Research, Society and Development, v. 11, n. 10, e157111032629, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i10.32629

Carbapenem-resistant bacteria in an intensive care unit: prevalence and associated factors

Bactérias resistentes aos carbapenêmicos em unidade de terapia intensiva: prevalências e fatores associados

Bacterias resistentes a carbapenémicos en una unidad de cuidados intensivos: prevalencia y factores asociados

Received: 07/07/2022 | Reviewed: 07/17/2022 | Accept: 07/18/2022 | Published: 07/26/2022

Jane Martins de Araújo de Menezes
ORCID: https://orcid.org/0000-0001-6902-0278
Universidade do Sul de Santa Catarina, Brasil
E-mail: araujojanemartins@gmail.com
Diego Zapelini do Nascimento
ORCID: https://orcid.org/0000-0002-7323-185X
Universidade do Sul de Santa Catarina, Brasil
E-mail: diegozapnasc@gmail.com
Gabriela Moreno Marques
ORCID: https://orcid.org/0000-0001-9296-7574
Universidade do Sul de Santa Catarina, Brasil
E-mail: gabidimoreno@gmail.com
Cássia Tasca Fortuna
ORCID: https://orcid.org/0000-0003-0376-4754
Universidade do Sul de Santa Catarina, Brasil
E-mail: cassiatascaf@gmail.com
Alessandra de Sá Soares
ORCID: https://orcid.org/0000-0002-3826-5536
Universidade do Sul de Santa Catarina, Brasil
E-mail: alessandra.ccdi@gmail.com
Fabiana Schuelter Trevisol
ORCID: https://orcid.org/0000-0003-0997-1594
Universidade do Sul de Santa Catarina, Brasil
E-mail: fastrevisol@gmail.com

Abstract
Antimicrobial resistance is a global threat that requires different care and factors involved including a unified, multidimensional approach, with greater epidemiological surveillance. The objective this study was to review the prevalence and factors associated with healthcare-related infections (HAI) caused by bacteria resistant to carbapenems in adult patients admitted to the Intensive Care Unit (ICU). This was a cross-sectional study accomplished through the review of electronic medical records and microbiological tests of patients admitted to the ICU of a hospital in southern Santa Catarina between 2010 and 2017. Demographic, clinical and antimicrobial use data were part of the variables of interest. A total of 1,273 HAI cases were included, 11.5% of the hospital infection rate. The mean age of patients was 60.4±18.5 years; 58.7% of the patients were men. The main cause of hospitalization was cardiac-related diseases (35.8%) and the median hospital stay was 31 days. Of the total number of cases, 24% were due to carbapenem resistance. HAIs caused by *Escherichia coli*, coagulase-negative *Staphylococcus*/*Staphylococcus aureus* and *Streptococcus* sp. were the pathogens that showed greater resistance to carbapenems. Resistance to carbapenems was associated with longer hospital stay (p=0.014), surgical procedure (p<0.001), use of nasoenteral tube (p=0.048) and death (p=0.003). There was a high rate of infection by bacteria resistant to carbapenems. The observed rate of HAIs increased in frequency significantly over the duration of the study period.
Keywords: Bacteria; Carbapenems; Intensive Care Units; Cross infection.

Resumo
A resistência antimicrobiana é uma ameaça global que requer diferentes cuidados e fatores envolvidos, incluindo uma abordagem unificada, multidimensional e com maior vigilância epidemiológica. O objetivo deste estudo foi analisar a prevalência e fatores associados às infecções relacionadas à saúde (IRAS) por bactérias resistentes aos carbapenêmicos em pacientes adultos hospitalizados em Unidade de Terapia Intensiva (UTI). Methods: Estudo transversal. Foram revisados prontuários eletrônicos e exames microbiológicos de pacientes com IRAS, entre 2010 e 2017, hospitalizados na UTI de um hospital no Sul de Santa Catarina. Dados demográficos, clínicos e relativos ao uso

de antimicrobianos fizeram parte das variáveis de interesse. Foram incluídos 1.273 casos de IRAS, o que representa uma taxa de 11,5% de infecção hospitalar. A média de idade dos pacientes foi de 60,4±18,5 anos, sendo que 58,7% eram homens. A principal causa de hospitalização foram as doenças do aparelho circulatório (35,8%) e a mediana de hospitalização foi de 31 dias. Do total, 24% apresentaram resistência aos carbapenêmicos. As IRAS causadas por *Escherichia coli*, *Staphylococcus* coagulase negativa e *Staphylococcus aureus* e *Streptococcus* sp. foram os patógenos que apresentaram maior resistência aos carbapenêmicos. A resistência aos carbapenêmicos se associou ao maior tempo de hospitalização (p=0,014), ter realizado procedimento cirúrgico (p<0,001), uso sonda nasoenteral (p=0,048) e óbito (p=0,003). Houve elevada taxa de infecção por bactérias resistentes aos carbapenêmicos, com tendência de aumento no período.
Palavras-chave: Bactérias; Carbapenêmicos; Unidades de Terapia Intensiva; Infecção hospitalar.

Resumen
La resistencia a los antimicrobianos es una amenaza global que requiere diferentes cuidados y factores involucrados, incluido un enfoque unificado, multidimensional, con mayor vigilancia epidemiológica. El objetivo de este estudio fue revisar la prevalencia y los factores asociados a las infecciones relacionadas con la atención de la salud (IRAS) causadas por bacterias resistentes a los carbapenémicos en pacientes adultos ingresados en la Unidad de Cuidados Intensivos (UCI). Este fue un estudio transversal realizado a través de la revisión de historias clínicas electrónicas y exámenes microbiológicos de pacientes ingresados en la UTI de un hospital en el sur de Santa Catarina entre 2010 y 2017. Los datos demográficos, clínicos y de uso de antimicrobianos fueron parte de las variables de interés. Se incluyeron un total de 1.273 casos de IRAS, el 11,5% de la tasa de infección hospitalaria. La edad media de los pacientes fue de 60,4±18,5 años; El 58,7% de los pacientes eran hombres. La principal causa de hospitalización fueron las cardiopatías (35,8%) y la mediana de estancia hospitalaria fue de 31 días. Del total de casos, el 24% se debió a la resistencia a carbapenémicos. HAI causadas por Escherichia coli, Staphylococcus coagulasa-negativo/Staphylococcus aureus y Streptococcus sp. fueron los patógenos que mostraron mayor resistencia a los carbapenémicos. La resistencia a los carbapenémicos se asoció con mayor estancia hospitalaria (p=0,014), procedimiento quirúrgico (p<0,001), uso de sonda nasoenteral (p=0,048) y muerte (p=0,003). Hubo una alta tasa de infección por bacterias resistentes a los carbapenémicos. La tasa observada de HAI aumentó significativamente en frecuencia durante la duración del período de estudio.
Palabras clave: Bacterias; Carbapenémicos; Unidades de Cuidados Intensivos; Infección hospitalaria.

1. Introduction

Currently, healthcare-associated infections (HAI) present a serious threat to global health. (Anvisa, 2013). HAIs cause a significant increase in morbidity and mortality rates, longer hospital stays, increased stress and suffering for patients and their families. In addition to the financial impact, as the costs of an inpatient with infection are three times higher than that of an inpatient without infection (Aliyu et al., 2017; Souza et al., 2015; Cielinski et al., 2013; (Muzlovič & Štubljar, 2019). One of the main concerns is the growing incidence of infections caused by resistant microorganisms in hospitals, but also in primary care, home care, clinics, nursing homes, among others, as these settings favor the selection and dissemination of multidrug-resistant bacteria (Guimarães et al., 2011; Loureiro et al., 2016; Mirón-Rubio, 2021).

The Intensive Care Unit (ICU) favors the occurrence of infections by multidrug-resistant agents, outbreaks caused by these agents and by bringing together patients who are vulnerable to infections and who undergo different invasive procedures, associate with HAI (9-11). The reduction of host defense mechanisms and low adherence to infection prevention and control are also important factors for the development of HAI (Alp & Damani, 2015). One of the main reasons for justifying the low adherence to prevention measures is the lack of qualification and training, and the excessive workload due to reduced staff, leading to the cross-transmission of microorganisms from patient to patient (Alp & Damani, 2015; de Oliveira et al., 2010).

Bacteria have developed resistance to antimicrobials that feature a broad spectrum of action and potency, both for outpatient and hospital use, raising concern among health professionals with the emergence of resistant strains that do not respond to the pharmacological therapy available (de Oliveira & Damasceno, 2010). Antibacterial resistance is responsible for serious clinical, social and economic consequences (Luyt et al., 2014).

Carbapenems are a broad line of infection defense drugs that are active against multidrug-resistant bacteria. The first case of *Klebsiella pneumoniae* bacteria resistant to carbapenems was reported by Mackenzie et al. in 1997. Different studies have described resistance mechanisms to carbapenems, including the production of enzymes–carbapenemases that degrade

carbapenems (Luyt et al., 2014; Zaha et al., 2019). Carbapenemases are enzymes capable of hydrolyzing not only carbapenems, but also other beta-lactams, such as cephalosporins, penicillins and monobactams (Pinto et al., 2014; Surveillance, 2020).

Given the high morbidity and mortality of HAIs, additional research is necessary to better understand the prevalence and factors associated with HAIs. It is known that the number of cases of patients' infection with strains resistant to carbapenems has increased leaving few viable therapeutic options, reducing these patients' chance of survival. The increased morbidity and mortality resulting from these infections is directly related to the difficulty of treatment due to the limited availability of effective antibacterial (Gavronski, 2017).

The aim of this study was to review the prevalence and factors associated with HAIs caused by bacteria resistant to carbapenems in ICU.

2. Methodology

This was a cross-sectional study carried out through the review of electronic medical records and microbiological tests of patients admitted to the ICU of a hospital in the south of Santa Catarina between 2010 and 2017. Patients admitted in ICU who presented infections caused by carbapenems (imipenem and meropenem) multidrug-resistant bacteria were assessed.

The study team retrospectively reviewed microbial culture and antibiotic sensitivity test information from electronic medical records during the study period. Resistance and identification of the etiological agent were sought based on microbial cultures and antibiotic sensitivity tests performed with biological material from patients hospitalized in the ICU.

The sample was of the census type. The data collected were entered and analyzed using the EpiData version 3.1 program (*EpiData Association, Odense, Denmark*). Charts and linear regression analysis were performed using Microsoft Office Excel 2016 (*Microsoft Corporation*). Statistical analysis was performed using SPSS v.21.0 software (*IBM, Armonk, New York, USA*). Mean, median and standard deviation were calculated for continuous variables and proportions for categorical variables. The normality of quantitative data was measured using the Kolmogorov Smirnov test. The association between categorical variables was performed using the Pearson's chi-square test. The comparison between means was performed using the Student's t test and the comparison of medians using the Mann Whitney U test.

The prevalence rate was calculated based on the number of HAI cases over the total number of patients hospitalized in the ICU during the study period. The lethality rate was calculated as the ratio between deaths and the total number of HAI cases; and the mortality rate was calculated by the ratio between deaths and the total number of patients hospitalized in the ICU during the study period. The rates were expressed as a percentage. The second-degree polynomial regression test was used to assess the temporal trend of HAIs in the period assessed.

This study was submitted and approved by the Research Ethics Committee of the University of Southern Santa Catarina, under registration 1,640,336 dated July 19, 2016.

3. Results

From January 1, 2010 to December 31, 2017, 11,045 medical records of patients admitted to the adult ICU of the hospital under study were evaluated. Out of this total, 1,273 patients had HAI, corresponding to an infection rate of 11.5% in the ICU. HAI patients' mean age was 60.4 (SD±18.5) years, ranging from 15 to 98 years. Among patients who developed bacterial infection, 677 (53.2%) had an unfavorable hospitalization outcome and died. The median length of stay in the ICU was 31 days, ranging from 1 to 238 days.

Table 1 shows the sociodemographic and clinical characteristics of the sample studied.

Table 1 – Sociodemographic and clinical characteristics of hospitazed patients in ICU with HAI, 2010-2017 (n=1,273).

Characteristics	n	%
Sex		
Male	747	58,7
Female	526	41.3
Age		
15-19	38	3.0
20-29	73	5.7
30-39	80	6.3
40-49	120	9.5
50-59	203	15.9
≥60	759	59.6
Race		
White	119	94.1
Non-white	61	4.6
Without information	14	1.3
Schooling		
Illiterate	75	5.9
Elementary school	958	75.3
High school	179	14.1
College degree	37	2.9
Without information	24	0.9
Reason for hospitalization		
Circulatory system diseases	408	32.0
Injuries, poisonings and other causes	214	16.8
Respiratory system diseases	130	10.2
Non-specific signals and symptons	109	8.5
Nervous system diseases	94	7.4
Digestive system diseases	81	6.4
Cancer	61	4.8
Infectious diseases	60	4.7
Geniturinary diseases	43	3.4
Muskuloskeletal and connective tissue diseases	30	2.4
Endocrine and metabolic diseases	24	1.9
Blood diseases	19	1.5
Outcome		
Discharge	583	45.8
Death	677	53.2
Transfer to another hospital	13	1.0

Source: Hospital Nossa Senhora da Conceição.

Table 2 shows the prevalence of HAI in the adult ICU distributed in the study period.

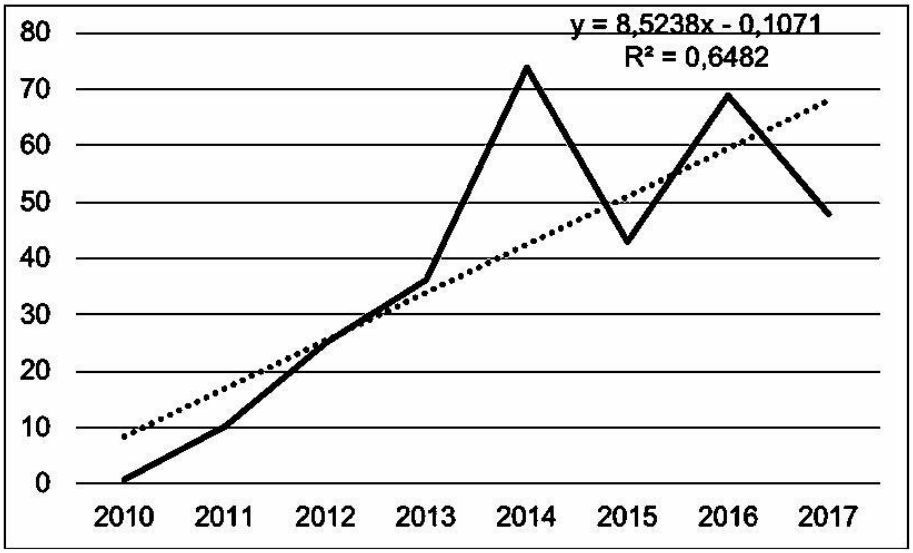
Table 2 – Prevalence of HAI in ICU, 2010-2017 (n=1,273).

Year	HAI	CRB	Deaths nº	Inpatients	Prevalence	Lethality %	Mortality
2010	7	1	6	1.049	0.7	85.7	0.6
2011	158	10	87	1.116	14.2	55.1	7.8
2012	228	25	127	1.217	18.7	55.7	10.4
2013	195	36	94	1.418	13.8	48.2	6.6
2014	246	74	121	1.463	16.8	49.2	8.3
2015	169	43	86	1.488	11.4	50.9	5.8
2016	176	69	94	1.640	10.7	53.4	5.7
2017	94	48	62	1.654	5.7	66.0	3.7
Total	1.273	306	677	11.045	11.5	53.2	6.1

HAI = healthcare-associated infections; CRB = carbapenem-resistant bacteria. Source: Hospital Nossa Senhora da Conceição.

Figure 1 shows the temporal trend of carbapenem-resistant strains cases. There is an upward trend of 8.5 percentage points per year, which is statistically significant (p=0.014).

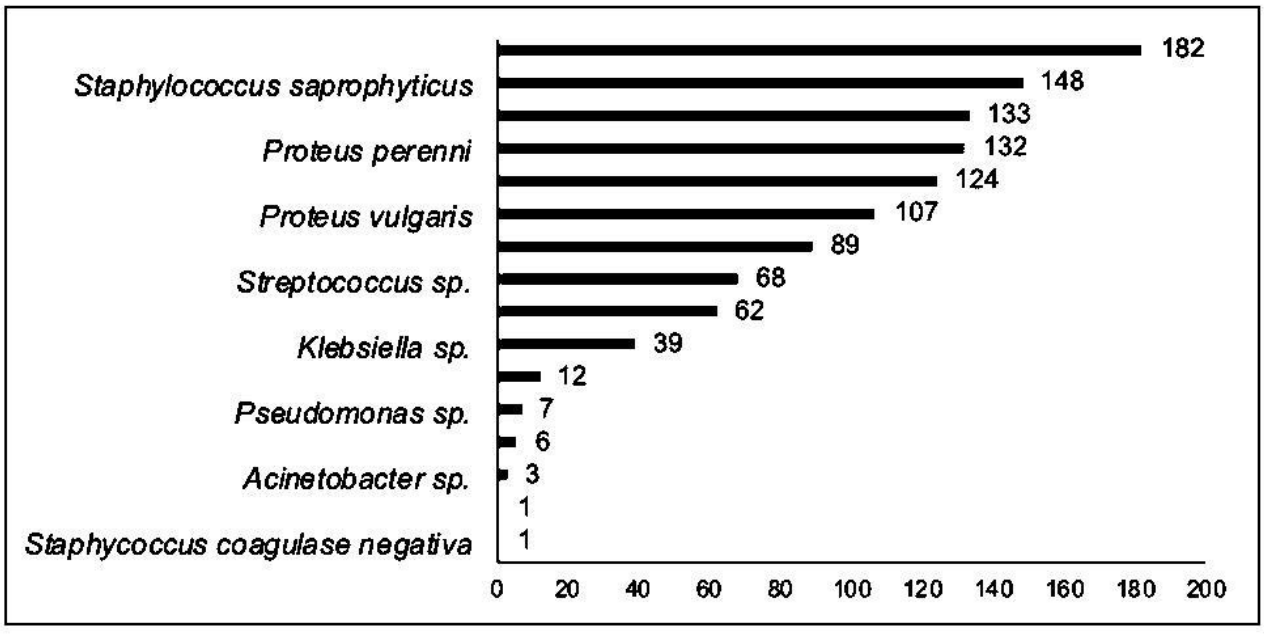
Figure 1 - Temporal trend of carbapenem-resistant strains cases.



Source: Hospital Nossa Senhora da Conceição.

The distribution of bacterial strains identified among HAI cases in adult ICU patients during the period is shown in Figure 2. In 527 (41.4%) patients, it was not possible to isolate the microbial agent causing the infection. Most patients had infections caused by more than one microbial agent, actually from one to seven etiological agents simultaneously. Among the patients tested, 306 were infected by carbapenem-resistant agents, corresponding to a rate of 24%. Out of the 527 (41.4%) patients in whom bacterial isolation or sensitivity testing was not performed, the infection diagnosis was based only on clinical, laboratory and/or imaging findings.

Figure 2 - Distribution of bacterial strains identified among HAI cases in adult ICU 2010-2017.



Source: Hospital Nossa Senhora da Conceição.

Regarding the location of the infection, the respiratory tract (57.7%) was the site of most HAIs, followed by the urinary tract (20.4%). This study revealed that 97.0% of patients admitted to the ICU used some type of invasive device and most patients used more than one device simultaneously.

All patients used more than one antimicrobial. In total, there were 4,951 prescriptions for antimicrobials, which results in an average of 3.9 antimicrobials per patient, ranging from 1 to 13 different antimicrobials in the same patient during the hospitalization period. There was greater use of different antimicrobials among patients who died ($p<0.001$) and those whose infection was resistant to carbapenems ($p<0.001$).

HAIs with strains resistant to carbapenems showed a statistically significant association with death outcome, as among patients who were infected by resistant bacteria, 64.7% died ($p=0.003$). The length of hospital stay was also longer among those with carbapenems-resistant infection: 50.9 days versus 43.9 days among those with infections non-carbapenems resistant ($p=0.014$). There was a statistically significant association between resistance to carbapenems and surgical procedure ($p<0.001$), and nasoenteral tube ($p=0.048$). There was no statistically significant association between carbapenem resistance and gender ($p=0.365$), age ($p=0.328$), education ($p=0.815$) or race ($p=0.180$).

4. Discussion

Although it is the first study on carbapenem-resistance carried out in the southern region, the prevalence found was high (24%) when compared to the rates found by the Antimicrobial Surveillance Program (SENTRY), which estimates an 11.1% rate of carbapenem-resistant bacteria in Brazil (OPAS, 2010; Dereli et al., 2013).

In countries such as Argentina, Chile and Mexico, the prevalence is estimated at 8.2%, 5.0% and 0.8%, respectively (Hrabák et al., 2014; Gomes, et al., 2016). In the Dominican Republic, around 28% of *K. pneumoniae* isolates were resistant to carbapenems (Souza et al., 2014; Tuon et al., 2016). In India, *K. pneumoniae* and *E. coli* exhibits carbapenems resistance rates of 57% and 12%, respectively (Garbati et al., 2016). In the United States, rates for these same species have been reported at 11% and 2%, respectively (Luyt et al., 2014). It is estimated that in Italy, the prevalence of carbapenem-resistant *K. pneumoniae* reaches 28.8%. In Greece, the prevalence of resistance to carbapenems exceeds 60% in the ICUs (Dehghan et al., 2016; Livermore et al., 2011). However, due to underreporting of cases, this description may not reflect the reality.

Among the patients evaluated, most of them were elderly. Elderly people are more susceptible to acquiring HAIs and death due to physiological changes caused by aging, declining immune response, and increased vulnerability to infections associated with invasive procedures (Dehghan et al., 2016; Correa et al., 2013).

When evaluating the HAIs, there was colonization/infection by more than one microbial agent, ranging from one to seven etiological agents, simultaneously. The most frequently isolated bacterium was the coagulase-negative *Staphylococcus*, followed by *Enterobacter* sp. and *Acinetobacter* sp. From an epidemiological point of view, Gram positive bacteria have emerged as the main agents in blood cultures, especially *Staphylococcus aureus*, coagulase negative *Staphylococcus* and *Enterococcus* spp.; however, Gram negative enteric microorganisms such as *E. coli*, *Klebsiella* sp. and *Enterobacter* sp., are also frequently associated with resistant strains HAIs (Dehghan et al., 2016; Livermore et al., 2011).

As to microorganisms' sensitivity/resistance profile to carbapenems, a higher rate of coagulase negative *Staphylococcus*, *Escherichia coli*, followed by *Staphylococcus aureus*, *Streptococcus* sp., was observed in addition to the fungus *Candida* sp. In one study, carbapenemases were observed in 66% of *K. pneumoniae* samples collected (Pinto et al., 2014).

The respiratory tract was the most common site found characterizing pneumonia, as the infection is directly related to the devices used for mechanical ventilation. Patients admitted to ICUs who remain on mechanical ventilation for more than 48 hours have a 9% to 27% higher incidence of complications than patients who did not use mechanical ventilation for the same

period of time Tuon et al., 2016; Dehghan et al., 2016; Correa et al., 2013; Vicent et al., 2009). Patients undergoing orotracheal intubation lose the natural barrier between the oropharynx and the trachea, reducing the cough reflex and promoting the accumulation of contaminated secretions above the cuff, which allows greater colonization of the tracheobronchial tree (Tuon et al., 2016). Studies reveal that VAP is considered one of the most frequent infections in ICUs. In southern Brazil, the incidence of VAP is 7.8% (Carvalho et al., 2015). However, its use is necessary for the maintenance of life in critically ill patients, for the replacement of organic functions by artificial methods, requiring continuous advanced monitoring and support to keep vital functions stable, increasing these patients' time of survival (Vicent et al., 2009).

Regarding the outcome, there was a statistically significant association between infection by bacteria resistant to carbapenems and longer ICU hospitalization and death. The variants in lethality rates related to the presence of bacteria resistant to carbapenems are also linked to a series of factors that enhance carbapenem resistance, such as immunity, characteristics of the infection, age, associated comorbidities and characteristics related to hospitalization (Leiser et al., 2007). Thus, due to the study design, it was difficult to assess whether death and longer hospital stay could be attributed to infection by resistant strains, or whether there were other pathological processes involved in the severity of the clinical condition.

As for the applied antimicrobial therapy, higher mortality rates are verified with the use of monotherapy, while combined antimicrobial therapy presents better rates of therapeutic success (Gavronski, 2017; OPAS, 2010; Leiser et al., 2007). Studies demonstrate the superiority of combined therapy over monotherapy (Surveillance, 2020; Dereli et al., 2013; Garbati et al., 2016; Axente et al., 2017). In a study published in 2011, the mortality rate was 0% and 46.7% for patients who received, respectively, combined antimicrobial therapy and monotherapy (Livermore et al., 2011). Therefore, the association of two or more antimicrobials is recommended in an attempt to create an interaction between the drugs, increasing the therapeutic efficacy of the treatment (Kalil et al., 2016). In addition, the combined therapeutic regimen reduces the chance of selective pressure on the isolates, preventing the development of resistance to the antimicrobials used (Gavronski, 2017).

Among the factors associated with resistance to carbapenems, there was an association between patients undergoing surgical procedures and the use of central venous catheters. Invasive devices, as well as surgical intervention interfere with body homeostasis, combined with the fact that the patient hospitalized in the ICU usually has a series of comorbidities that favor the installation of an infectious condition and surgical site infections are among the most frequent HAI (Guimarães et al., 2011; Dereli et al., 2013; Gomes et al., 2016; Garbati et al., 2016; Leiser et al., 2007; Axente et al., 2017).

Among the limitations of the present study, the use of retrospective data, with missing data or inadequate filling.

5. Conclusion

This study showed that there was a high rate of infections by bacteria resistant to carbapenems, with an increasing tendency in the period from 2010 to 2017. Antimicrobial resistance is a global threat that requires different care and factors involved including a unified, multidimensional approach, with greater epidemiological surveillance; the use of appropriate antimicrobials in humans and animals; improved prevention of infections; the development of new therapies; and constant innovation in the antimicrobial research and development sector.

References

Aliyu, S., Smaldone, A., & Larson, E. (2017). Prevalence of multidrug-resistant gram-negative bacteria among nursing home residents: A systematic review and meta-analysis. *American journal of infection control*, *45*(5), 512–518. https://doi.org/10.1016/j.ajic.2017.01.022

Alp, E., & Damani, N. (2015). Healthcare-associated infections in intensive care units: epidemiology and infection control in low-to-middle income countries. *Journal of infection in developing countries*, *9*(10), 1040–1045. https://doi.org/10.3855/jidc.6832

ANVISA. Agência Nacional de Vigilância Sanitária (2013) *Critérios Diagnósticos de Infecção Relacionada à Assistência à Saúde*. Disponível em: www.anvisa.gov.br

Axente, C., Licker, M., Moldovan, R., Hogea, E., Muntean, D., Horhat, F., Bedreag, O., Sandesc, D., Papurica, M., Dugaesescu, D., Voicu, M., & Baditoiu, L. (2017). Antimicrobial consumption, costs and resistance patterns: a two year prospective study in a Romanian intensive care unit. *BMC infectious diseases*, *17*(1), 358. https://doi.org/10.1186/s12879-017-2440-7

Carvalho MR, Moreira ICCC, Amorim Neta FL, Guimarães MSO,Viana VGF, Oliveira FW. Incidência de bactérias multirresistentes em uma unidade de terapia intensiva. Rev Interdisciplinar. 2015;8(2):75–85.

Cieslinski, J. M., Arend, L., Tuon, F. F., Silva, E. P., Ekermann, R. G., Dalla-Costa, L. M., Higgins, P. G., Seifert, H., & Pilonetto, M. (2013). Molecular epidemiology characterization of OXA-23 carbapenemase-producing Acinetobacter baumannii isolated from 8 Brazilian hospitals using repetitive sequence-based PCR. *Diagnostic microbiology and infectious disease*, *77*(4), 337–340. https://doi.org/10.1016/j.diagmicrobio.2013.07.018

Correa, L., Martino, M. D., Siqueira, I., Pasternak, J., Gales, A. C., Silva, C. V., Camargo, T. Z., Scherer, P. F., & Marra, A. R. (2013). A hospital-based matched case-control study to identify clinical outcome and risk factors associated with carbapenem-resistant Klebsiella pneumoniae infection. *BMC infectious diseases*, *13*, 80. https://doi.org/10.1186/1471-2334-13-80

Dehghan, F., Zolghadri, N., Boostani, V., Shafii, A., & Eftekhaari, T. E. (2016). Resistance of gram negative bacteria in hospital acquired pneumonia: a prospective study. *The Brazilian journal of infectious diseases: an official publication of the Brazilian Society of Infectious Diseases*, *20*(1), 113–114. https://doi.org/10.1016/j.bjid.2015.11.006

Dereli, N., Ozayar, E., Degerli, S., Sahin, S., & Koç, F. (2013). Three-year evaluation of nosocomial infection rates of the ICU. *Brazilian journal of anesthesiology (Elsevier)*, *63*(1), 73–78. https://doi.org/10.1016/S0034-7094(13)70199-5

Garbati, M. A., Sakkijha, H., & Abushaheen, A. (2016). Infections due to Carbapenem Resistant Enterobacteriaceae among Saudi Arabian Hospitalized Patients: A Matched Case-Control Study. *BioMed research international*, *2016*, 3961684. https://doi.org/10.1155/2016/3961684

Gavronski, S. (2017) *Investigação da resistência aos carbapenêmicos em enterobactérias isoladas em um hospital de blumenau/sc: detecção laboratorial e aspectos epidemiológicos*. Brasil: Programa de Pós Graduação em Farmácia, Universidade Federal de Santa Catarina.

Gomes, D. B., Genteluci, G. L., de Souza, M. J., Zahner, V., Carvalho, K. R., & Villas Bôas, M. H. (2016). Presence of the blaOXA-72 gene in Acinetobacter baumannii from a public hospital in Brazil. *Journal of global antimicrobial resistance*, *5*, 90–91. https://doi.org/10.1016/j.jgar.2015.11.007

Guimarães, A. C., Donalisio, M. R., Santiago, T. H., & Freire, J. B. (2011). Óbitos associados à infecção hospitalar, ocorridos em um hospital geral de Sumaré-SP, Brasil [Mortality associated with nosocomial infection, occurring in a general hospital of Sumaré-SP, Brazil]. *Revista brasileira de enfermagem*, *64*(5), 864–869. https://doi.org/10.1590/s0034-71672011000500010

Hrabák, J., Chudáčková, E., & Papagiannitsis, C. C. (2014). Detection of carbapenemases in Enterobacteriaceae: a challenge for diagnostic microbiological laboratories. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, *20*(9), 839–853. https://doi.org/10.1111/1469-0691.12678

Kalil, A. C., Metersky, M. L., Klompas, M., Muscedere, J., Sweeney, D. A., Palmer, L. B., Napolitano, L. M., O'Grady, N. P., Bartlett, J. G., Carratalà, J., El Solh, A. A., Ewig, S., Fey, P. D., File, T. M., Jr, Restrepo, M. I., Roberts, J. A., Waterer, G. W., Cruse, P., Knight, S. L., & Brozek, J. L. (2016). Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *63*(5), e61–e111. https://doi.org/10.1093/cid/ciw353

Leiser, J. J., Tognim, M. C. B., Bedendo, (2007) J. Infecções hospitalares em um centro de terapia intensiva de um hospital de ensino no norte do Paraná. *Ciência, Cuidado e Saúde*, *6*(2):181–186.

Livermore, D. M., Warner, M., Mushtaq, S., Doumith, M., Zhang, J., & Woodford, N. (2011). What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. *International journal of antimicrobial agents*, *37*(5), 415–419. https://doi.org/10.1016/j.ijantimicag.2011.01.012

Loureiro, R.J., Roque, F., Teixeira Rodrigues, A., Herdeiro, M. T., Ramalheira, E. (2016) O uso de antibióticos e as resistências bacterianas: breves notas sobre a sua evolução. *Revista Portuguesa de Saúde Pública*, *34*(1):77-84. https://doi.org/10.1016/j.rpsp.2015.11.003

Luyt, C. E., Bréchot, N., Trouillet, J. L., & Chastre, J. (2014). Antibiotic stewardship in the intensive care unit. *Critical care (London, England)*, *18*(5), 480. https://doi.org/10.1186/s13054-014-0480-6

Mirón-Rubio M. (2021). Treatment of infections caused by multi-resistant microorganisms in hospital at home units. *Revista espanola de quimioterapia : publicacion oficial de la Sociedad Espanola de Quimioterapia*, *34 Suppl 1*(Suppl1), 18–21. https://doi.org/10.37201/req/s01.05.2021

Muzlovič, I., & Štubljar, D. (2019). Stress ulcer prophylaxis as a risk factor for tracheal colonization and hospital-acquired pneumonia in intensive care patients: impact on latency time for pneumonia. *Acta clinica Croatica*, *58*(1), 72–86. https://doi.org/10.20471/acc.2019.58.01.10

de Oliveira, A. C., Silva, R. S., Díaz, M. E., & Iquiapaza, R. A. (2010). Bacterial resistance and mortality in an intensive care unit. *Revista latino-americana de enfermagem*, *18*(6), 1152–1160. https://doi.org/10.1590/s0104-11692010000600016

de Oliveira, A. C., & Damasceno, Q. S. (2010). Superfícies do ambiente hospitalar como possíveis reservatórios de bactérias resistentes: uma revisão [Surfaces of the hospital environment as possible deposits of resistant bacteria: a review]. *Revista da Escola de Enfermagem da U S P*, *44*(4), 1118–1123. https://doi.org/10.1590/s0080-62342010000400038

OPAS. Organización Panamericana de la Salud. (2010). *Informe Anual de la Red de Monitoreo/ Vigilancia de la Resistencia a los Antibióticos*. Disponível em: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=24101&Itemid=270&lang=en

Pinto, F.D.M., Simas, D.M., Baldin, C.P., Limberger, I.I., Cassol, R., Antochevis, L.C, Vieira, F.J., Ribeiro, V.B., Magagnin, C.M., Rozales, F.P., Falci, D.R. (2014) Prevalência de carbapenemases em enterobatérias resistentes a carbapenemicos em quatro hospitais terciários de Porto Alegre. *Clinical Biomedical Research*,*34*(1):47–52.

Sousa, M.A., Medeiros, N.M., Carneiro, J.R., Cardoso, A.M. Hemoculturas positivas de pacientes da unidade de terapia intensiva de um hospital escola de goiânia-go, entre 2010 e 2013. (2014) *Revista Estudos Vida e Saúde*,*41*(3):627–35.

Souza, E.S., Belei, R.A., Carrilho, C.M.D.M., Matsuo, T., Yamada-Ogatta, S.F., Andrade, G., Perugini, M.R.E., Pieri, F.M., Dessunti, E.M., Kerbauy, G. Mortality and risks related to healthcare-associated infection. (2015) *Texto & Contexto Enfermagem*,*24*(1):220–228. DOI: 10.1590/0104-07072015002940013

Surveillance C. (2020). Healthcare-associated infections and antimicrobial resistance in Canadian acute care hospitals, 2014-2018. *Canada communicable disease report = Releve des maladies transmissibles au Canada*, *46*(5), 99–112. https://doi.org/10.14745/ccdr.v46i05a01

Tuon, F. F., Graf, M. E., Merlini, A., Rocha, J. L., Stallbaum, S., Arend, L. N., & Pecoit-Filho, R. (2017). Risk factors for mortality in patients with ventilator-associated pneumonia caused by carbapenem-resistant Enterobacteriaceae. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases*, *21*(1), 1–6. https://doi.org/10.1016/j.bjid.2016.09.008

Vincent, J. L., Rello, J., Marshall, J., Silva, E., Anzueto, A., Martin, C. D., Moreno, R., Lipman, J., Gomersall, C., Sakr, Y., Reinhart, K., & EPIC II Group of Investigators (2009). International study of the prevalence and outcomes of infection in intensive care units. *JAMA*, *302*(21), 2323–2329. https://doi.org/10.1001/jama.2009.1754

Zaha, D. C., Kiss, R., Hegedűs, C., Gesztelyi, R., Bombicz, M., Muresan, M., Pallag, A., Zrinyi, M., Pall, D., Vesa, C. M., & Micle, O. (2019). Recent Advances in Investigation, Prevention, and Management of Healthcare-Associated Infections (HAIs): Resistant Multidrug Strain Colonization and Its Risk Factors in an Intensive Care Unit of a University Hospital. *BioMed research international*, *2019*, 2510875. https://doi.org/10.1155/2019/2510875