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ORIGINAL ARTICLE

# Real-World Use of Ceftazidime–Avibactam for Carbapenem-Resistant Enterobacterales Infections in Children: A 7-Year Cohort from a Latin American Referral Center

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***Background:*** Pediatric data on ceftazidime-avibactam (CAZ-AVI) for carbapenem-resistant Enterobacterales (CRE) infections remain limited, particularly in Latin America, where *Klebsiella pneumoniae* carbapenemase (KPC)-producing organisms are endemic. We describe the clinical characteristics, microbiological profile, and outcomes of children with CRE infections treated with CAZ-AVI at a tertiary referral center in Colombia.

***Methods:*** We conducted a retrospective cohort study of children younger than 18 years with clinically significant CRE infections treated with CAZ-AVI between January 2018 and June 2025. Clinical, microbiological, treatment, and outcome data were collected. The primary outcome was clinical response at the end of therapy.

***Results:*** Forty-three patients were included (median age, 11 years [IQR, 6-15]); 25 patients (58%) were immunocompromised, 29 (67%) required PICU admission, and 16 (37%) presented with septic shock. *K. pneumoniae* was the predominant pathogen (33 patients, 77%), and KPC was the most common carbapenemase detected (39 patients, 91%). Clinical improvement within 72 h occurred in 40 patients (93%), with a median time to response of 2 days (IQR, 2-3). Overall, 40 patients (93%) achieved clinical cure. The estimated 30-day survival probability was 95.3% (95% CI, 88.8-100), recurrence occurred in 3 patients (7%), and no treatment-related adverse events were documented.

***Conclusion:*** In this real-world pediatric cohort from a KPC-endemic setting, CAZ-AVI was associated with favorable clinical outcomes and good tolerability. These findings support its role as an important therapeutic option for pediatric CRE infections and underscore the importance of mechanism-guided antimicrobial management.

**Key words:** ceftazidime-avibactam; carbapenem-resistant Enterobacterales; pediatrics; antimicrobial resistance; *Klebsiella pneumoniae* carbapenemase.

## INTRODUCTION

Carbapenem-resistant Enterobacterales (CRE) represent one of the most challenging multidrug-resistant pathogens encountered in pediatric practice, particularly among medically complex children with frequent healthcare exposure.[1–4] Historically, treatment options for CRE infections relied on agents such as colistin, tigecycline, and aminoglycosides, which are limited by toxicity and suboptimal clinical outcomes.[3,5,6] Ceftazidime-avibactam (CAZ-AVI) has transformed the therapeutic landscape for *Klebsiella pneumoniae* carbapenemase (KPC)- and some OXA-48-producing organisms, offering an alternative to these toxic agents.[5]

Since its approval for pediatric use in children older than 3 months, CAZ-AVI has been increasingly adopted in clinical practice; however, pediatric data regarding its real-world use and outcomes remain limited, and much of the current therapeutic experience continues to be extrapolated from adult populations despite important differences in epidemiology, pharmacokinetics, and clinical characteristics between adults and children.[6] Although recent pediatric studies have reported favorable outcomes with CAZ-AVI,[7] important gaps remain regarding its real-world performance, particularly in KPC-endemic regions. A systematic review including 6 pediatric

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studies reported clinical response rates ranging from 54.5% to 100%, highlighting substantial heterogeneity of available pediatric evidence.[8] A more recent systematic review and meta-analysis similarly reported high clinical and microbiological cure rates (>80%) across pediatric study designs, while identifying major evidence gaps for pneumonia, bacteremia, and infections caused by resistant organisms.[9]

Hospital Pablo Tobón Uribe is a private, high-complexity referral hospital in Medellín, Colombia, that serves both adult and pediatric populations and receives referrals from multiple regions across the country. The institution offers solid organ and hematopoietic stem cell transplantation programs and provides care for a broad range of medically complex pediatric patients, including children with hematologic and oncologic disease, transplant recipients, and other populations with substantial healthcare exposure. The pediatric service comprises 120 general ward and 30 pediatric intensive care unit beds, reflecting the high acuity and complexity of the population cared for at this center. CAZ-AVI is available on the institutional drug formulary. There are no formal restrictions on its prescription, however, there are specific indications for both empiric and targeted therapy by institutional guidelines. All prescriptions are reviewed by a pediatric infectious diseases specialist and by the institutional Antimicrobial Stewardship Program within 24 h of initiation.

Therefore, we sought to describe the clinical characteristics, microbiological findings, treatment patterns, and outcomes of children with CRE infections treated with CAZ-AVI at our center, a setting with endemic KPC circulation.

## METHODS

### Study Design and Population

We conducted a retrospective cohort study of consecutive pediatric patients hospitalized with CRE infections between January 2018 and June 2025. No formal sample size calculation was performed. All consecutive eligible patients identified during the study period were included. Eligible patients were younger than 18 years and had a diagnosis of CRE infection, defined as either: (1) a positive culture from a sterile or non-sterile site showing an Enterobacterales isolate with phenotypic resistance to at least one carbapenem (ertapenem, imipenem, or meropenem) by antimicrobial susceptibility testing, associated with clinical evidence of infection; or (2) molecular detection of a carbapenemase gene in an Enterobacterales organism—either from a positive culture or directly from a clinical specimen (eg, blood culture identification or pneumonia panels)—in the setting of a compatible clinical syndrome, as determined by the treating infectious diseases team, regardless of the phenotypic susceptibility result or even in the absence of culture confirmation. Phenotypic carbapenem resistance was not required when carbapenemase detection was molecular. Patients with infections caused by non-Enterobacterales Gram-negative organisms, including *Pseudomonas aeruginosa* and *Acinetobacter* spp., were excluded.

Clinical infection was defined by compatible signs and symptoms together with physician assessment supporting active infection. Patients were required to have received CAZ-AVI as targeted therapy for at least 24 h, either as monotherapy or in combination with other antimicrobial agents. Patients who received only 1 or 2 doses of CAZ-AVI before discontinuation or a change in antimicrobial therapy were excluded, as this was considered insufficient to evaluate treatment response. Patients with positive surveillance cultures (including rectal swabs, tracheal aspirates, or periostomal samples) without evidence of active infection, as well as those classified as colonized by the treating team, were excluded.

### Data Collection

Clinical and microbiological data were obtained through retrospective review of electronic medical records, microbiology laboratory databases, and institutional pharmacy records. Data were collected using a standardized case report form developed in the REDCap platform (version 14.6.11). Before formal data collection, a pilot assessment including approximately 10% of the expected sample was conducted to refine data collection procedures and improve data quality.

Collected variables included demographic characteristics, healthcare-associated exposures, prior antimicrobial exposure (any receipt within 90 days preceding the CRE infection regardless of treatment duration), underlying medical conditions, source of infection, microbiological findings, carbapenemase profiles, antimicrobial susceptibility results, treatment characteristics, clinical and microbiological response, recurrence, and mortality outcomes. Safety outcomes included documented adverse events potentially attributable to CAZ-AVI, including hypersensitivity reactions, hepatotoxicity, nephrotoxicity, gastrointestinal intolerance, hematologic abnormalities, and neurologic events. Adverse events were identified through retrospective review of medical records and documented assessments by treating physicians during therapy.

Antimicrobial susceptibility testing was performed in the institutional microbiology laboratory and interpreted according to Clinical and Laboratory Standards Institute (CLSI) breakpoints. Susceptibility to CAZ-AVI and other routinely tested antimicrobial agents was determined using the VITEK® 2 automated system (bioMérieux, Marcy-l'Étoile, France). For isolates harboring NDM-1, aztreonam susceptibility was assessed by gradient diffusion using Etest® strips according to manufacturer instructions and CLSI interpretive criteria.

Once phenotypic carbapenem resistance was identified by antimicrobial susceptibility testing, routine carbapenemase characterization was performed using NG-Test® CARBA 5, an immunochromatographic assay. Molecular confirmation of

carbapenemase genes was performed only when requested by the infectious diseases physician. Molecular panels (FilmArray®) on blood and respiratory clinical specimens were not systematically performed but were available upon request to support antimicrobial treatment decisions. Unlike the Blood Culture Identification Panel, which requires prior bacterial growth, the Pneumonia Panel could be performed directly on respiratory specimens, which accounts for CRE diagnosis by molecular methods alone in patients without a positive respiratory culture.

#### Antimicrobial Dosing

CAZ-AVI was dosed according to institutional protocol based on age and expressed as the ceftazidime component: 30 mg/kg/dose every 8 h in infants younger than 3 months, 40 mg/kg/dose every 8 h in infants 3 to younger than 6 months, and 50 mg/kg/dose (maximum 2000 mg/dose) every 8 h in children 6 months of age and older, corresponding to 37.5, 50, and 62.5 mg/kg/dose of the combined CAZ-AVI product, respectively. Doses were adjusted for renal function using the bedside Schwartz formula in patients with impaired renal function. Therapeutic drug monitoring was not available at our institution. Standard 2-h infusion time was used for most patients; prolonged infusion (3 h) was reserved for patients admitted to the pediatric intensive care unit at the request of the treating pediatric infectious diseases specialist.

#### Outcomes

The primary outcome was clinical response at the end of therapy, classified as clinical cure or treatment failure. Clinical cure was defined as resolution of infection-related signs and symptoms without the need for escalation or modification of antimicrobial therapy. Treatment failure was defined as lack of clinical improvement or clinical deterioration after at least 72 h of CAZ-AVI initiation, requirement for escalation or modification of antimicrobial therapy, or recurrence of infection. Recurrence was defined as isolation of the same microorganism from the same or a different site in the presence of compatible clinical evidence of active infection within 90 days after completion of CAZ-AVI therapy.

Secondary outcomes included microbiological response, duration of hospitalization and pediatric intensive care unit stay, recurrence of infection, and 30- and 90-day mortality. Microbiological response was assessed only in patients with available follow-up cultures and was defined as at least one negative culture obtained after initiation of therapy.

#### Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable national regulations governing research involving human participants. The study protocol was reviewed and approved by the institutional ethics committees. Given the retrospective design and use of anonymized data, informed consent was not required according to institutional policies. Patient confidentiality was protected through data anonymization and the use of coded identifiers.

#### Statistical Analysis

Categorical variables were summarized as absolute and relative frequencies. Continuous variables were reported as median with interquartile range or mean with standard deviation, as appropriate according to data distribution. Overall survival was estimated using the Kaplan–Meier method, and mortality rates were reported with corresponding 95% confidence intervals. Statistical analyses were performed using SPSS version 30 (IBM Corp., Armonk, NY, USA).

## RESULTS

#### Patient Population

During the study period, 48 pediatric patients with CRE infections were identified. Five patients were excluded because they were considered colonized, resulting in a final cohort of 43 patients.

The median age was 11 years (IQR, 6-15), and 22 patients (51%) were male. Most patients had substantial prior healthcare exposure, including previous hospitalization in 35 patients (81%), prior surgery in 30 (70%), and prior CRE colonization in 24 (56%). Additional baseline characteristics are summarized in Table 1.

#### Underlying Conditions and Clinical Presentation

Immunosuppression was the most common underlying condition, affecting 25 patients (58%), including 17 (68%) with underlying hematologic or oncologic disease. Severe acute malnutrition, gastrointestinal disease, and pulmonary disease were also frequent comorbidities. Overall, the cohort represented a medically complex population with substantial underlying chronic illness (Table 1).

Fever was the most common presenting manifestation, occurring in 32 patients (74%), followed by sepsis in 25 (58%). Septic shock and multiple organ dysfunction syndrome were present in 16 (37%) and 12 (28%) patients, respectively. Reflecting the severity of illness, 29 patients (67%) required admission to the pediatric intensive care unit and 27 (63%) underwent surgical intervention during hospitalization, either for source-control or unrelated surgical procedures (Table 1).

#### Microbiological Findings

Bloodstream infections were the most common source of infection, occurring in 15 patients (35%), followed by urinary tract infections in 11 (26%). *K. pneumoniae* was the predominant pathogen, accounting for 33 infections (77%). The distribution of infection sources and bacterial isolates is shown in Table 2.

**Table 1.** Baseline Characteristics and Clinical Presentation of Pediatric Patients with CRE Infections

| **Demographics characteristics** | ***n* = 43 (%)** |
|---|---|
| Male sex | 22 (51) |
| Age, years (IQR) | 11 (6.0-15.0) |
| Weight, kg (IQR) | 33.5 (18.9-51.0) |
| Urban residence | 40 (93) |
| **Healthcare exposure** | ***n* = 43 (%)** |
| Prior hospitalization | 35 (81) |
| Prior surgery | 30 (70) |
| Hospitalization in the last 90 days | 26 (60) |
| Prior CRE colonization (last year) | 24 (56) |
| Central venous catheter | 15 (35) |
| Prior PICU admission within 90 days | 8 (18) |
| Mechanical ventilation | 5 (12) |
| Solid organ transplant | 4 (9) |
| Hematopoietic stem cell transplant | 4 (9) |
| **Underlying conditions** | ***n* = 43 (%)** |
| Immunosuppression | 25 (58) |
| Severe acute malnutrition | 16 (37) |
| Gastrointestinal disease[a] | 13 (30) |
| Pulmonary disease[b] | 12 (28) |
| Chronic kidney disease | 10 (23) |
| Neurologic disease[c] | 8 (19) |
| Renal replacement therapy[d] | 5 (12) |
| Cardiac disease[e] | 3 (7) |
| **Prior antimicrobial exposure (last 90 days)** | ***n* = 43 (%)** |
| Broad-spectrum antibiotic exposure | 18 (42) |
| Carbapenem exposure | 6 (14) |
| Third- or fourth-generation cephalosporin exposure | 6 (14) |
| Fluoroquinolone exposure | 5 (12) |
| **Clinical presentation** | ***n* = 43 (%)** |
| Fever | 32 (74) |
| Sepsis | 25 (58) |
| Septic shock | 16 (37) |
| MODS | 12 (28) |
| Pediatric intensive care unit admission during infection | 29 (67) |

Abbreviations: CRE = carbapenem-resistant Enterobacterales; IQR = interquartile range; MODS = multiple organ dysfunction syndrome; PICU = pediatric intensive care unit. Continuous variables are presented as median (interquartile range [IQR]); categorical variables are presented as *n* (%). [a]Gastrointestinal disease included erosive gastropathy, parenteral nutrition-associated cholestasis, neutropenic colitis, chronic liver disease, cystic fibrosis with gastrointestinal involvement, and complex postoperative abdominal disease. [b]Pulmonary disease included asthma, obstructive sleep apnea, diffuse parenchymal lung disease, cystic fibrosis, severe pulmonary hypertension, bronchomalacia, bronchopulmonary dysplasia, hepatopulmonary syndrome, and prior thromboembolic pulmonary disease. [c]Neurologic disease included epilepsy, posterior reversible encephalopathy syndrome, central nervous system hemorrhage, traumatic brain injury, central nervous system involvement by acute myeloid leukemia, traumatic paraplegia, and Ochoa syndrome. [d]Renal replacement therapy included intermittent hemodialysis and continuous renal replacement therapy. [e]Cardiac disease included congenital heart disease and chemotherapy-related myocardial dysfunction.

**Table 2.** Microbiological Characteristics, Carbapenemase Profiles, and Antimicrobial Susceptibility of Pediatric Patients with Carbapenem-Resistant Enterobacterales Infections

| **Characteristic** | **Value** |
|---|---|
| **Microbiological diagnosis** | ***n* = 43 (%)** |
| Culture-confirmed infection | 35 (81) |
| Molecular diagnosis only | 8 (19) |
| Molecular assay with concordant culture result | 5 (12) |
| **Source of infection[a]** | ***n* = 43 (%)** |
| Bloodstream infection | 15 (35) |
| Urinary tract infection | 11 (26) |
| Respiratory infection | 11 (26) |
| Other | 6 (14) |
| **Microorganisms identified** | ***n* = 43 (%)** |
| *Klebsiella pneumoniae* | 33 (77) |
| *Klebsiella oxytoca* | 4 (9) |
| *Escherichia coli* | 2 (5) |
| Other Enterobacterales | 4 (9) |
| **Carbapenemase profile** | ***n* = 43 (%)** |
| KPC alone | 39 (91) |
| KPC + NDM-1 | 3 (7) |
| VIM alone | 1 (2) |
| **Antimicrobial susceptibility[b,d]** | ***n* = 35 (%)** |
| CAZ-AVI | 32 (91) |
| Colistin | 30 (86) |
| Amikacin[c] | 29 (97) |
| Tigecycline | 22 (63) |
| Ciprofloxacin | 5 (14) |

Abbreviations: CAZ-AVI = ceftazidime-avibactam; CRE = carbapenem-resistant Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; NDM-1, New Delhi metallo-β-lactamase-1; VIM, Verona integron-encoded metallo-β-lactamase. [a]Other sources included intra-abdominal infections (*n* = 4) and skin and soft tissue infections (*n* = 2). [b]Antimicrobial susceptibility testing was available for 35 isolates with microbiological confirmation, including 5 patients initially identified through molecular assays who subsequently had concordant culture results. Eight patients diagnosed exclusively by molecular methods had no susceptibility data available. All culture-confirmed isolates were resistant to ertapenem, imipenem, and meropenem according to CLSI interpretive criteria. [c]Amikacin susceptibility results were available for 30 isolates. [d]Susceptibility to trimethoprim-sulfamethoxazole, fosfomycin, and nitrofurantoin was not assessed, as these agents were not included in the institutional VITEK® 2 antimicrobial susceptibility panel for Enterobacterales during the study period.

#### Carbapenemase Detection and Antimicrobial Susceptibility

Among the 43 included patients, 35 (81%) had microbiological confirmation by culture, including 5 patients initially identified through molecular assays who subsequently had concordant culture results. The remaining 8 patients were diagnosed exclusively by molecular detection of carbapenemase-producing organisms in the setting of a compatible clinical syndrome. Molecular identification was performed using the FilmArray Blood Culture Identification Panel in 5 patients and the FilmArray Pneumonia Panel in 8 patients.

KPC was the predominant resistance mechanism, identified alone in 39 patients (91%) and in combination with New Delhi metallo-β-lactamase-1 (NDM-1) in 3 additional patients (7%). One patient (2%) harbored a Verona integron-encoded metallo-β-lactamase-producing isolate (Table 2).

Antimicrobial susceptibility testing was available for 35 culture-confirmed isolates, all of which (35/35, 100%) demonstrated resistance to ertapenem, imipenem, and meropenem. Among these, 32 (91%) were susceptible to CAZ-AVI, whereas 3 (9%) were resistant. All 3 CAZ-AVI-resistant isolates corresponded to organisms co-producing KPC and NDM-1, while no resistance was observed among isolates harboring KPC alone. Susceptibility to cefepime was uncommon, with only one isolate (3%) classified as susceptible and one isolate

(3%) demonstrating intermediate susceptibility. Additional microbiological characteristics are summarized in Table 2.

#### Treatment Characteristics and Outcomes

CAZ-AVI was initiated empirically in 7 patients (16%) who presented with septic shock and had documented prior colonization with KPC-producing CRE. In the 8 patients without antimicrobial susceptibility results (diagnosed exclusively by molecular methods), treatment decisions were guided by molecular detection of KPC, previous CRE colonization or infection, clinical presentation, and treating physician assessment.

Following microbiological or molecular characterization of resistance mechanisms, antimicrobial therapy was individualized. Most patients received CAZ-AVI as monotherapy (40, 93%). Three patients (7%) with NDM-1-producing isolates received CAZ-AVI in combination with aztreonam. The median duration of CAZ-AVI therapy was 11 days (IQR, 8-21). All 3 patients with NDM-1-producing isolates who received CAZ-AVI plus aztreonam achieved clinical cure. All 43 patients completed treatment with CAZ-AVI.

Clinical improvement within 72 h of treatment initiation occurred in 40 patients (93%), with a median time to response of 2 days (IQR, 2-3). Overall, 40 patients (93%) achieved clinical cure at the end of therapy, whereas treatment failure occurred in 3 patients (7%) because of recurrent infection.

Microbiological clearance was documented in all 20 patients who underwent follow-up culture assessment. Follow-up cultures were obtained according to clinical indications and were not routinely performed after clinical improvement; therefore, microbiological response could not be systematically assessed in the entire cohort. No treatment-related adverse events attributable to CAZ-AVI were documented in the medical records during the treatment period.

Overall mortality was 16% (7/43), whereas infection-attributable mortality was 12% (5/43). Only 2 deaths occurred within the first 30 days; the remaining occurred later during follow-up. Kaplan–Meier analysis demonstrated an estimated 30-day survival probability of 95.3% (95% CI, 88.8-100), as shown in Figure 1. Treatment characteristics and outcomes are summarized in Table 3.

**Table 3.** Treatment Characteristics and Clinical Outcomes of Pediatric Patients with Carbapenem-Resistant Enterobacterales Infections Treated with Ceftazidime–Avibactam

| Characteristic | Value |
|---|---|
| **Treatment characteristics** | ***n* = 43 (%)** |
| Empiric CAZ-AVI initiation | 7 (16) |
| CAZ-AVI monotherapy | 40 (93) |
| CAZ-AVI plus aztreonam | 3 (7) |
| Duration of CAZ-AVI therapy, median (IQR), days | 11 (8-21) |
| **Clinical outcomes** | ***n* = 43 (%)** |
| Clinical improvement within 72 h | 40 (93) |
| Time to clinical response, median (IQR), days | 2 (2-3) |
| Clinical cure | 40 (93) |
| Treatment failure[b] | 3 (7) |
| Microbiological clearance[a] | 20/20 (100) |
| Recurrence | 3 (7) |
| **Mortality outcomes** | ***n* = 43 (%)** |
| Infection-attributable mortality | 5 (12) |
| Overall mortality | 7 (16) |

Data are presented as *n* (%) unless otherwise specified. Continuous variables are presented as median (IQR). Abbreviation: IQR = interquartile range. [a]Microbiological clearance was assessed only among patients who underwent clinically indicated follow-up cultures ($n = 20$). [b]All treatment failures represented recurrent infection.

## DISCUSSION

In this cohort, CRE infections occurred predominantly in children with substantial medical complexity, including immunosuppression, severe acute malnutrition, chronic gastrointestinal and pulmonary disease, and frequent use of invasive devices, consistent with previous pediatric studies.[6,10,11] More than half of our patients had prior CRE colonization, and nearly two-thirds required PICU admission, underscoring the high-risk nature of this population.

Prior broad-spectrum antibiotic exposure was documented in 42% of patients, consistent with its previously described association with antimicrobial resistance.[11] Although this proportion was lower than that reported in some pediatric cohorts and meta-analyses,[9,11] previous antimicrobial exposure has been associated with CRE infection and likely reflects the cumulative antimicrobial pressure experienced by medically complex children.

The high frequency of invasive devices, PICU admission, and surgical interventions reflects the complexity of children who develop CRE infections, consistent with associations reported in pediatric populations.[11–17] These exposures have been associated with increased contact with multidrug-resistant organisms and may contribute to both colonization and subsequent infection.

From a microbiological perspective, *K. pneumoniae* and KPC-type carbapenemases predominated, consistent with reports from Colombia and other Latin American pediatric cohorts, where KPC-producing Enterobacterales remain the most common CRE pathogens.[11,17] This profile is particularly relevant because CAZ-AVI retains reliable activity against these resistance mechanisms and supports its use in KPC-endemic settings.

An important feature of our cohort was the use of rapid carbapenemase detection to support a mechanism-based approach, in which targeted therapy was selected according to the specific carbapenemase identified.[18,19] The co-detection of KPC and NDM-1 in 3 isolates (7%) reflects the growing emergence of multi-carbapenemase organisms worldwide,[20,21] narrowing

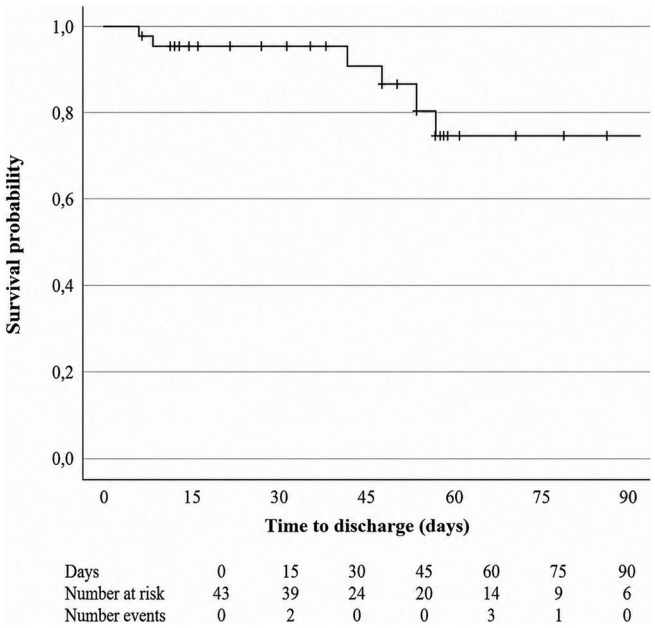



**Figure 1.** Kaplan–Meier Survival Curve of 43 Children with Carbapenem-Resistant Enterobacterales Infections Treated with Ceftazidime-Avibactam. The estimated 30-day overall survival probability was 95.3% (95% CI, 88.8-100)

therapeutic options and compromising β-lactam/b β-lactamase inhibitor monotherapy. In this context, CAZ-AVI combined with aztreonam has emerged as an effective strategy for infections caused by metallo-β-lactamase-producing organisms.[22] In our cohort, combination therapy was reserved for patients with NDM-1-producing isolates, consistent with current recommendations.[23] Notably, all 3 CAZ-AVI-resistant isolates belonged to this subgroup, highlighting the importance of accurately identifying metallo-β-lactamase production before selecting targeted therapy. All 3 children with NDM-1-producing infections achieved clinical cure following treatment with CAZ-AVI plus aztreonam. A small number of isolates demonstrated apparent cefepime susceptibility despite harboring carbapenemase-producing mechanisms. However, in vitro susceptibility does not reliably predict clinical efficacy[24–26] or support cefepime as a reliable treatment option for CRE infections.

Despite the high prevalence of septic shock and need for PICU admission, clinical cure rates were high, and treatment failure was uncommon. The infection-attributable mortality was lower than that reported in previous pediatric series, where mortality rates have reached 37.8%.[15,27] The predominance of KPC-producing isolates, for which CAZ-AVI retains reliable activity, may partially explain these favorable outcomes.

The safety profile observed in our cohort is consistent with previous pediatric and adult studies demonstrating favorable tolerability of CAZ-AVI.[15,28–32] No treatment-related adverse events were documented, and no patient required treatment discontinuation because of drug toxicity. Although the retrospective design may have limited detection of mild adverse events, no clinically significant toxicity was identified.

These findings are particularly relevant because historical treatment options for CRE infections have relied on agents associated with substantial nephrotoxicity and neurotoxicity.[29] The dosing strategy used in our cohort was consistent with recently published pediatric consensus guidance for CAZ-AVI dosing in the treatment of antimicrobial-resistant Gram-negative infections.[33] Prolonged infusion, recommended in this guidance to optimize pharmacodynamic target attainment, was used selectively in critically ill patients requiring pediatric intensive care unit admission, while standard infusion was used in the remainder of the cohort. Although therapeutic drug monitoring was not available at our institution, the favorable clinical outcomes observed, together with dosing consistent with current consensus recommendations, support the adequacy of the dosing strategy employed.

This study has several limitations, including its retrospective, single-center design, which may limit generalizability, and a small sample size that precluded comparative analyses. The absence of a comparator group prevented direct assessment of CAZ-AVI effectiveness relative to alternative regimens. Assessment of microbiological response was limited, as follow-up cultures were obtained based on clinical indications rather than systematically. Susceptibility to trimethoprim-sulfamethoxazole, fosfomycin, and nitrofurantoin could not be assessed, as these agents were not routinely included in the institutional susceptibility panel during the study period, limiting evaluation of potential oral step-down options for non-severe infections. Additionally, the timing and indication of surgical interventions performed during hospitalization were not systematically classified as related or unrelated to the CRE

infection, limiting interpretation of this variable. Lastly, adverse events were identified through review of clinical documentation and may have been underrecognized.

Nevertheless, this study provides important real-world data on CAZ-AVI use in a highly complex, critically ill pediatric population from a region with endemic KPC circulation. Our findings support CAZ-AVI within a mechanism-based approach to pediatric CRE infections, adding to the growing evidence supporting its role as an important therapeutic option in KPC-endemic regions.

## CONCLUSION

In this real-world cohort of medically complex children with CRE infections, CAZ-AVI was associated with favorable clinical outcomes and good tolerability, supporting its use in regions where KPC-producing organisms predominate. The successful use of CAZ-AVI plus aztreonam in NDM-1-producing infections highlights the importance of resistance mechanism-guided therapy. Prospective multicenter studies are needed to further define its role in pediatric CRE infections.


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### Conflicts of Interest

All authors declare no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

### Use of Artificial Intelligence

AI-based language tools (including Claude and ChatGPT) were used solely to assist with grammar review and language editing during manuscript preparation. These tools were not used for data analysis, interpretation of results, or generation of scientific content. All scientific content, analysis, and conclusions are the sole responsibility of the authors.

### Prior Presentation

Preliminary data from this study were presented at the European Society for Paediatric Infectious Diseases (ESPID) Annual Meeting, Bucharest, Romania, 2025, and at the Latin American Society of Pediatric Infectious Diseases (SLIPE) Congress, Puerto Varas, Chile, 2025.

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