Detection of carbapenemases in Pseudomonas aeruginosa isolates: an emerging challenge

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ABSTRACT

Aims: Determine the clinical characteristics of patients and the microbiological characteristics of the *Pseudomonas aeruginosa* isolates in respiratory samples from Adult Intensive Care Unity (ICU) of a University Hospital from Fortaleza, Brazil; Analyze the resistance profile of *Pseudomonas aeruginosa* isolates; Determine the phenotypic prevalence of Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA); Relate the prevalence to resistent *Pseudomonas aeruginosa* with patients' death rate. **Study Design**: This is a epidemiological, descriptive and retrospective study, carried out between January and December 2022 at a university hospital in Fortaleza, Brazil. **Place and Duration of Study**: Microbiology Sector of the Central Laboratory of the Walter Cantídio University Hospital between January 2022 and December 2022. **Methodology**: All tracheal aspirate and bronchoalveolar lavage samples that showed a positive culture for *Pseudomonas* aeruginosa from patients admitted to the Adult Intensive Care Unit at the Walter Cantídio University Hospital were included in the study. Their identification (ID) and the Antibiotic Sensitivity Test (TSA) were carried out using the automated system VITEK® 2 (BioMérieux®, Marcyl'Etoile, France), which uses the OBSERVA system for data archiving. The detection of carbapenemases production was performed using the immunochromatographic test NG-Test Carba 5 (Laborclin - Centerlab). The data was collected by the Microbiology Sector of the hospital's Central Clinical Analysis Laboratory through patient reports issued by the hospital management system, REDCap. The reposts were reviewed by a microbiologist pharmacist from the microbiology service. The data were analyzed and audited in the Excel® program for statistical validation using the SPSS Statistics® program, version 17.0. **Results**: After applying exclusion criteria, 25 bacterial isolates from respiratory samples of patients admitted to the Adult ICU of the hospital tested positive for Pseudomonas aeruginosa. 80% (n=20) of these isolates originated from tracheal aspirate samples and 20% (n=5) from bronchoalveolar lavage. Of these 25 isolates, 72% (n=18) were identified as Carbapenem-Resistant Pseudomonas aeruginosa (CRPA), of which NG-Test Carba 5 identified 33% (n=6) as producers of serine carbapenemase, 28% (n=5) as producers of enzyme not identified by the test, 22% (n=4) as producers of metallo-beta-lactamase, and 17% (n=3) as non-enzymatic. Considering only isolates producing serine carbapenemases, 50% showed resistance to ceftazidime/avibactam, 83.3% to amikacin, and 100% to tigecycline and ciprofloxacin. NG-Test Carba 5 identified all isolated serine carbapenemases as KPC producers and all isolated metallo-beta-lactamases as IMP producers. It was found that patients admitted to the Adult ICU with isolates of CRPA with enzymatic resistance mechanism in respiratory samples are related to patient mortality ($p < 0.05$). **Conclusion**: The study highlights high mortality rates and detection of carbapenemases in respiratory samples from patients with Pseudomonas aeruginosa infection in ICUs. The reduced effectiveness of last-line antimicrobial therapies such as ceftazidime-avibactam and the high mortality rate associated with enzymatic resistance in CRPA, underscores the importance of hospital infection control to improve patient care.

Keywords: Pseudomonas aeruginosa; Gram negative bacilli; carbapenemase; nosocomial infection; Carba-5 test.

1. INTRODUCTION

Healthcare-Associated Infections (HAIs), also called nosocomial infections, can be defined as an infection acquired after the patient is admitted to the hospital environment for the purposes of hospitalization or performing health care procedures. They are highly relevant to public health because they are considered a multifactorial problem, influencing economic, biological and hospital safety aspects [1]. Its spread can be due to cross-contamination, during contact between patients and health professionals, or through the colonization of abiotic surfaces [1,2].

According to the World Health Organization (WHO), the mortality rate for patients with HAI is close to 10%, increasing by almost 3 times when analyzing only patients in Intensive Care Units (ICUs), due to the critical profile of the unit, usually treating post-operative, transplant and/or immunocompromised patients [3]. Although the number of ICU beds is considerably small within a hospital, this sector represents about 25% of the registered infections, implying the worsening of the patient's clinical condition, an increase in the number of invasive procedures for diagnosis and treatment, prolongation of the length of hospital stay, and the addition of antimicrobial therapy [4].

These infections can occur in several systems of the human body, so they can be classified by their site of infection. HAIs are more of a concern when they are bloodstream infections (BSI) and respiratory tract infections (RTI), although they are also very common in the urinary tract (UTI) and surgical sites (SSI). Respiratory tract infections are highly relevant because they are an easily accessible gateway for microorganisms, and tracheal aspirate and bronchoalveolar lavage samples are the main clinical specimens collected in cases of suspected infection by this site [4].

An aggravating factor in HAI is the development of Antimicrobial Resistance (AMR), which is defined as the ability of microorganisms to survive and remain viable through contact with antimicrobial agents, including antibiotics, antifungals, antiparasitics, disinfectants and preservatives. Although it is a natural process, the development of resistance is intensified by the selective pressure exerted through the excessive use of antimicrobials, both by the misinformation of lay patients and inadequate prescription of the drug class, and by the method of empirical therapy employed in hospital institutions to treat infections not yet identified through microbiological culture [5].

Numerous microorganisms are associated with HAIs, with bacteria being the most relevant isolates in percentage and severity, both Gram-positive (GP) and Gram-negative (GN) bacteria. Among the GP species, the most significant are Staphylococcus aureus, Streptococcus spp, and Enterococcus spp. For GN bacteria, the most prevalent are Klebsiella pneumoniae, Escherichia coli, Acinetobacter baumannii and Pseudomonas aeruginosa [6].

Pseudomonas aeruginosa is a Gram-negative, non-sporulated, straight or slightly curved rod-shaped, facultative anaerobic bacterium characterized as a non-fermenting bacillus due to the inability to obtain energy through the fermentation of carbohydrates such as glucose [7]. It is a relevant bacteria in epidemiological studies because it is one of the most prevalent microorganisms in nosocomial infections and has many virulence factors and resistance mechanisms that can be developed, justifying its inclusion in the ESKAPE group (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.), a set of bacteria of similar high pathogenicity [8].

The production of enzymes capable of hydrolyzing antibiotics is one of the main mechanisms of resistance associated with NG bacteria, and P. aeruginosa is one of the species that has increasingly shown this ability. Carbapenemic enzymes are enzymes responsible for degrading carbapenem antibiotics, an important class used in the treatment of HAIs, making carbapenem-resistant Pseudomonas aeruginosa (CRPA) isolates responsible for reducing the microbial therapeutic arsenal available in hospitals [9].

Carbapenemases can be classified based on the gene that expresses the synthesis of these enzymes, and may be serine carbapanemases, which have as their main representatives the KPC (Klebsiella pneumoniae carbapenemase) and OXA-48 (Oxacillinase-48) genes, or metallo-β-lactamases, with IMP (Imipenemase), VIM (Metallo-β-lactamase encoded by Verona Integron) and NDM (New Delhi Metal-β-lactamase) as the most important genes [9,10].

The detection of the bacterial resistance profile is a step of great importance for the effectiveness of the treatment of nosocomial infections, allowing the implementation of a drug therapy with greater efficacy and with less risk to the patient. The epidemiological survey of this profile is essential to contribute to scientific knowledge on bacterial resistance, fostering the study, improving good practices in care and generating warning signs for the research of new therapeutic alternatives that are capable of reducing mortality associated with HAIs, as well as improving safety in the services offered by hospitals. Therefore, the objective of this article was to detect the production of carbapenemase enzymes in isolates of Pseudomonas aeruginosa associated with the lower respiratory tract in an Adult Intensive Care Unit of a tertiary hospital in Fortaleza, Ceará, Brazil.

2. MATERIAL AND METHODS

This is an epidemiological, descriptive, retrospective study with a quantitative approach to tracheal aspirate and bronchoalveolar lavage samples positive for Pseudomonas aeruginosa, from patients admitted to the Adult Intensive Care Unit of the Walter Cantídio University Hospital (HUWC), located in the city of Fortaleza, Ceará.

The identification of the samples and the antimicrobial susceptibility profile were performed using the VITEK® 2 Compact system (bioMérieuxTM). The detection of carbapenemase production was performed by the immunochromatographic test NG-Test Carba 5 (Laborclin - Centerlab), in addition to the mCIM (Modified Carbapenem Inactivation Method) assays. The minimum inhibitory concentrations were interpreted according to the Brazilian Antimicrobial Susceptibility Testing Committee (BrCAST, 2022).

Data were collected by the Microbiology Sector of the Central Laboratory of Clinical Analysis of the hospital through the REDCap management system. All positive cultures of lower respiratory tract samples (tracheal aspirate and bronchoalveolar lavage) from the study population from January to December 2022 were included. Patients who presented two or more culture results with the same resistance profile and isolated microorganism in a short period of time were identified for the inclusion of only one report for the research.

The data were analyzed and audited in the program Excel® and statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), using Pearson's chi-squared test ($\chi 2$) and 95% confidence interval (95% CI). For interpretation, p

< 0.05 were considered significant. This research was carried out in accordance with the ethical and legal principles that govern research on human beings, as recommended in Resolution No. 466/2012 of the National Health Council (CNS), approved by the Research Ethics Committee of the HUWC under n°. 6.717.757.

3. RESULTS AND DISCUSSION

In 2022, 50 respiratory tract samples positive for Pseudomonas aeruginosa were identified, isolated from 25 patients admitted to the hospital's Adult ICU. After applying the exclusion criteria, only 25 isolates were kept for the development of this survey due to the repetition of the isolation of microorganisms with the same profile in a short time interval.

Considering the selected data, 80% (n= 20) were samples of tracheal aspirate and 20% (n= 5) of bronchoalveolar lavage. The mean age of the patients was 61.16 years, with a standard deviation of 18.25, justified by the discrepancy in age of the selected patients, which ranged from 22 to 85 years of age. Regarding gender, 56% (n= 14) were male and 44% (n= 11) were female. As a clinical outcome, 20% (n= 5) were medical discharged and 80% (n= 20) died.

The respiratory tract is considered one of the most relevant sites of infection because it is associated with a large part of the mortality rate in patients with HAI, mainly due to the facilitation of physical access for bacteria through ventilatory support and/or other medical devices associated with the respiratory canal. In addition, the upper respiratory tract is an environment highly colonized by several microorganisms, which can hinder microbiological diagnosis due to the presence of contaminating microorganisms in the sample [11].

Studies indicate that the rates of Healthcare-Associated Infections in Brazil are higher than in other countries, with the bacterium Pseudomonas aeruginosa being one of the most worrisome in terms of incidence and virulence, especially those strains that have the ability to produce enzymes that attribute resistance mechanisms to it and restrict the therapeutic options available [12,13].

Table 1 presents the absolute and relative frequency of the susceptibility tests successfully performed by the VITEK® 2 Compact system (bioMérieuxTM) for the selected Pseudomonas aeruginosa isolates.

Table 1. Absolute and relative frequency of antimicrobials tested in *Pseudomonas aeruginosa* isolates

Antimicrobials	N	%	CI (95%)
Piperacilin/Tazobactam	23	92	72,49 - 98,61
Ceftazidime/Avibactam	11	44	25,02 - 64,73
Ceftazidime	25	100	83,42 - 100
Cefepime	25	100	83,42 - 100
Imipenem	25	100	83,42 - 100
Meropenem	25	100	83,42 - 100

Amikacin	25	100	83,42 - 100
Gentamicin	15	60	38,89 - 78,19
Ciprofloxacin	25	100	83,42 - 100
Tigecycline	11	44	25,02 - 64,73

*CI, confidence index;

Table 2 shows the susceptibility profile of Pseudomonas aeruginosa isolates to the antimicrobials exposed in Table 1 of this article.

Table 2.Antimicrobial susceptibility profile tested on *Pseudomonas aeruginosa*

Antimicrobials	Sensitive	Sensitive, increasing exposure	Resistant
	N (%)	N (%)	N (%)
Piperacilin/Tazobactam	2 (8,70)	2 (8,70)	19 (82,60)
Ceftazidime/Avibactam	3 (27,27)	0 (0)	8 (72,72)
Ceftazidime	5 (20)	2 (8)	18 (72)
Cefepime	5 (20)	2 (8)	18 (72)
Imipenem	6 (24)	1 (4)	18 (72)
Meropenem	7 (28)	0 (0)	18 (72)
Amikacin	10 (40)	3 (12)	12 (48)
Gentamicin	6 (40)	0 (0)	9 (60)
Ciprofloxacin	5 (20)	3 (12)	17 (68)
Tigecycline	0 (0)	0 (0)	11 (100)

The antimicrobial susceptibility profile of this study indicated high resistance of the isolates to all antimicrobials tested, with the antibiotic amikacin being the one with the lowest resistance rate (48%), in coherence with the profile of the study by Bastos et al. [14], although this one got only 22%. The profile of all antibiotics differs from the study, and the resistance detected in this article is superior in most cases, with the exception of gentamicin. For comparison purposes, we have: cefepime, imipenem and meropenem - 72% vs 56%; ciprofloxacin - 68 vs 44%; e piperacilin/tazobactam - 82,6% vs 44% - respectively data from this study in comparison with Bastos et al. 15. Even if it is not a favorable profile, this evolution of the resistance of P. aeruginosa strains was already expected through the excessive use of antibiotics in recent years, especially with the advent of the SARS-CoV-2 pandemic [15].

The antibiotic ceftazidime/avibactam was developed for the treatment of infections caused by serine-carbapenemase Gram-negative bacteria resistance [16]. The study by Santevecchi et al. [17] carried out in 2021, pointed to 25% resistance to this drug in strains of P. aeruginosa isolated from respiratory samples, while this research found 50%. Although there is a strong hypothesis of the evolution of resistance in this short period of time, both studies had a small sample, which is not enough to prove this theory.

The isolates of P. aeruginosa were classified according to the mechanism and resistance gene presented, as shown in Table 3. In addition, it was possible to evaluate the relationship between phenotypic characterization and the clinical outcome of the patients (Table 3).

Table 3. Characterization of the resistance of *Pseudomonas aeruginosa* isolates regarding the mechanism and gene of resistance and relationship with the clinical outcome.

Variables	**N (%)**	**Clinical outcome**		**(χ^2) p-value**
		Discharge	**Death**	
Mechanism of Resistance (n= 25)				
Carbapenems-resistant *P.aeruginosa*(CRPA)	18 (72%)	3 (17%)	15 (83%)	0,9113
Carbapenems-sensitive *P.aeruginosa*	7 (28%)	2 (29%)	5 (71%)	
CRPA Resistance Type (n= 18)				
Serine carbapenemase	6 (33%)	0 (0%)	6 (100%)	0,1116
Metalo-β-lactamase	4 (22%)	2 (50%)	2 (50%)	
Enzyme not detected	5 (28%)	0 (0%)	5 (100%)	
Non-enzymatic	3 (17%)	1 (33%)	2 (67%)	
Enzyme resistance genes (n= 15)				
KPC	6 (40%)	0 (0%)	6 (100%)	0,0418*
IMP	4 (27%)	2 (50%)	2 (50%)	
Indeterminate	5 (33%)	0 (0%)	5 (100%)	

CRPA - Carbapenems-resistant *Pseudomonas aeruginosa*; KPC - *Klebsiella pneumoniae* carbapenemase; IMP - Imipenemase. * Statistically significant value
NOTE: percentage of clinical outcome expressed in line.

Considering only the serine-producing isolates carbapenemases, 50% were resistant to ceftazidime/avibactam, 83.3% to amikacin and 100% to tigecycline and ciprofloxacin.

In 2021, an epidemiological study published by Yang et al. [13] resulted in the isolation of Pseudomonas aeruginosa in 34.5% of the analyzed population. The study analyzed respiratory tract samples from 229 patients with nosocomial infection at a large Chinese hospital. Among the isolates of P. aeruginosa, 54.4% had genes that produce carbapenemase enzymes, in contrast to this study, which found 72% of CPPA (Carbapenemase-producing Pseudomonas aeruginosa), an estimate closer to the research by Tenover, Nicolau and Gill et al. [18]., which showed 86% of strains producing these enzymes.

Although the identification of CRPA strains is a common profile worldwide, the genes that produce these enzymes show high variability according to geographic distribution. This study followed the national profile and found KPC and IMP genes, which are common to the region, but there was no presence of other usual genes, such as OXA-48, NDM and VIM [18].

The association of the clinical outcome with enzyme resistance genes showed a statistically significant value, with a p-value of = 0.0418. Death was the clinical outcome of all patients infected with P. aeruginosa producing carbapenemases mediated by the KPC gene or indeterminate genes (genes not tested by immunochromatographic assay NG-Test® Carba 5). This profile is for great relevance, since the KPC gene is quite common and can be found in numerous species of Enterobacteriaceae that cause HAIs. As for cases of enzymatic resistance by indeterminate genes, the incomplete characterization of resistance compromises the implementation of an effective antimicrobial therapy for the patient and makes it difficult to broadly know the strains responsible for these infections that contribute to the high rate of deaths [19,20].

The clinical outcome was statistically analyzed to assess whether there is significance in its relationship with other variables, such as gender and age. The results of these analyses can be seen in Table 4.

Table 4. Statistical analysis of the clinical outcome ratio with gender variables, age and type of resistance.

Variables	N (%)	Clinical outcome		(χ^2) p-value
		Discharge	Death	
Sex (n=18)				
Male	10 (55,55)	3 (30%)	7 (70%)	0,2888
Female	8 (44,45)	0 (0%)	8 (100%)	
Age group (n=18)				
< 40 years	2 (11,12)	0 (0%)	2 (100%)	
40 to 60 years old	4 (22,22)	0 (0%)	4 (100%)	0,4066
> 60 years old	12 (66,66)	3 (25%)	9 (75%)	

χ^2 - Pearson's chi-squared;

The mortality rate of the patients included in this study was 80%. Although it is an extremely high percentage, according to the survey by Fujitani and collaborators [21], mortality associated with P. aeruginosa infection in the respiratory tract can range from 42.1% to 87%. The same authors further discuss that the mortality rate that is in fact attributable to infection varies between 32 and 42.8%, even if patients receive adequate antimicrobial therapy. This percentage is reduced by the presence of comorbidities, pathologies and other problems that weaken the body and lead to death, a situation that hinders the statistical analysis of the impact of nosocomial infections.

The statistical association of the clinical outcome with the variables sex ($p = 0.2888$) was not statistically significant, p-value < 0.05. Other studies in the literature also do not show significance in this relationship with the gender variable, since there is no consensus among the published data on the prevalence of sex in hospital admissions, which may vary according to region and hospital institution, for example [22]. Regarding the association between the outcome and the age group, $p = 0.4066$ was obtained, indicating no significance in the relationship. This is justified because, although the elderly population is more vulnerable, other factors associated with the health condition of patients prevail in this relationship with mortality, regardless of age [23].

A relevant limitation of this article was the difficulty in finding other studies that developed a statistical analysis on P. aeruginosa strains isolated in respiratory samples, since, although relevant, it is a line of research with in-depth analysis of a biological sample and a microorganism, while the most common clinical microbiology studies specify only one of these. Another important point refers to the place of study, since the hospital in question belongs to the tertiary level and performs activities at the quaternary level, therefore, most of the patients treated and, consequently, included in this study, have serious and/or delicate health conditions from a medical point of view.

4. CONCLUSION

This study shows high mortality rates and detection of carbapenemases in patients admitted to intensive care units and presenting with a healthcare-associated Pseudomonas aeruginosa respiratory tract infection in a reference hospital from Ceará, Brazil. The reduction in the effectiveness of new antimicrobial therapies, such as ceftazidime-avibactam, to treat isolates with enzyme resistance mechanisms is an important warning data for hospital infection and control committees. Therefore, these data reinforce the relevance of nosocomial infections for public health and the constant need to improve and review HAI control and prevention practices in order to improve the care offered to patients.

CONSENT (WHEREEVER APPLICABLE)

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this article.

ETHICAL APPROVAL (WHEREEVER APPLICABLE)

This research belongs to an Umbrella Project approved by the Research Ethics Committee of the Federal University of Ceará/Walter Cantídio University Hospital, according to approval opinion number 3.717.757. The research was developed in accordance with the requirements of Resolution No. 466 of December 12, 2012, of the National Health Council (CNS) of the Ministry of Health, considering the respect for human dignity and the special protection due to participants in scientific research involving human beings.

REFERENCES

1. Silva JKB, Cabral JR, Monteiro EPG, Cordeiro MFFD, Freire DA, Oliveira RC. Microbiological and clinical profile of health-related infections in a hospital in Pernambuco. Rev. de Fr. Care is Fundamental, v. 13, p. 1277-1282, 2021. DOI: https://doi.org/10.9789/2175-5361.rpcfo.v13.9697

2. Camargo LKIO, Caretaker MM, Gagliani LH. Review: Analysis of the situation of healthcare-associated infections (HAIs) in Brazil. UNILUS Ensino e Pesquisa, v. 16, n. 45, p. 203-223, 2020.

3. OMS. Organização Mundial da Saúde. Global report on infection prevention and control: executive summary. Geneva: World Health Organization; 2022.

4. Silva LS, Leite CA, Simões MRL, Azevedo DSS. Profile of healthcare-associated infections in an intensive care unit in Minas Gerais. Rev. of Epidemiology and Infection Control, v. 9, n. 4, p. 264-269, 2019.

5. Abushaheen MA et al. Antimicrobial resistance, mechanisms and its clinical significance. Disease-a-Month, v. 66, n. 6, 2020. DOI: https://doi.org/10.1016/j.disamonth.2020.100971

6. Batista WS et al. Microbiological profile of patients hospitalized in the intensive care unit of a public hospital in Baixada Maranhão. Research, Society and Development, v. 11, n. 11, 2022. DOI: https://doi.org/10.33448/rsd-v11i11.33883

7. Diggle SP, Whiteley M. Microbe Profile: Pseudomonas aeruginosa: opportunistic pathogen and lab rat. Microbiology, v. 166, n. 1, p. 30, 2020. DOI: https://doi.org/10.1099/mic.0.00086

8. Qin S et al. Pseudomonas aeruginosa: pathogenesis, virulence factors, antibiotic resistance, interaction with host, technology advances and emerging therapeutics. Sig Transduct Target Ther, v. 7, n. 199, 2022. DOI: https://doi.org/10.1038/s41392-022-01056-1

9. Dalmolin J et al. Mechanisms of expression of antibiotic resistance and public health. UNIPAR Health Sciences Archives, v. 26, n. 3, 2022. DOI: https://doi.org/10.25110/arqsaude.v26i3.2022.8851

10. Boyd SE, Livermore DM, Hooper DC, Hope WW. Metallo-β-lactamases: structure, function, epidemiology, treatment options, and the development pipeline. Antimicrobial agents and chemotherapy, v. 64, n. 10, 2020. DOI: https://doi.org/10.1128/aac.00397-20

11. Yang X, Lai Y, Li C, Yang J, Jia M, Sheng J. Molecular epidemiology of Pseudomonas aeruginosa isolated in patients with lower respiratory tract infections admitted to the ICU. Brazilian Journal of Biology, v. 81, p. 351-360, 2020. DOI: https://doi.org/10.1590/1519-6984.226309

12. Nangino GO, Oliveira CD, Correia PC, Machado NM, Dias ATB. Financial impact of nosocomial infections in intensive care units of a philanthropic hospital in Minas Gerais. Rev. Bras. de TerapiaIntensiva, v. 24, p. 357-361, 2012. DOI: https://doi.org/10.1590/S0103-507X2012000400011

13. Bassetti M, Vena A, Croxatto A, Righi E, Guery B. How to manage Pseudomonas aeruginosa infections. Drugs in context, v. 7, 2018. DOI: https://doi.org/10.7573/dic.212527

14. Bastos IDM et al. Bacterial profile of microbiological samples from patients admitted to the Surgical Clinic of a University Hospital in Pernambuco. VITTALLE - Rev. de Ciências da Saúde, v. 32, n. 1, p. 108-121, 2020.

15. Dias MLS, Molinaro CGS, Aragão LCM, Lima EM, Correal JCD. Comparative analysis of bacterial resistance of bacteremia-causing microorganisms in critically ill patients in the pre-pandemic and COVID-19 periods in a private tertiary hospital in Rio de Janeiro. The Brazilian Journal of Infectious Diseases, v. 26, p. 102227, 2022. DOI: https://doi.org/10.1016/j.bjid.2021.102227

16. Soriano A, Carmeli Y, Omrani A, Moore LSP, Tawadrous M, Irani P. Ceftazidime-avibactam for the treatment of serious Gram-negative infections with limited treatment options: a systematic literature review. Infectious diseases and therapy, v. 10, p. 1989-2034, 2021. DOI: https://doi.org/10.1007/s40121-021-00507-6

17. Santevecchi BA, Smith TT, Macvane SH. Clinical experience with ceftazidime/avibactam for treatment of antibiotic-resistant organisms other than Klebsiella pneumoniae. International journal of antimicrobial agents, v. 51, n. 4, p. 629-635, 2018. DOI: https://doi.org/10.1016/j.ijantimicag.2018.01.016

18. Tenover FC, Nicolau DP, Gill CM. Carbapenemase-producing Pseudomonas aeruginosa–an emerging challenge. Emerging microbes & infections, v. 11, n. 1, p. 811-814, 2022. DOI: https://doi.org/10.1080/22221751.2022.2048972

19. Yoon EJ, Jeong SH. Mobile carbapenemase genes in Pseudomonas aeruginosa. Frontiers in microbiology, v. 12, p. 614058, 2021. DOI: https://doi.org/10.3389/fmicb.2021.614058

20. Bella BD et al. Resistance to ceftazidime/avibactam in infections and colonisations by KPC-producing Enterobacterales: a systematic review of observational clinical studies. Journal of Global Antimicrobial Resistance, v. 25, p. 268-281, 2021. DOI: https://doi.org/10.1016/j.jgar.2021.04.001

21. Fujitani S, Sun HY, Yu VL, Weingarten JA. Pneumonia due to Pseudomonas aeruginosa: part I: epidemiology, clinical diagnosis, and source. Chest, v. 139, n. 4, p. 909-919, 2011. DOI: https://doi.org/10.1378/chest.10-0166

22. Garbuio DC, Baldavia NE, Silva RB, Lino AA. Characterization of healthcare-associated infections in an adult intensive care unit. Rev. of Epidemiology and Infection Control, v. 12, n. 1, 24 May 2022. DOI: https://doi.org/10.17058/reci.v12i1.16471

23. Alvares FA, Oliveira CS, Alves DCI, Braun G. Ventilator-associated pneumonia: incidence, microbial etiology, and antimicrobial resistance profile. Rev. of Epidemiology and Infection Control, v. 11, n. 4, 29 mar. 2022. DOI: https://doi.org/10.17058/reci.v11i4.16781