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Original Article

Susceptibility to Ceftazidime-avibactam in pediatric bloodstream infections caused by multidrug-resistant Enterobacterales and *Pseudomonas aeruginosa*

Suscetibilidade de Ceftazidime-avibactam em bacteremias causadas por Enterobacterales e Pseudomonas aeruginosa multirresistentes em crianças

Susceptibilidad a ceftazidima-avibactam en bacteriemias pediátricas por Enterobacterales y Pseudomonas aeruginosa multirresistentes

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Corresponding author:

E-mail: aricardo@id.uff.br

Address: Professor Gabizo Street 252, Rio de Janeiro, Rio de Janeiro, Brazil.

André Ricardo Araujo da Silva¹

Luisa Benigno Barbosa Araujo da Silva²

¹Federal Fluminense University, Niterói, Rio de Janeiro, Brazil.

²Federal Fluminense Institute, Rio de Janeiro, Rio de Janeiro, Brazil.

ABSTRACT

Background and Objectives: Ceftazidime-avibactam (CAZ-AVI) is one of the last-resort treatment options for carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*. The aim of this study was to describe the susceptibility profile of bloodstream isolates of Enterobacterales and *Pseudomonas aeruginosa* to ceftazidime-avibactam (CAZ-AVI) among strains resistant to third- and fourth-generation cephalosporins and/or carbapenems in children. **Methods:** A retrospective descriptive study was conducted at two pediatric hospitals in the city of Rio de Janeiro, Brazil, between January 2023 and February 2025. All bloodstream isolates resistant to third- and/or fourth-generation cephalosporins and/or carbapenems were tested for susceptibility to CAZ-AVI according to the BrCAST methodology. CAZ-AVI susceptibility, as well as the clinical characteristics and outcomes of the patients were described. **Results:** A total of 116 bloodstream isolates were analyzed. Of these, 107/116 (92.2%) were resistant to third- and/or fourth-generation cephalosporins but remained susceptible to carbapenems, while 9/116 (7.8%) were resistant to both third- and/or fourth-generation cephalosporins and carbapenems. Overall susceptibility to CAZ-AVI was observed in 107/116 (92.2%) isolates. The 116 bloodstream isolates corresponded to 73 bloodstream infection (BSI) episodes in 66 patients, including 66 single episodes and 7 persistent BSIs. Of the 73 infections, 69 (94.5%) were caused by Enterobacterales and 4 (5.5%) by *Pseudomonas aeruginosa*. Twenty-two (30.1%) infections were detected at hospital admission, and 51 (69.9%) were healthcare-associated infections. Five of 73 patients (6.8%) died. Length of hospital stay was significantly longer among non-survivors than among survivors ($p = 0.01596$). CAZ-AVI was prescribed to four patients with Enterobacterales or *Pseudomonas aeruginosa* bloodstream infections, all of whom achieved bloodstream clearance. **Conclusion:** Susceptibility to CAZ-AVI among bloodstream isolates from children was high, and this antibiotic could be an option for treating carbapenem-resistant infections caused by Enterobacterales and *Pseudomonas aeruginosa*.

Keywords: Child. Sepsis. Multi-Drug Resistance.

RESUMO

Justificativa e Objetivos: O ceftazidime-avibactam (CAZ-AVI) é uma das últimas opções para o tratamento de Enterobacterales e *Pseudomonas aeruginosa* resistentes a carbapenêmicos. O objetivo foi descrever o perfil de suscetibilidade de isolados de corrente sanguínea de Enterobacterales e *Pseudomonas aeruginosa* ao ceftazidima-avibactam (CAZ-AVI), entre cepas resistentes a cefalosporinas de terceira e quarta geração e/ou a carbapenêmicos. **Métodos:** Foi realizado um estudo retrospectivo descritivo em dois hospitais pediátricos da cidade do Rio de Janeiro, Brasil, entre janeiro de 2023 e fevereiro de 2025. Todas as amostras de sangue com resistência a cefalosporinas de terceira/quarta geração e/ou a carbapenêmicos foram testadas para CAZ-AVI, de acordo com a metodologia BrCAST. Foram descritos a suscetibilidade ao CAZ-AVI, o perfil clínico dos pacientes e os desfechos. **Resultados:** Foram analisadas 116 amostras de sangue, das quais 107/116 (92,2%) foram resistentes a cefalosporinas de terceira/quarta geração, porém suscetíveis a carbapenêmicos, e 9/116 (7,8%) eram resistentes tanto a cefalosporinas de terceira/quarta geração quanto a carbapenêmicos. A suscetibilidade geral ao CAZ-AVI foi de 107/116 (92,2%). As 116 amostras representaram 73 episódios de infecção de corrente sanguínea (ICS) em 66 pacientes, incluindo 66 episódios únicos e 7 ICS persistentes. Das 73 infecções, 69 (94,5%) foram causadas por Enterobacterales e 4 (5,5%) por *Pseudomonas aeruginosa*. Vinte e duas (30,1%) infecções foram detectadas na admissão hospitalar e 51 (69,9%) foram infecções relacionadas à assistência à saúde. Houve óbito em 5/73 (6,8%) dos pacientes. O tempo de internação hospitalar ($p = 0,01596$) foi estatisticamente maior nos não sobreviventes em comparação aos sobreviventes. O CAZ-AVI foi prescrito para quatro pacientes com infecção por Enterobacterales ou *Pseudomonas aeruginosa*, com negatificação das bactérias na corrente sanguínea. **Conclusão:** A suscetibilidade ao CAZ-AVI nas ICS em crianças foi elevada, e este antibiótico pode ser uma opção para o tratamento de infecções por Enterobacterales e *Pseudomonas aeruginosa* resistentes a carbapenêmicos.

Descritores: Criança. Sepsis. Farmacorresistência Bacteriana Múltipla.

RESUMEN

Justificación y Objetivos: La ceftazidima-avibactam (CAZ-AVI) es una de las últimas opciones terapéuticas para el tratamiento de Enterobacterales y *Pseudomonas aeruginosa* resistentes a los carbapenémicos. El objetivo era describir el perfil de susceptibilidad de aislados de torrente sanguíneo de Enterobacterales y *Pseudomonas aeruginosa* a ceftazidima-avibactam (CAZ-AVI), entre cepas resistentes a cefalosporinas de tercera y cuarta generación y/o a carbapenémicos en niños. **Métodos:** Se realizó un estudio descriptivo retrospectivo en dos hospitales pediátricos de la ciudad de Río de Janeiro, Brasil, entre enero de 2023 y febrero de 2025. Todas las aislamientos de sangre con resistencia a cefalosporinas de tercera/cuarta generación y/o a carbapenémicos fueron analizadas para CAZ-AVI, de acuerdo con la metodología BrCAST. Se describieron la susceptibilidad a CAZ-AVI, el perfil clínico de los pacientes y los desenlaces. **Resultados:** Se analizaron 116 muestras de sangre, de las cuales 107/116 (92,2 %) fueron resistentes a cefalosporinas de tercera y/o cuarta generación, pero susceptibles a carbapenémicos, mientras que 9/116 (7,8 %) fueron resistentes tanto a cefalosporinas de tercera y/o cuarta generación como a carbapenémicos. La susceptibilidad global a CAZ-AVI fue del 92,2 % (107/116). Las 116 muestras correspondieron a 73 episodios de infección del torrente sanguíneo (ITS) en 66 pacientes, incluidos 66 episodios únicos y 7 episodios de ITS persistentes. De las 73 infecciones, 69 (94,5 %) fueron causadas por Enterobacterales y 4 (5,5 %) por *Pseudomonas aeruginosa*. Veintidós (30,1 %) infecciones se detectaron al ingreso hospitalario y 51 (69,9 %) fueron infecciones asociadas a la atención sanitaria. Se registraron 5 muertes entre 73 pacientes (6,8 %). La duración de la hospitalización ($p = 0,01596$) fue significativamente mayor en los no sobrevivientes en comparación con los sobrevivientes. El CAZ-AVI se prescribió a cuatro pacientes con infección por Enterobacterales o *Pseudomonas aeruginosa*, logrando la eliminación de la bacteria del torrente sanguíneo. **Conclusión:** La susceptibilidad a CAZ-AVI en las ITS en niños fue elevada, y este antibiótico podría ser una opción para el tratamiento de infecciones por Enterobacterales y *Pseudomonas aeruginosa* resistentes a carbapenémicos.

Palabras Clave: Niño. Sepsis. Farmacorresistencia Bacteriana Múltiple.

INTRODUCTION

In the last ten years, there has been a global concern about the spread of Carbapenem-resistant Enterobacterales (CRE) including *Klebsiella pneumoniae* and *Escherichia coli* organisms, as well as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The prevalence of carbapenem resistance varies depending on the country and bacterial pathogen studied.^{1,2}

The Global Antimicrobial Resistance and Use Surveillance System (GLASS) initiative of the World Health Organization (WHO) has been providing worldwide data on the susceptibility and resistance of these pathogens. For example, in the 2025 update, the global resistance rates to meropenem in blood samples were 49.6% for *Acinetobacter baumannii*, 15.1% for *Klebsiella pneumoniae* and less than 3.5% for *Escherichia coli*.³

Carbapenem resistance in children is usually lower than in adults, but historical trends have also shown an increase in resistance rates. In Brazil, the largest country in South America, data from the Brazilian National Health Surveillance Agency (ANVISA) in 2024 indicated that, among notified cases of central line-associated bloodstream infection (CLABSI) in children admitted to pediatric intensive care units (PICUs), resistance rates were 36.6% for *Pseudomonas aeruginosa*, 30.9% for carbapenems in *Klebsiella pneumoniae*, 30.2% for *Acinetobacter baumannii*, and 10.2% for *Escherichia coli*.^{4,5}

Ceftazidime-avibactam (CAZ-AVI) is a relatively recent treatment option for Gram-negative infections, particularly those caused by carbapenem-resistant Enterobacterales (CRE), including *Klebsiella pneumoniae* and *Escherichia coli*, as well as multidrug-resistant *Pseudomonas aeruginosa*. Several reports have described a favorable efficacy and safety profile in different clinical settings, including urinary tract infections (UTIs), bacteremia, sepsis, and infections in patients with cancer.^{6,7}

Despite recent data on CAZ-AVI use in the pediatric population, there is limited information on CAZ-AVI susceptibility and resistance among bloodstream isolates, particularly those resistant to third- and fourth-generation cephalosporins and carbapenems.

Given the growing global concern regarding carbapenem-resistant Gram-negative bacteria and the limited availability of novel antibiotic treatment options for the pediatric population, including ceftazidime-avibactam, for the management of bloodstream infections, there is a pressing need to investigate this issue and report data on the activity of this agent against multidrug-resistant microorganisms.

The aim of this study was to describe the susceptibility profile of bloodstream isolates of

Enterobacterales and *Pseudomonas aeruginosa* to ceftazidime-avibactam (CAZ-AVI) among strains resistant to third- and fourth-generation cephalosporins and/or carbapenems in children.

METHODS

A retrospective study was conducted to evaluate the *in vitro* susceptibility of bloodstream isolates of Enterobacterales and *Pseudomonas aeruginosa* to ceftazidime-avibactam (CAZ-AVI) in pediatric patients aged 0–18 years admitted to two pediatric hospitals in Rio de Janeiro, Brazil, between January 2023 and February 2025. The isolates included in the analysis exhibited resistance to third- or fourth-generation cephalosporins and/or carbapenems, as interpreted according to the guidelines of the Brazilian Committee on Antimicrobial Susceptibility Testing (BrCAST). All isolates were tested for CAZ-AVI susceptibility using an automated system (BACTEC FX/BD). CAZ-AVI susceptibility testing has been available as part of our routine clinical practice since January 2023 and has been systematically performed for clinical purposes. According to BrCAST guidelines, isolates were considered resistant to CAZ-AVI when the MIC was >8 mg/L for Enterobacterales and >4 mg/L for *Pseudomonas* spp. No exclusion criteria were applied.

For the clinical analysis, some patients had two or more blood samples collected during the same suspected infectious episode. For the purposes of this study, two or more positive blood samples collected from the same patient within 48 hours were considered a single episode of infection. If a positive blood sample persisted beyond the third day after the initial isolation, the episode was classified as a persistent infection. Finally, if a new positive sample was detected after the initial episode, a new infection episode was considered after 14 days.

Infections were considered healthcare-associated if they occurred more than 72 hours after hospital admission and were considered community-acquired or acquired from other healthcare facilities if blood samples were collected within 72 hours of hospital admission. Comorbidity was considered as any disease diagnosed before hospital admission and included, but was not limited to, heart disease, chronic pulmonary disease, cancer, metabolic or genetic diseases, and chronic skin diseases.

Hospital A has 130 beds and provides 24-hour, 7-day-a-week emergency services, as well as clinical, oncology, and surgical wards and four pediatric intensive care units (PICUs). Hospital B has 45 beds and a similar structure to Hospital A, except for the absence of surgical and oncology wards. Both hospitals have maintained active infection control teams operating continuously since 2005 and implemented an

antimicrobial stewardship program in 2017. The program includes CAZ–AVI as a restricted antibiotic, available only after prior approval by a pediatric infectious disease specialist. CAZ–AVI became available for clinical use at both hospitals in 2020; however, microbiological susceptibility testing was introduced only in 2023.

The data were compiled in an Excel file. Descriptive analyses were performed using means and medians. The Mann–Whitney U test was used to compare continuous variables, and Fisher’s exact test was used for categorical variables. A *p*-value < 0.05 was considered statistically significant.

The study was submitted to and approved by the Research Ethics Committee of the Faculty of Medicine at Universidade Federal Fluminense (UFF), under approval number 5.022.885, dated October 6, 2021.

RESULTS

Table 1. CAZ–AVI resistance profile according to year and resistance to third- and/or fourth-generation cephalosporins alone or in combination with carbapenems (Rio de Janeiro, 2023–2025).

	Third- and/or fourth-generation cephalosporin-resistant isolates		Third- and/or fourth-generation cephalosporin-resistant and carbapenem-resistant isolates	
	CAZ/AVI susceptible	CAZ/AVI resistant	CAZ/AVI susceptible	CAZ/AVI resistant
	N (%)	N (%)	N (%)	N (%)
2023	29 (27.1)	0 (0)	1 (11.1)	0 (0)
2024	66 (61.7)	7 (6.5)	5 (55.6)	2 (22.2)
2025	5 (4.7)	0 (0)	1 (11.1)	0 (0)

Abbreviation: CAZ/AVI- ceftazidime/avibactam.

The 116 bloodstream isolates corresponded to 73 bloodstream infection episodes in 66 patients, including 66 single episodes and 7 persistent bloodstream infections. (Table 2).

Table 2. Bloodstream infection episodes by year among patients tested for CAZ–AVI with isolates resistant to third- and/or fourth-generation cephalosporins alone or in combination with carbapenems (Rio de Janeiro, 2023–2025).

Years	Single episodes of BSI (N)	Persistent episodes of BSI (N)
2025	5	0
2024	44	4
2023	17	3

Abbreviation: BSI- bloodstream infections.

Of the 73 BSI episodes, 69 (94.5%) were caused by Enterobacterales and 4 (5.5%) by *Pseudomonas aeruginosa*. Only 7 of 73 BSI episodes (9.6%) involved carbapenem-resistant isolates. Twenty BSI episodes occurred in 2023, 48 in 2024, and 5 in 2025. Twenty-two (30.1%) BSI episodes were identified at hospital admission, while 51 (69.9%) were diagnosed more than 72 hours after admission. (Table 3).

A total of 116 bloodstream isolates resistant to third- and/or fourth-generation cephalosporins and/or carbapenems were isolated and tested for CAZ–AVI susceptibility. Of these, 107/116 (92.2%) were resistant to third- and/or fourth-generation cephalosporins but susceptible to carbapenems, whereas 9/116 (7.8%) were resistant to both third- and/or fourth-generation cephalosporins and carbapenems. No isolates were identified that were resistant to carbapenems but susceptible to third- and/or fourth-generation cephalosporins. Considering both groups, only 9/116 (7.8%) isolates were also resistant to CAZ–AVI: 7/100 (7%) in the third- and/or fourth-generation cephalosporin-resistant group and 2/9 (22.2%) in the group resistant to both third- and/or fourth-generation cephalosporins and carbapenems (*p* = 0.0892) (Table 1).

Table 3. Clinical profile of patients with bloodstream infections caused by isolates resistant to third- and/or fourth-generation cephalosporins and/or carbapenems and tested for CAZ–AVI susceptibility (Rio de Janeiro, January 2023–February 2025).

Variables	Values
Gender# N (%)	
Male	44 (66.7)
Female	22 (33.3)
Mean age# in months (range)	30 (0-208)
Type of infection*N (%)	
Community/From other healthcare facilities	22 (30.1)
Healthcare-associated infection	51 (69.9)
Invasive device use prior to infection* N (%)	
Yes	58 (79.5)
No	15 (20.5)
Comorbidity# N (%)	
Yes	61 (92.4)
No	5 (7.6)
Outcome after 30 days of infection* N (%)	
Discharged	48 (65.7)
Still hospitalized	19 (26)
Dead/Transferred	5 (6.8)
	1 (1.5)

Abbreviation: # Number of patients=66 *Number of infections=73.

We also analyzed carbapenem and/or third- and fourth-generation cephalosporin resistance and length of hospital stay before infection among survivors and non-survivors. Transferred patients were excluded from this analysis. (Table 4).

Table 4. Use of carbapenems and/or third- and fourth-generation cephalosporins and length of hospital stay before infection among survivors and non-survivors.

Variables	Survivors	Non-survivors	P value
Use of carbapenem and/or third/fourth cephalosporin generation before infection – N/total (%)	20/61 (32.8)	4/5 (80)	0.0547
Length of hospital stay before the infection-Mean in days (range)	19.7 (0-173)	39.4 (13-66)	0.01596

CAZ–AVI was prescribed for four patients, all of whom had infections caused by Enterobacterales or *Pseudomonas aeruginosa* resistant to carbapenems. In two of these patients, the isolates were susceptible to CAZ–AVI; one patient was discharged, while the other died. In the remaining two patients, CAZ–AVI was used despite resistance confirmed by antimicrobial susceptibility testing; one patient died, while the other remained hospitalized 30 days after the infection. All four patients achieved clearance of Enterobacterales or *Pseudomonas aeruginosa* from the bloodstream.

DISCUSSION

The global response to antimicrobial resistance includes research, development, and strategies to prevent and control infections caused by pathogens classified by the WHO as critical priorities, including carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant Enterobacterales, third-generation cephalosporin-resistant Enterobacterales, and carbapenem-resistant *Pseudomonas aeruginosa*.⁸

CAZ–AVI is a recently developed broad-spectrum antibiotic with activity against infections caused by drug-resistant Gram-negative bacteria, including AmpC-producing and extended-spectrum β-lactamase (ESBL)-producing Enterobacterales, OXA-48-producing Enterobacterales, *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacterales, and multidrug-resistant (MDR), extensively drug-resistant (XDR), ceftazidime-non-susceptible, and carbapenem-resistant *Pseudomonas aeruginosa* strains. Despite its broad and clinically relevant spectrum, CAZ–AVI maintains a favorable susceptibility profile for the treatment of these infections, although increasing resistance rates have been reported worldwide. A recent meta-analysis of global trends in CAZ–AVI resistance among Gram-negative bacteria supports this concern.⁹⁻¹¹

Antimicrobial resistance in pediatric populations is further complicated by the fact that several agents used to treat third-generation cephalosporin-resistant Enterobacterales and carbapenem-resistant *P. aeruginosa*, such as cefiderocol and tigecycline, are either not approved for use in children or are only available in certain countries. For these reasons, we aimed to evaluate the susceptibility of bloodstream isolates to CAZ–AVI among BSIs caused by Enterobacterales resistant to third- and/or fourth-generation cephalosporins and by Enterobacterales or *P.*

aeruginosa resistant to carbapenems. Currently, CAZ–AVI remains one of the few available treatment options for infections caused by these resistant pathogens.¹²

In our study, CAZ–AVI susceptibility testing of bloodstream isolates from pediatric patients with BSIs caused by third- and/or fourth-generation cephalosporin-resistant Enterobacterales and carbapenem-resistant Enterobacterales or *P. aeruginosa* showed a favorable susceptibility profile, with resistance observed in only 7.8% of all tested isolates. These results are consistent with those reported in a global meta-analysis of CAZ–AVI activity against Gram-negative bacteria, although that analysis included multiple infection sites, whereas our study focused exclusively on BSIs. Data specifically addressing CAZ–AVI susceptibility in pediatric BSIs are scarce. However, a Colombian study including isolates from blood, abdominal fluid, urine, soft tissue, and respiratory tract specimens from both pediatric and adult patients reported resistance rates of 59.26% for carbapenem-resistant *P. aeruginosa* and 1.64% for MDR Enterobacterales. Similarly, in a large analysis of the in vitro activity of CAZ–AVI against Gram-negative bacteria in patients with bacteremia and skin and soft-tissue infections, 19 of 29 *K. pneumoniae* isolates from children were classified as MDR, and 10.53% were non-susceptible to CAZ–AVI, representing a higher rate than that observed in our study.^{11,13,14}

As expected, at least one comorbidity was present in nearly all children with BSIs in our cohort (92.4%), along with the presence of an invasive device. This finding is similar to that reported in a systematic review and meta-analysis of CRE bacteremia in pediatric patients in Latin America and the Caribbean, in which all 149 analyzed patients had an underlying disease and a central venous catheter.¹⁵

When survival was analyzed according to prior exposure to carbapenems and/or third- or fourth-generation cephalosporins, no statistically significant association was found. However, length of hospital stay prior to infection was significantly longer among non-survivors. Prolonged hospitalization before infection with non-fermentative Gram-negative bacteria has been reported to reach 51.1 days in a cohort of 131 children from Turkey.¹⁶ In our study, the 30-day mortality rate was 6.8%, which was lower than the rates of 28% and 8.7% reported in studies from Turkey and China, respectively.^{16,17}

At our institution, since CAZ-AVI became available in 2020, its use has remained highly restricted, even in pediatric intensive care units. Both hospitals have experienced infection control teams, and a core component of the local antimicrobial stewardship program is the pre-approval of selected antimicrobials, defined according to local microbiological epidemiology. Under this policy, CAZ-AVI was prescribed to only four patients with infections caused by resistant isolates, all of which were carbapenem-resistant. In all cases, bloodstream clearance was achieved; however, two patients died. In two cases, CAZ-AVI was used as salvage therapy due to resistance identified in initial susceptibility testing. Reports on CAZ-AVI use in pediatric populations remain scarce, with most describing patients with underlying conditions such as malignancy and infections including urinary tract infections, sepsis, and bacteremia, often in the salvage setting.^{6,7,18}

This study has several limitations. First, although CAZ-AVI has been available since 2020, systematic susceptibility testing was only implemented at the end of 2022; nevertheless, the data presented represent two years of clinical experience. Second, due to the descriptive design, multivariate logistic regression analyses were not performed to identify potential risk factors for 30-day mortality. Finally, CAZ-AVI prescribing patterns in our setting are strongly influenced by an active antimicrobial stewardship program, and our results may be most applicable to institutions with similar characteristics. In conclusion, CAZ-AVI susceptibility among bloodstream isolates from pediatric patients was high, suggesting that this antibiotic may be an important therapeutic option for carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa* infections in children.

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AUTHORS' CONTRIBUTIONS

André Ricardo Araujo da Silva contributed to the research design, literature review, drafting of the abstract, introduction, methodology, discussion, interpretation and description of the results, preparation of tables, conclusions, revision, statistical analysis, and final review. **Luisa Benigno Barbosa Araujo da Silva** contributed to the literature review, drafting of the abstract, introduction, methodology, discussion, interpretation and description of the results, conclusions, revision, and statistical analysis.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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