meropenem and imipenem.

N°	Culture 1	Bacteria Identified	Meropenem Sensitivity	Meropenem Sensitivity	Culture 2	Bacteria Identified	Meropenem Sensitivity	Meropenem Sensitivity	Culture 3	Bacteria Identified	Meropenem Sensitivity	Meropenem Sensitivity
1	ST	*A.baumannii*	R	R	ST	*M.Morganii*	S	TNR	BC	NFgativo	CN	CN
2	BC	*K.PNFumoniae*	R	R	CT	*K.PNFumoniae*	R	R	CT	*P.Aeruginosa*	I	R
3	BC	*S.Marcescens*	S	S	NF	No exam	SA	SA	NF	No exam	SA	SA
4	BC	*K.PNFumoniae*	R	R	ST	*P.Aeruginosa*	S	S	ST	*A.Baumannii*	R	R
5	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
6	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
7	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
8	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
9	BC	NFgativo	CN	CN	NF	No exam	SA	SA	NF	No exam	SA	SA
10	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
11	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
12	LA	*E.Coli*	S	S	BC	NFgativo	CN	CN	NF	No exam	SA	SA
13	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
14	ST	*P.Aeruginosa*	S	S	BC	NFgativo	CN	CN	NF	No exam	SA	SA
15	BC	*S.Cohnii*	TNR	TNR	BC	*S.Epidermidis*	TNR	TNR	NF	No exam	SA	SA
16	BC	*S.Cohnii*	TNR	TNR	URC	NFgativo	CN	CN	NF	No exam	SA	SA
17	ST	*S.Aureus*	TNR	TNR	ST	*AciNFto junii*	S	S	ST	*P.Aeruginosa*	S	S
18	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
19	CT	*K.PNFumoniae*	R	R	ST	*P.Aeruginosa*	S	S	BC	*K.PNFumoniae*	R	R
20	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
21	CT	*P.Mirabilis*	S	TNR	CT	*E.FaecLAis*	TNR	TNR	BC	NFgativo	CN	CN
22	BC	NFgativo	CN	CN	NF	No exam	SA	SA	NF	No exam	SA	SA
23	URC	NFgativo	CN	CN	NF	No exam	SA	SA	NF	No exam	SA	SA
24	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
25	AT	*S.Aureus*	TNR	TNR	NF	No exam	SA	SA	NF	No exam	SA	SA
26	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
27	BC	*S.Epidermidis*	TNR	TNR	URC	NFgativo	CN	CN	NF	No exam	SA	SA
28	BC	NFgativo	CN	CN	NF	No exam	SA	SA	NF	No exam	SA	SA
29	LA	*S.SLAivarius*	S	TNR	NF	No exam	SA	SA	NF	No exam	SA	SA
30	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
31	URC	*E.Coli*	S	S	BC	NFgativo	CN	CN	NF	No exam	SA	SA
32	BC	NFgativo	CN	CN	NF	No exam	SA	SA	NF	No exam	SA	SA
33	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
34	BC	*E.Coli*	S	S	URC	*K.PNFumoniae*	R	R	NF	No exam	SA	SA
35	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
36	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA

Table 2. Culture samples collected from patients admitted to the ICU for adults between July and September 2021, who underwent treatment with carbapenems and their respective results, including culture types, bacteria identified, and sensitivity to meropenem and imipenem.

N°	Culture 1	Bacteria Identified	Meropenem Sensitivity	Meropenem Sensitivity	Culture 2	Bacteria Identified	Meropenem Sensitivity	Meropenem Sensitivity	Culture 3	Bacteria Identified	Meropenem Sensitivity	Meropenem Sensitivity
37	BC	NFgativo	CN	CN	NF	No exam	SA	SA	NF	No exam	SA	SA
38	BC	*K.PNFumoniae*	R	R	URC	NFgativo	CN	CN	NF	No exam	SA	SA
39	BC	*S.Epidermidis*	TNR	TNR	NF	No exam	SA	SA	NF	No exam	SA	SA
40	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
41	BC	*S.Epidermidis*	TNR	TNR	URC	Fungo	SA	SA	NF	No exam	SA	SA
42	BC	Fungo	SA	SA	URC	Fungo	SA	SA	NF	No exam	SA	SA
43	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
44	BC	*S.Capitis*	TNR	TNR	ST	*P.Mirabilis*	S	TNR	ST	*A.lwoffii*	S	S
45	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
46	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
47	BC	NFgativo	CN	CN	ST	*S.MLAtophilia*	TNR	TNR	NF	No exam	SA	SA
48	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
49	ST	*E.Coli*	S	S	URC	Fungo	SA	SA	BC	NFgativo	CN	CN
50	BC	NFgativo	CN	CN	URC	*E.FaecLAis*	TNR	TNR	NF	No exam	SA	SA
51	BC	NFgativo	CN	CN	ST	*P.Aeruginosa*	S	S	URC	NFgativo	CN	CN
52	ST	*K.PNFumoniae*	S	S	BC	*E.FaecLAis*	TNR	TNR	BC	*S.Aureus*	TNR	TNR
53	URC	*P.Mirabilis*	S	TNR	NF	No exam	SA	SA	NF	No exam	SA	SA
54	BC	*S.Aureus*	TNR	TNR	NF	No exam	SA	SA	NF	No exam	SA	SA
55	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
56	CT	*K.PNFumoniae*	S	S	CT	*P.Aeruginosa*	S	S	BC	NFgativo	CN	CN
57	URC	*P.Aeruginosa*	S	S	ST	*S.Marcescens*	S	S	ST	*K.PNFumoniae*	S	S
58	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
59	BC	*K.PNFumoniae*	R	R	CT	*P.Aeruginosa*	S	S	NF	No exam	SA	SA
60	ST	*P.Aeruginosa*	S	S	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN
61	BC	*S.Marcescens*	S	S	URC	Fungo	SA	SA	NF	No exam	SA	SA
62	BC	*S.Hominis*	TNR	TNR	URC	NFgativo	CN	CN	NF	No exam	SA	SA
63	BC	NFgativo	CN	CN	NF	No exam	SA	SA	NF	No exam	SA	SA
64	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
65	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
66	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN	NF	No exam	SA	SA
67	URC	*E.Coli*	S	S	BC	*S.Capitis*	TNR	TNR	NF	No exam	SA	SA
68	BC	*S.Epidermidis*	TNR	TNR	NF	No exam	SA	SA	NF	No exam	SA	SA
69	NF	No exam	SA	SA	NF	No exam	SA	SA	NF	No exam	SA	SA
70	URC	*E.FaecLAis*	TNR	TNR	NF	No exam	SA	SA	NF	No exam	SA	SA
71	BC	*S.Capitis*	TNR	TNR	NF	No exam	SA	SA	NF	No exam	SA	SA
72	BC	NFgativo	CN	CN	NF	No exam	SA	SA	NF	No exam	SA	SA
73	BC	NFgativo	CN	CN	URC	Fungo	SA	SA	NF	No exam	SA	SA
74	CT	*P.Aeruginosa*	S	S	CT	*P.Mirabilis*	S	TNR	BC	*K.PNFumoniae*	R	R
75	CT	*S.Haemolyticus*	TNR	TNR	BC	NFgativo	CN	CN	URC	NFgativo	CN	CN
76	CT	*S.Haemolyticus*	TNR	TNR	BC	NFgativo	CN	CN	NF	No exam	SA	SA
77	BC	*S.Epidermidis*	TNR	TNR	NF	No exam	SA	SA	NF	No exam	SA	SA
78	BC	*K.PNFumoniae*	R	R	CT	*K.PNFumoniae*	R	R	CT	*E. FaecLAis*	TNR	TNR
79	BC	*A.Baumannii*	R	R	NF	No exam	SA	SA	NF	No exam	SA	SA
80	BC	NFgativo	CN	CN	ST	NFgativo	CN	CN	URC	NFgativo	CN	CN
81	CT	*K.PNFumoniae*	R	R	CT	*P.Aeruginosa*	S	S	BC	NFgativo	CN	CN

No.: report number; HMC – blood culture; URC: urine culture; ST: tracheal secretion; PC: catheter tip; AL: liquid sample; AT: tissue sample; NE: not found; CN: negative culture; AS: no antibiogram; S: sensitive; A: resistant; I: intermediate; TNR: test not performed.

In relation to the samples with positive results, the majority corresponded to blood culture results, totaling 27; followed by tracheal secretion (18 samples), catheter tip (16 samples) and urine culture (12 samples). The others involved a liquid sample (2 samples) and 1 tissue sample (Table 3). It is important to highlight that no samples collected during the period analyzed were found for 16 of the patients considered for the research. In 18 cases, we found up to 3 different samples for the same patient (Table 2).

Table 3. Frequency of bacterial findings in the different culture types performed.

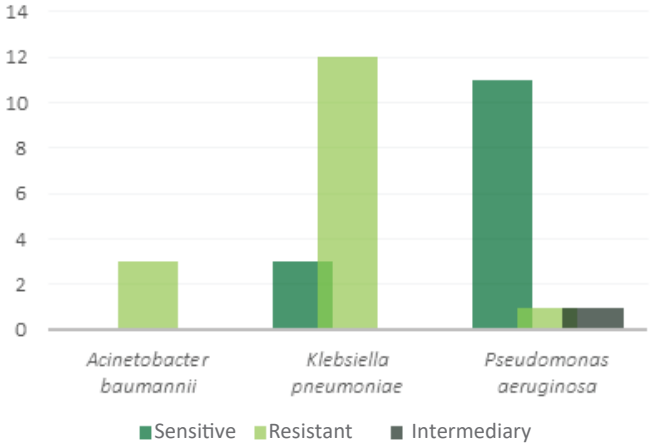
Espécie	BC	URC	ST	CT	LA	TS	Total
Acineto baumannii	1	0	2	0	0	0	3
Acineto junii	0	0	1	0	0	0	1
Acineto lwoffii	0	0	1	0	0	0	1
Escherichia coli	1	2	1	0	1	0	5
Klebsiella pneumoniae	7	1	2	5	0	0	15
Morganella morganii	0	0	1	0	0	0	1
Proteus mirabilis	0	1	1	2	0	0	4
Pseudomonas aeruginosa	0	1	6	5	0	0	12
Serratia marcescens	2	0	1	0	0	0	3
Stenotrophononas maltophilia	0	0	1	0	0	0	1
Enterococcus faecalis	1	2	0	2	0	0	5
Staphylococcus aureus	2	0	1	0	0	1	4
Staphylococcus capitis	3	0	0	0	0	0	3
Staphylococcus epidermidis	6	0	0	0	0	0	6
Staphylococcus haemolyticus	0	0	0	2	0	0	2
Staphylococcus cohnii	2	0	0	0	0	0	2
Staphylococcus hominis	1	0	0	0	0	0	1
Streptococcus salivarius	0	0	0	0	1	0	1
Fungos	1	5	0	0	0	0	6
	27	12	18	16	2	1	76

BC – blood culture; URC: urine culture; ST: tracheal secretion; CT: catheter tip; LA: liquid sample; TS: tissue sample.

The antibiograms performed found that most of the microorganisms were sensitive to carbapenems. Unfortunately, sensitivity tests were not performed for some bacteria; this includes practically all gram-positive bacteria, with the exception of *Streptococcus salivarius,* where the sample was tested as sensitive to meropenem, although the test was not performed for imipenem. Even for gram-negatives, some tests were also not performed, as in the case of *Morganela morganii* and *Proteus mirabilis,* which were not tested for imipenem, but were determined to be sensitive to meropenem. As for the *Stenotrophomonas maltophilia* sample, the test was not performed for any of the carbapenems and it was observed that its antibiogram only included the analysis of one antimicrobial, namely sulfamethoxazole+trimethoprim, where it was sensitive to the medication.

Of the 46 gram-negative cultures, 15 (32%) were resistant to meropenem and 16 were resistant to imipenem. Among the bacteria that showed resistance we found Acinetobacter baumannii, where the 3 samples detected were resistant to both medications, and *Klebsiella pneumoniae,* which resulted in 12 resistant samples and only 3 sensitive ones, with the same result for both carbapenems. The only different result in relation to sensitivity was for *Pseudomonas aeruginosa,* which showed sensitivity to meropenem and imipenem in 11 of the samples, but was considered intermediate for meropenem in 1 of them, and the same sample was determined to be resistant to imipenem (Figure 1).

Figure 1. Frequency of findings corresponding to gram-negative bacteria that were resistant, intermediate and sensitive to meropenem and imipenem.



Other samples, including *Acinetobacter junii, Acinetobacter lwoffii, Escherichia col*i and *Serratia marcescens*, were all sensitive to both carbapenems.

Discussion

Our study was conducted in an intensive care unit, a place with presence of critically-ill patients that are more exposed to the use of invasive devices and procedures such as mechanical ventilation and catheters, that is, they are patients at risk for HAIs, including carbapenem-resistant gram-negative infections. Over the three-month period, carbapenems were prescribed to 70 patients. For 11 of them, 2 reports were sent within the research period and there was only one for 59 of them, thus totaling 81 reports. As expected, most treatments were determined to be empirical, with cultures not performed in 16 cases. One of the risk factors for increased resistance to carbapenems is using inappropriate empirical antimicrobial therapies. On the other hand, proper empirical therapies initiated as early as possible can reduce the mortality rate[13-16,26].

Table 4. Correlation between the "gender", "age", "previous antimicrobial use" and "carbapenem-resistant strains" variables.

Demographic characteristics	*Total*	*Pseudomonas aeruginosa* resistant	*Klebsiella pneumoniae* resistant	*Acinetobacter baumannii* resistant
Female, n (%)	2 (12.5%)	0	2 (16.7%)	0
Male , n (%)	14 (87.5%)	1 (100%)	10 (83.3%)	3 (100%)
Age, mean +/- SD	50% > 60 anos	100% > 60 anos	41,7% > 60 anos	66,7% > 60 anos
Previous use of antimicrobials n(%)	50 (61.7%)	não preenchido	8 (66.7%)	2 (66.7%)

SD: Standard Deviation

Previous antimicrobial use was included in 50 reports, and recent studies have highlighted that this use is one of the risk factors for the development of bacterial resistance mechanisms, especially the previous carbapenem use. In our study, we observed that eleven out of fifteen patients who had meropenem-resistant gram-negatives had previously used antimicrobials (Tables 1 and 2)[1,3,13,15,22,26].

The most prescribed carbapenem was meropenem, in 59 (72%) of the reports, as this carbapenem is the most used daily in hospitals, as its adverse reactions are milder than for imipenem and it is stable for long infusions, in addition to presenting greater efficacy against gram-negative bacilli, thus favoring its use[17].

Excessive consumption of carbapenems has contributed to increased resistance to these medications. The 2019 Antimicrobial Resistance Threats Report issued by the United States CDC (*Centers* for *Disease Control* and *Prevention*) declares that Acinetobacter and carbapenem-resistant *Enterobacteriaceae* such as *Escherichia Coli* and *Klebsiella pneumoniae* are urgent threats, as they can transmit their resistance mechanisms to other bacteria, in addition to the limited treatment options18.

During the current research period, the most prevalent gram-negative in cultures was *Klebsiella pneumoniae* (15 samples), with 12 carbapenem-resistant strains. *Acinetobacter baumannii* (3/3) and *Klebsiella pneumoniae (*12/15) were the isolates with the highest carbapenem-resistance rate. These data corroborate the literature which reports that the most common gram-negatives found in patient cultures are *Escherichia Coli, Klebsiella pneumoniae, Acinetobacter spp* and *Pseudomonas spp.* CETIN et al. investigated 211 cases, among which the most prevalent microorganism was *Escherichia Coli,* followed by *Klebsiella pneumoniae* and, similarly to our study, the microorganism with the highest carbapenem-resistance rate was *Acinetobacter spp.* Other studies have also detected a higher incidence of carbapenem-resistant *Acinetobacter baumannii* in critically-ill patients, mainly in respiratory tract isolates. In our study, three *Acinetobacter baumannii* samples were isolated, with 2 tracheal secretion samples[14,19].

Stenotrophomonas maltophilia is a bacterium considered naturally resistant to carbapenems, which justifies not carrying out the sensitivity test. As for *Staphylococcus spp*, during data collection it was observed that all the identified strains of this species were resistant to oxacillin, which leads us to consider them as carbapenem-resistant, as Methicillin-Resistant *Staphylococcus aureus* (MRSA) is resistant to all beta-lactams[20,28].

According to a study carried out in the Dominican Republic, gram-negatives were detected in greater numbers in the intensive care sector, through a survey of data related to patients admitted to three hospitals, where the carbapenem-resistance rates were 28.4% for *Acinetobacter* (102 samples) and 63.1% for *Pseudomonas* (160 samples), showing that resistance is a global health problem[21].

Despite the small sample size, our study revealed a relevant finding, as it was observed that male patients were more likely to be infected with carbapenem-resistant strains, and that older ones were also more likely to be infected by resistant pathogens (Table 4).

Knowledge of the nosocomial microbiota is extremely important for developing institutional protocols targeted at rational antimicrobial use and prevention measures against HAIs; as the epidemiology of microorganisms varies geographically, the study of the prevalence of microorganisms in the institution supports the choice of the most appropriate empirical therapy[7,22-23].

The institution locus to this study follows internal protocols, which are periodically reviewed and updated. Our study contributed with relevant data on the prevalence of carbapenem-resistant pathogens, as bacterial resistance is constantly evolving, rendering updated studies necessary for decision-making in clinical management. In addition to that, new antimicrobial agents such as ceftazidime/avibactam are potential antimicrobials for inclusion in the institution's standard, as they are a therapeutic option in case of resistance to carbapenems.

Among the limitations of our retrospective study is the short study period culminating in a small sample from a single institution, in addition to the absence of data regarding patients' morbidity and mortality and the analysis of health service resources spent on these patients, as these patients' hospitalization time in the ICU was not evaluated. Another limiting factor, although not the objective of our study, was the absence of tests to identify antimicrobial resistance mechanisms.

Conclusion

In the current study, a high rate of carbapenem-resistant pathogens was observed, where the main gram-negative pathogens found were *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, with *Acinetobacter baumannii* and *Klebsiella pneumoniae* as the pathogens with the highest carbapenem-resistance rate. Carbapenem-resistance development in critically-ill patients is high, and effective therapeutic options to combat multidrug-resistant strains are scarce. The current study described bacterial susceptibility to antimicrobials in an ICU. These data are relevant for updating protocols and health professionals on the problem of bacterial resistance in our institution. AS our study was carried out in a single institution with a small sample, our data cannot be extrapolated to other institutions; however, we conclude that bacterial resistance to carbapenems is an important factor in the hospital environment and that periodic studies of the nosocomial microbiota of each institution are necessary to update protocols and implement prevention and treatment measures.

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Collaborators

KTSO and VABSM: they participated in development of this research. KTSO: data collection and survey. KTSO and VABSM: writing and review of the article, data analysis and interpretation, and responsibility for the information included in the paper. Both approve the final version to be published.

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Conflict of interest statement

The authors declare that there is no conflict of interest in relation to this article.

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