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Comparative analysis of mortality of critically ill patients with infections due to carbapenem-resistant Gram-negative bacilli treated with ceftazidime-avibactam or polymyxin B

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Abbreviations: CR-GNB, carbapenem-resistant Gram-negative bacteria; GNB, Gram-negative bacteria; COVID-19, Coronavirus disease 2019; CR, Carbapenem-resistant; PB, polymyxin B; CAZ/AVI, ceftazidime-avibactam; AMR, antimicrobial resistance; CDC, Centers for Disease Control and Prevention; ESBL, Extended spectrum beta-lactamases; MDR, Multidrug-resistant; WHO, World Health Organization; CRE, Carbapenem-resistant Enterobacterales; CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; CRAB, Carbapenem-resistant *Acinetobacter baumannii* ; SD, Standard deviation

Introduction

The emergence and spread of carbapenem-resistant Gram-negative bacteria (CR-GNB) represents a challenge in global public health,[1] since it increases the morbidity and mortality of patients,[2] the length of hospital stay[3] and healthcare-associated costs.[4] The urgency to find new drugs that can treat serious infections caused by these microorganisms increased even more with the COVID-19 pandemic[5,6,7] in which the conditions were given for a "perfect storm" of dissemination in hospitals around the world according to the U.S. Centers for Disease control and Prevention.[8]

Infectious episodes due to CR-GNB are most often observed in elderly patients due to the state of immunosenescence of this population[9] and the high prevalence of colonization by CR-GNBs consequent to the previous use of antibiotics and recurrent hospitalizations for chronic pathologies such as diabetes, lung diseases, urinary tract diseases or cancer.[10]

Until recently the only antibiotics available for the treatment of infections caused by CR-GNB were aminoglycosides, tigecycline, polymyxin B (PB) or colistin (polymyxin E) and the associations of these antibiotics,[11,12] but the efficiency of these therapies has been progressively decreasing in the last two decades due to difficulties related to their pharmacokinetic / pharmacodynamic profiles of these antibiotics and the growing phenomenon of antimicrobial resistance (AMR).[13]

The PB is a polypeptide antibiotic that acts by targeting the lipopolysaccharide layer of the GNB outer membrane, disrupting its integrity and leading to cell death. It has played a crucial role in the treatment of patients infected by bacteria that exhibit strains that produce carbapenemases, such as bla_{KPC}, bla_{OXA}, and bla_{NDM} enzymes.[14]

The combinations of ß-lactam antibiotics with new ß-lactamase inhibitors created options for the treatment of CR-Enterobacterales (CRE), CR-*Pseudomonas aeruginosa* (CRPA), CR-*Acinetobacter baumannii*(CRAB) and other multidrug-resistant (MDR) bacteria for which there were few alternatives.[15] These compounds are also carbapenem-sparing options in the treatment of other more common infections.[16] The ceftazidime-avibactam (CAZ/AVI) is an antibiotic association between a third-generation cephalosporin, whose mechanism of action is the inhibition of the synthesis of the bacterial cell wall, and avibactam, a new beta-lactamase inhibitor with activity against extended spectrum beta-lactamases (ESBL) and CRE (preferred treatment for CR-GNB harboring bla_{KPC}, bla_{OXA-48}, genes).[17] This antibiotic has been used mainly in the treatment of sepsis by serious nosocomial infections such as pneumonia, intra-abdominal infections and complicated urinary tract infections caused by CRE or CRPA.[18,19]

Several studies have shown therapeutic failure in the use of these new associations due to problems related to bacterial resistance[22,23] and related to adverse effects in therapy.[24] The aim of this study was to evaluate the 30-day mortality in critically ill elderly patients with infections caused by CR-GNB who were treated with CAZ/AVI or PB. In addition, a study was conducted to determine the economic impact of the use of these antimicrobial therapies on this patient population.

Methods

A retrospective cross-sectional study was conducted in critically ill elderly patients treated in the intensive care unit of a tertiary urban hospital of the Rio de Janeiro, Brazil (Hospital Rede Casa Portugal), from January 2021 to June 2022. Only adult patients who had severe infections caused by RC-GNB and who were treated with PB or CAZ/AVI were selected.

The demographic and clinical variables of these patients were obtained from the databases of the institutional committee for hospital infection control, clinical chards and pharmacy records. Bacterial isolation and antimicrobial susceptibility tests were performed according to institutional protocols and using automated methodologies (BD Phoenix™ M50 - Becton Dickinson Diagnostics, Sparks, MD, USA). The microbiological data were selected from the databases of the microbiology laboratory of the unit, recorded in an epidemiological form and consolidated in an Excel® sheet (Microsoft Corporation, 2018. Microsoft Excel).

The diagnostic criteria used for infection and sepsis characterization were based on the current sepsis guidelines[23,24] and the clinical criteria for establishing the infectious focus according to the CDC criteria.[25]

The main outcome was the 30-day all-cause mortality estimated from the first day of initiation of treatment with PB or CAZ/AVI. Only one septic episode was evaluated per patient in the same month and only outcomes of patients who received at least 72 hours of antimicrobial therapy were considered.

The dose of CAZ/AVI (Torgena®, Pfizer,USA) and polymyxin B (Polymixin B sulfate®, Eurofarma, SP, Brasil) administered was the one standardized by the manufacturer. In the CAZ/AVI group was 2.5 gr (2 g/0.5 gr) IV q8hr infused over two hours and in PB group was 15,000-25,000 units/kg/day IV q12hr[26,27] infused over three hours. In patients with renal failure, dose adjustments of the antibiotic were made on the second day according to the creatinine clearance estimation. In addition, an analysis of the costs of the antimicrobial therapy used was carried out based on the updated costs generated by the institutional pharmacy department.

The study was approved by the institutional research committee and the consent form was spared due to the retrospective non-interventionist nature of the study.

Statistical analysis

The results were expressed in frequency, mean ± standard deviation (SD) or as a proportion of the total number of samples. The differences in proportions were compared using the $\chi 2$ test or Fisher's exact test, as appropriate. All significance tests were two-tailed; a value of $p < 0.05$ was considered significant. The Mann-Whitney U test was performed to test the equality of continuous variables. In addition, a bivariate analysis of mortality was conducted by selecting for multivariate analysis those variables that had a p-value <0.2. Finally, a survival analysis was performed in the groups using the Kaplan-Méier survival curve and a Cox proportional hazards model. All statistical analyses were performed in the Stata 12.1 software (StataCorp; TX, USA).

Results

In total, 216 patients were included (PB group N=190 and CAZ/AVI Group N=26), whose clinical and demographical characteristics are described in Table 1. Most patients were female (102/52.7%) and there was no significant difference in the age of patients of the groups (PB:73.9 ± 1.3 years; CAZ/AVI:79.1 ± 2.5 years; p = 0.2), length of hospital stay (PB:15.7 ± 1.7 days; CAZ/AVI: 13.4 ± 1.6 days; p=0.4) or comorbidities (CharlsonComorbidity Index PB:4.8 ± 0.2 and CAZ/AVI: 4.6 ± 0.2; p=0,07).

There were more cases of pneumonia in the PB-treated group (79.5% vs 61.5% in the CAZ/AVI group; p=0.04) and a higher frequency of polymicrobial cultures was observed in the group treated with CAZ/AVI (34.6% vs 16.3% in the PB group; p=0.02). The most frequent etiology in the PB-treated group was CR-*Acinetobacter baumannii* (41%), and in the CAZ/AVI-treated group it was CR-*Klebsiella pneumoniae* (50%) (p< 0.05).

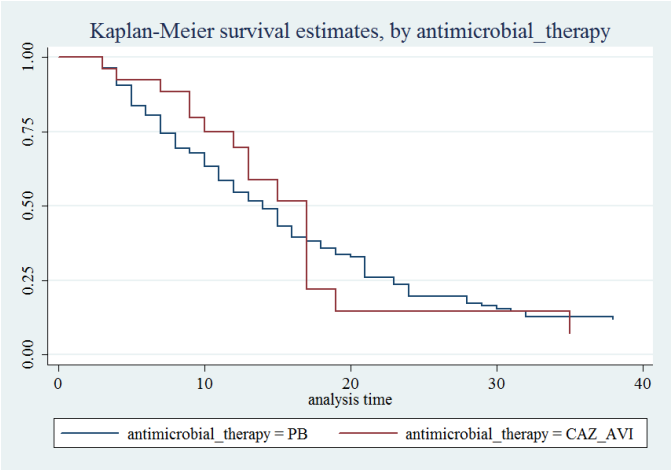
The 30-day all-cause mortality in both groups was similar (75.8% in the PB group and 61.5% in the CAZ/AVI group; p=0.12) (Graph 1). In the multivariate analysis the use of empirical antimicrobial therapy (negative cultures) was a risk factor independently related to mortality (Table 2). The adjusted cost of antimicrobial therapy was higher in the CAZ/AVI group (US$3,550.6 per episode) compared to the PB group (US$94.6 per episode) (p<0.05).

Table 1. Clinical characteristics and 30-day mortality of critically ill elderly patients with severe infections caused by multidrug-resistant Gram-negative bacilli treated with polymyxin B or ceftazidime/avibactam in Rio de Janeiro, Brazil (Jan 2021 - jun 2022)

Characteristics	Polymyxin B (N=190; 87.9%)	Ceftazidime/avibactam (N=26;12%)	p-value
Age (mean ± SE; years)	73.9 ± 1.3	79.1 ± 2.5	0.2
Male sex	90 (47.3)	12 (46.1)	0.9
Length of hospital stay (mean ± SE; days)	15.7 ± 1.7	13.4 ± 1.6	0.4
Comorbidities			
Hypertension	122 (64.2)	16 (61.5)	0.7
Atrial fibrillation	36 (18.9)	4 (15.4)	0.6
Diabetes	62 (32.6)	12 (46.1)	0.1
Heart failure	39 (20.5)	10 (38.5)	0.04
Chronic kidney disease	31 (16.3)	6 (23)	0.3
Coronary disease	13 (6.8)	2 (7.6)	0.8
Chronic obstructive pulmonary disease	15 (7.8)	3 (11.5)	0.5
Hemodialysis	8 (4.2)	2 (7.6)	0.4
Hypothyroidism	30 (15.7)	3 (11.5)	0.5
Peripheral arterial disease	9 (4.7)	2 (7.7)	0.5
Mental ilnesess	14 (7.3)	2 (7.6)	0.9
Central nervous system diseases	16 (8.4)	1 (3.8)	0.4
Charlson Comorbidity Index ((mean ± SE)	4.8 ± 0.2	4.6 ± 0.2	0,07
Source of infection			
Pneumonia	151 (79.5)	16 (61.5)	0.04
Urinary tract infection	37 (19.4)	8 (30.7)	0.1
Skin and soft tissue infection	8 (4.2)	4 (15.3)	0.02
Other infections	7 (3.6)	3 (11.5)	0.07
Sepsis of unknown origin	7 (3.6)	2 (7.7)	0.3
Cultures			
Polimicrobial cultures	31 (16.3)	9 (34.6)	0.02
Acinetobacter baumannii	78 (41)	7 (26.9)	0.7
Pseudomonas aeruginosa	37 (19.4)	8 (30.7)	0.1
Klebsiella pneumoniae	36 (18.9)	13 (50)	< 0.05
Other Gram-negative bacilli	17 (8.9)	4 (15.3)	0.3
Antibiotics			
Empirical therapy	41 (21.6)	2 (7.7)	0.1
Time of antibiotic use (mean ± SE; days)	10 ± 0.4	8.3 ± 0.6	0.1
Outcome			
30-day all-cause mortality	144 (75.8)	16 (61.5)	0.12

Table 2. Multivariate analysis of factors associated with 30-day mortality of critically ill elderly patients with severe infections caused by multidrug-resistant Gram-negative bacilli treated with polymyxin B or ceftazidime/avibactam in Rio de Janeiro, Brazil (Jan 2021 - jun 2022)

Variable	Risk Ratio	CI 95%	p-value
Hypothyroidism	0.79	0.56 - 1.05	0.05
Central nervous system diseases	0.69	0.44 - 1.09	0.03
Infectious episode due to *Pseudomonas aeruginosa*	0.73	0.56 - 0.95	0.005
Empirical therapy (negative cultures)	1.25	1.08 - 1.44	0.01



Graph 1 Kaplan-meier analysis of 30-day all-cause mortality in elderly ill critical patients with severe infections treated with polymyxin B or ceftazidime/avibactam in Rio de Janeiro 2021-2022.

Discussion

The worldwide increase in the prevalence of MDRbacteria in recent decades, especially of CR-GNB, generates high mortality rates and the costs of treating infections reach 34 billion dollars per year in the United States.[28,29] The World Health Organization (WHO) listed the CRAB, CRPA and CRE as "Priority 1: Critical pathogens", which urgently require new antibiotics.[30]

In the last two decades polymyxins were the maintherapeutic option for the treatment of infections caused by CR-GNB.[31,32,33] However, due to the emergence of bacterial resistance to polymyxins, increase of dissemination in ICUs of naturally polymyxin-resistant bacteria and difficulties related to the pharmacokinetics and pharmacodynamics of this antibiotic in critical infections,[34] several classes of new combinations of antibiotics appeared for the treatment of CR-GNB.[35]

Currently, in Brazil, ceftazidime/avibactam (CAZ/AVI) and ceftolozane/tazobactam are the only new associations available, and there is a more widespread use with CAZ/AVI due to the spectrum of bacteria it reaches (basically strains of CRE and CRPA).[36,37] Other interesting therapeutic possibilities such as meropenem/varbobactam, Imipenem/relebactam, cefiredocol, eravacycline, omadacycline, and plazomycinare not yet available in Brazil. Although the new associations represent a hope to treat these infections, in low-income countries the high costs of these new therapies seriously limit their availability to treat critical infections.

In our study we did not observe differences in the 30-day all-cause mortality in the two groups. This fact contradicts other previously published studies, suggesting the superiority and better therapeutic responses with the use of these new associations of antibiotics.[38–42] There are divergences in the currently available literature on these new antibiotic therapies. Some studies have shown similar activity of CAZ/AVI and PB against CR-GNB (in CRE: 97.5% and 90.5% respectively; in CRPA98.2% and 96.9% respectively and in CRAB 96.6% and 96.6% respectively.[43]

On the other hand, a recent meta-analysis suggests that CAZ-AVI treatment the treatment was more efficient thanpolymyxins in CRE. However, in this meta-analysis were included only observational studies with small series of cases.[44]

To our best knowledge, this is the first Brazilian study to compare the efficiency and associated costs of antimicrobial therapy of ß-lactam antibiotics / new ß-lactamase inhibitors and polymyxins in the treatment of infections due to CR-BGNs in elderly critical patients. We hypothesize that there are some characteristics in the infectious episodes of critical ill elderly patients that can explain this phenomenon. The antibiotic therapeutic failure in the treatment of sepsis in this age group is frequent because of the elderly frailty syndrome and chronic diseases that increase renal, cardiac and immune system complications in post-sepsis states.[45] In addition, the selection of CAZ/AVI resistant enterobacteria has already been demonstrated during treatment by the acquisition of plasmids carrying bla_{NDM-5} genes leading to resistance to CAZ/AVI[46] and, due to selection of clones with loss of porin *Omp*K35/36 along with DHA-1 β-lactamases production.[47]

Recent local molecular epidemiological studies in Brazil have shown a progressive increase in CR-GNB clones producers of metallobetalactamases, especially bla_{NDM} that degrade CAZ/AVI and a significant decrease in $bla_{KPC-1}$and bla_{KPC-2} -producing Enterobacterales.[48] Another factor that may increase the mortality of these patients may also be related to adverse effects associated with antimicrobial therapy such as renal failure, or other factors that influence the steady-state plasma concentration of antibiotics that variates among patients with renal impairment.

The most important limitation of the study was the low number of patients treated with CAZ/AVI. To try to obtain a more appropriate comparison, we made a 1:7 pairing with patients who were treated with PB. Because it is a retrospective study, we also observed some differences between the two groups. Due to the characteristics of healthcare-pneumonia of elderly critical patients (associated or not with the use of mechanical ventilation), a higher incidence was found in the group treated with PB compared to the group treated with CAZ/AVI. On the other hand, we noticed that the use of CAZ/AVI was more frequent in urinary sepsis or bloodstream infections. In addition, the presence of co-infection (polymicrobial cultures) was higher in the patients treated with CAZ/AVI. Regarding the etiologies of infectious episodes, co-infections with CRAB were more prevalent in the group treated with PB and those caused by CR-*Klebsiella pneumoniae* in the group treated with CAZ/AVI.

Finally, our study showed a large difference in the costs associated with the use of CAZ/AVI compared to PB and that reinforces the question: is it worth making such a high investment if there is no impact on 30-day all-cause mortality of these patients?

New randomized controlled studies are needed to validate these findings and explore additional factors that influence the clinical outcomes and cost of patients treated with polymyxin B and E or combinations of ß-lactam antibiotics with the new ß-lactamase inhibitors to treat infections due to CR-GNB in critically elderly patients in the post-pandemic era.[49]

Conclusion

The 30-day all-cause mortality of critically ill elderly patients with CR-GNB infections were similar in those that use ceftazidime/avibactam or polymyxin B (75.8% in the PB group and 61.5% in the CAZ/AVI group; p=0.12). There was a significant increase in antibiotic therapy costs in the ceftazidime/avibactam group (CAZ/AVI group: US$3,550.6 per episode compared to the PB group: US$94.6 per episode).

Conflicts of interest disclosure

All authors declare that they have no conflicts of interest.

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