ORIGINAL RESEARCH

Use of Ceftazidime-Avibactam for Suspected or Confirmed Carbapenem-Resistant Organisms in Children: A Retrospective Study

Haiyang Meng ^{1,2}, Yongmei Zhao^{1,2}, Qi An^{1,2}, Baoling Zhu³, Zhe Cao⁴, Jingli Lu ^{1,2}

¹Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, People's Republic of China; ²Henan Key Laboratory of Precision Clinical Pharmacy, Zhengzhou University, Zhengzhou, People's Republic of China; ³Department of pharmacy, Xiangcheng Hospital of Chinese Medicine, Xiangcheng, People's Republic of China; ⁴Department of pharmacy, Zhenping People's Hospital, Zhenping, People's Republic of China

Correspondence: Jingli Lu, The First Affiliated Hospital of Zhengzhou University, No. I Jianshe East Road, Zhengzhou, People's Republic of China, Tel +86 371 66913047, Email lujingli123@163.com

Background: The incidence of carbapenem-resistant organism (CRO) infections is increasing in children. However, pediatric-specific treatment strategies present unique challenges. Ceftazidime/avibactam is a \beta-lactam/β-lactamase inhibitor combination, showing adequate efficiency against CRO isolates. However, clinical data on the efficacy of ceftazidime/avibactam in children are still lacking. Methods: This was a retrospective study of children (aged <18 years) infected with confirmed or suspected carbapenem-resistant pathogens and treated with ceftazidime-avibactam at the First Affiliated Hospital of Zhengzhou University between 2020 and 2022. **Results:** We identified 38 children aged 14 (5.0–16.3) years; 20 (52.6%) had hematologic malignancies. 25 children with confirmed CRO infections were administered ceftazidime-avibactam as targeted therapy. The median treatment was 10 (6.0-16.5) days. Among them, 24 had infections caused by carbapenem-resistant Enterobacterales (CRE) (18 carbapenem-resistant Klebsiella pneumoniae and six carbapenem-resistant Escherichia coli species) and one with carbapenem-resistant Pseudomonas aeruginosa strains. The source of infection was the bloodstream in 60.0% of the cases (15/25). The clinical response rate was 84.0% (21/25), and 30-day mortality rate was 20% (5/25). 13 children were administered ceftazidime-avibactam as empiric therapy for suspected infections. The median treatment was 8 (6.0-13.0) days. No deaths occurred and clinical response was achieved in 12 of the 13 patients (92.3%) who empirically treated with ceftazidime-avibactam.

Conclusion: Ceftazidime-avibactam is important for improving survival, and clinical response in children with infections caused by CRO. Keywords: ceftazidime-avibactam, carbapenem-resistant organisms, children

Introduction

Multidrug resistance, caused mainly by excessive use of antibiotics, is one of the greatest challenges to public health worldwide. The search for new antimicrobial strategies is urgent.¹ In children, the incidence of infections caused by carbapenem-resistant Gram-negative bacteria is increasing. A study on carbapenem resistance prevalence in US children reported that, from January 1999 to July 2012, the frequency of carbapenem resistance increased from 0% in 1999–2000 to 0.47% in 2010-2011 among Enterobacterales species,² from 9.4% in 1999 to 20% in 2012 among Pseudomonas aeruginosa species,³ and from 0.6% in 1999 to 6.1% in 2012 among Acinetobacter Baumannii species,⁴ Available pediatric case series suggest that infections due to these organisms are associated with significant mortality, ranging from 8% to 50%.⁵⁻¹⁴ In pediatric cancer patients with bloodstream infections, the mortality rate is as high as 57%.¹⁵ Despite widespread attention paid to carbapenem-resistant threats, antibiotic treatment of these infections in children remains challenging, given the limited clinical data on active drugs.

Ceftazidime-avibactam is a β-lactam-β-lactamase inhibitor approved by the Food and Drug Administration (FDA) in 2019 for children aged \geq 3 months. This drug has potent in vitro activity against carbapenem-resistant Enterobacterales (CRE) and carbapenem-resistant *Pseudomonas aeruginosa*. Observational studies in adults have shown that ceftazidime-avibactam may be associated with improved outcomes compared to other treatment regimens for carbapenem-resistant infections.^{16–19} However, data on the use of ceftazidime-avibactam in children with carbapenem-resistant infections are limited, with only case reports and case series available.^{20–23} Similarly, a pediatric case series that included eight children reported successful clinical and microbiological responses to ceftazidime-avibactam in CRE infections.²² Another retrospective study evaluated the use of ceftazidime-avibactam in 21 children with hematologic malignancies and multi-drug resistant gram-negative bacteria infections, ceftazidime-avibactam resolved infection in >90% of cases.²³ Despite these findings, a more detailed understanding of the outcomes and effects of this agent in children with carbapenem-resistant infections is required.

We conducted a retrospective evaluation of 38 children with serious infections caused by suspected or confirmed carbapenem-resistant organism (CRO), who were treated with ceftazidime-avibactam. We described the clinical characteristics, microbiological features, and resistance mechanisms associated with the isolates, focusing specifically on the clinical outcomes after ceftazidime-avibactam treatment.

Materials and Methods

Patients

We retrospectively reviewed the electronic medical records of all children aged < 18 years who were diagnosed with a suspected or confirmed infection caused by CRO and received at least 72 h of ceftazidime-avibactam treatment at the First Affiliated Hospital of Zhengzhou University between 2020 and 2022. This study was approved by the Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University. As patient data were analyzed anonymously and maintained confidential, the patient consent was waived. We certify that the study was performed in accordance with the Declaration of Helsinki.

Clinical Data and Outcomes

Clinical data were collected from electronic medical records using a standardized report form. Information regarding patient demographics, comorbidities, clinical status, laboratory variables, source of infection, antimicrobial therapies, and antimicrobial susceptibility was extracted. Ceftazidime-avibactam treatment was categorized as empirical therapy (administered to treat a suspected CRO infection) or targeted therapy (administered to treat a confirmed CRO infection). CRO infection was confirmed when CRO was detected in the sterile or eligible specimens. CRO infection was highly suspected when a patient had clinical features of infection, such as a fever pattern and inflammatory indicators, and had one or more risk factors, such as immune suppression and CRO colonization, despite the absence of positive pathogenic bacterial culture results. Perirectal swabs were screened for CRO colonization. The primary outcome was 30-day mortality after the initiation of ceftazidime-avibactam treatment. Clinical response was assessed at the end of ceftazidime-avibactam treatment, which defined as resolution of signs and symptoms of the infection, absence of recurrence of the infection, and no requirement of additional antibiotic therapy. Microbiologic success was defined as a negative culture after 72 h of ceftazidime-avibactam therapy, when repeated cultures were available. The length of hospital stay and ICU stay were calculated from the day of ceftazidime-avibactam treatment to the day of discharge from the hospital or ICU, respectively.

Microbiology

Carbapenem-resistant organisms were defined as bacteria that tested resistant to any carbapenem (meropenem, ertapenem, or imipenem) or were positive for carbapenemase production. The VITEK 2 Compact system (bioMérieux, Marcy l'Etoile, France) and Phoenix100 automated system (Becton Biosciences, Franklin Lakes, NJ, USA) were used for microbial identification and antimicrobial susceptibility testing, respectively. The minimum inhibitory concentration (MICs) for polymyxin B was interpreted according to the clinical breakpoints published by the European Committee on Antimicrobial Susceptibility Testing.²⁴ Others were interpreted using the Clinical and Laboratory Standards Institute (CLSI) breakpoints.²⁵ Ceftazidime-avibactam Susceptibility was not assessed routinely during the study period. The combined modified carbapenem inactivation method (mCIM) and EDTA-CIM (eCIM) were used to detect carbapenemases according to the CLSI guidelines.²⁶ The mCIM was considered positive (detection of carbapenemase) if the zone diameter was 6 to 15 mm, or 16 to 18 mm with small colonies.

When the mCIM result showed positive, if a \geq 5 mm increase in the zone diameter for eCIM as compared to that for mCIM suggests the production of a metallo-carbapenemase, if a \leq 4 mm increase suggests the production of a serine carbapenemase.

Statistical Analysis

Continuous variables with non-normal distributions are presented as medians with interquartile ranges (IQR), and categorical variables are presented as frequencies (percentages). Due to the limited sample size, descriptive statistical analysis was performed using SPSS (version 25.0).

Results

Patient Characteristics

38 children receiving ceftazidime-avibactam were eligible for this analysis, including nine (23.7%) children aged 5 years or younger, eight (21.1%) aged 5–11 years, and 21 (55.3%) aged 12–17 years. The most common comorbid condition was hematologic malignancy, which was present in 20 (52.6%) children. Bloodstream infection was the most common type of infection, accounting for 21 cases (55.3%), followed by pneumonia (14 cases; 36.8%). The predominant causative CRO was carbapenem- resistant *Klebsiella pneumoniae* (n = 18; 72.0%), followed by carbapenem-resistant *Escherichia coli* (n = 6; 24.0%), and carbapenem-resistant *Pseudomonas aeruginosa* (n = 1; 4.0%). Of the 25 culture-confirmed isolates, 17 were tested for carbapenemase production, 8 produced serine β -lactamases (SBL), 7 produced metallo- β lactamases (MBL), and 2 produced both SBL and MBL. Among 13 patients with suspected infections, after treated with ceftazidime-avibactam, three isolates were found to be carbapenem-sensitive *Klebsiella pneumoniae*, one was carbapenem-sensitive *Pseudomonas aeruginosa*, one was *Stenotrophomonas maltophilia*, three were carbapenem-resistant *Klebsiella pneumoniae* strains, five isolates were culture negative (see Table 1).

Characteristics	Total (N=38)	Targeted Therapy (N=25)	Empirical Therapy (N=I3)		
Age, median (IQR), years	14.0 (5.0–16.3)	11.6 (5.0–16.5)	14.0 (5.0–16.5)		
< 5 years	9 (23.7%)	6 (24.0%)	3 (23.1%)		
5 ~ 11 years	8 (21.1%)	21.1%) 7 (28.0%)			
12 ~ 17 years	21 (55.3%) 12 (48.0%)		9 (69.2%)		
Male, gender	22 (57.9%)	2 (57.9%) 15 (60.0%)			
Comorbidities					
Premature infants	I (2.6%)	I (4.0%)	0 (0)		
Solid tumors	I (2.6%)	I (4.0%)	0 (0)		
Solid organ transplantation	2 (5.3%)	I (4.0%)	I (7.7%)		
Hematologic malignancies	20 (52.6%)	11 (44.0%)	9 (69.2%)		
нѕст	6 (15.8%) 2 (8.0%)		4 (30.8%)		
Others	11 (28.9%)	10 (40.0%)	I (7.7%)		
Location at the time of infection					
Medical ward	18 (47.4%) 8 (32.0%)		10 (76.9%)		
Surgical ward	7 (18.4%) 4 (16.0%)		3 (23.1%)		
ICU	3 (34.2%) 3 (52.0%)		0 (0)		

 Table I Characteristics of Study Population According to Ceftazidime-Avibactam Treatment Strategy

(Continued)

Table I (Continued).

Characteristics	Total (N=38)	Targeted Therapy (N=25)	Empirical Therapy (N=13)	
ICU admission within 3 months prior to infection	21 (55.3%)	17 (68.0%)	5 (38.5%)	
Carbapenems exposure within 3 months prior to infection	28 (73.7%)	16 (64.0%)	11 (84.6%)	
CRO colonization within 3 months prior to infection (n/N, colonization/tested)	5/15 (33.3%)	3/7 (42.9%)	2/8 (25.0%)	
Neutropenia	22 (57.9%)	13 (52.0%)	9 (69.2%)	
ICU admission	24 (63.2%)	19 (76.0%)	5 (38.5%)	
Septic shock	12 (31.6%)	12 (31.6%) 10 (40.0%)		
Mechanical ventilation	14 (36.8%)	13 (52.0%)	I (7.7%)	
CRRT	3 (7.9%)	3 (12.0%)	0 (0)	
Type of infection				
Pneumonia	14 (36.8%)	(44.0%)	3 (23.1%)	
Genitourinary	4 (10.5%)	3 (12.0%)	I (7.7%)	
Surgical sites	2 (5.3%)	I (4.0%)	I (7.7%)	
Skin	I (2.6%)	0 (0)	I (7.7%)	
Bloodstream	21 (55.3%)	15 (60.0%)	6 (46.2%)	
Intra-abdominal	3 (7.9%)	(7.9%) 2 (8.0%)		
Intracranial	2 (5.3%) I (4.0%)		I (7.7%)	
Unknown	(2.6%)	0 (0)	I (7.7%)	
Species				
Carbapenem-resistant Klebsiella pneumoniae	1	18 (72.0%)	1	
Carbapenem-resistant Escherichia coli	1	6 (24.0%)	1	
Carbapenem-resistant Pseudomonas aeruginosa	1	I (4.0%)	1	
Carbapenemases	•		1	
MBL	7 (18.4%)	7 (28.0%)	1	
SBL	8 (21.1%)	8 (32.0%)	1	
MBL+SBL	2 (5.3%)	2 (8.0%)	1	
Not tested	21 (55.3%)	8 (32.0%) 13 (100%)		
Ceftazidime-avibactam treatment				
Duration of ceftazidime-avibactam treatment (days)	8.5 (6.0–14.2)	2) 10.0 (6.0–16.5) 8.0 (6.0-		
Time from infection onset to ceftazidime-avibactam treatment (days)	4.0 (2.0–5.3)	4.0 (3.5–6.0) 2.0 (1.0–3.		
Monotherapy	6 (15.8%)	4 (16.0%) 2 (15.4%)		
Combination therapy	32 (84.2%)	21 (84.0%) 11 (84.6%)		

(Continued)

Table I (Continued).

Characteristics	Total (N=38)	Targeted Therapy (N=25)	Empirical Therapy (N=13)		
Meropenem	5 (13.2%)	4 (16.0%)	I (7.7%)		
Imipenem	9 (23.7%)	4 (16.0%)	5 (38.5%)		
Tigecycline	10 (26.3%)	0 (26.3%) 5 (20.0%)			
Aztreonam	15 (39.5%) 11 (44.0%)		4 (30.8%)		
Polymyxin B	2 (5.3%)		I (7.7%)		
Outcomes					
Length of hospitalization after infection (days)	37.0 (25.0–64.3)	35.0 (24.0–64.0)	39.0 (29.5–64.5)		
Length of ICU stay after infection (days)	7.0 (0–25.0)	16.0 (1.0-29.5)	0.0 (0.0-4.5)		
30-day mortality	5 (13.2%) 5 (20.0%)		0 (0)		
Clinical response	33 (86.8%) 21 (84.0%)		12 (92.3%)		
Microbiological eradication	20/26 (76.9%)	76.9%) 17/23 (73.9%) 3/			

Abbreviations: CRO, Carbapenem-resistant organisms; CRRT, continuous renal replacement therapy; HSCT, hematopoietic stem cell transplant; ICU, Intensive care unit; IQR, interquartile range; MBL, metallo-β-lactamases; SBL, serine β-lactamases.

Microbiological Characteristics

The susceptibility profiles of the 24 CRE isolates are summarized in Table 2. One isolate did not undergo susceptibility testing for carbapenems but produced carbapenemase SBL. The remaining 23 isolates were resistant to imipenem and meropenem (23/23) and almost all strains had a MIC \geq 16 µg/mL. The majority were resistant to levofloxacin (18/23), ciprofloxacin (19/23), aztreonam (19/23), and TMP/SMX (17/21). None of the tested isolates was resistant to colistin or tigecycline.

Clinical Outcomes for Ceftazidime-Avibactam as Empiric Therapy

Thirteen children received ceftazidime-avibactam as empirical therapy; however, their isolates were not confirmed to be CRO by culture. Of these patients, 84.6% (11/13) had previous carbapenem exposure, the median time from initiation of

Antibiotic	Isolates Tested	Sensitive	Intermediate	Resistance			
Colistin	23	22 (95.7%)	I (4.3%)	0 (0)			
Tigecycline	23	22 (95.7%)	I (4.3%)	0 (0)			
TMP/SMX	21	4 (19.0%)	0 (0)	17 (81.0%)			
Meropenem	23	0 (0)	0 (0)	23 (100%)			
Imipenem	23	0 (0)	0 (0)	23 (100%)			
Aztreonam	23	3 (13.0%)	I (4.3%)	19 (82.6%)			
Amikacin	23	12 (51.2%)	0 (0)	11 (47.8%)			
Ciprofloxacin	23	2 (8.7%)	2 (8.7%)	19 (82.6%)			
Levofloxacin	23	2 (8.7%)	3 (13.0%)	18 (78.3%)			

Table 2 Antimicrobial Susceptibility Testing for Carbapenem-Resistant Enterobacteriaceae
Isolates

Abbreviation: TMP/SMX, trimethoprim/sulfamethoxazole.

carbapenem treatment to infection onset was 17 (10–67) days, and the median duration of carbapenem therapy was 17 (9–30) days. Two patients had CRO colonization within the past 3 months, which were confirmed by perirectal swabs on day of 15 and day 47, respectively, prior to infections. 38.5% (5/13) had prior ICU admission due to sepsis (n=1), shock (n=1), liver transplant (n=1), convulsion (n=1) and bronchofiberscopy with hematologic malignancy (n=1), respectively.

The median duration of ceftazidime-avibactam therapy was 8.0 (6.0-13.0) days. The median time from the onset of infection to initiation of ceftazidime-avibactam treatment was 2 (1.0-3.5) days. 12 of the 13 patients showed a favorable clinical response. No deaths occurred within 30 days of ceftazidime-avibactam administration.

Clinical Outcomes for Ceftazidime-Avibactam as Targeted Therapy

Twenty-five children with confirmed CRO infections received targeted ceftazidime-avibactam therapy. Time from the onset of infection to initiation of ceftazidime-avibactam treatment was 4 (3.5-6.0) days. The median duration of therapy was 10 (6.0-16.5) days. Among the 21 patients who received concomitant antibiotics, carbapenems were used in 8 patients, aztreonam in 11 patients, tigecycline in 5 patients, polymyxin B in 1 patient. Of the nine patients whose isolates produced MBL, seven received aztreonam as combination therapy.

Among the 25 cases, the clinical response was considered successful in 21. Follow-up cultures were available for 23 patients, and 6 of them showed microbiological failure. Within 30 days, 5 (20.0%) cases died. Table 3 summarizes five cases who died. The cause of death in 2 patients was not directly attributed to the failure of ceftazidime-avibactam, as the pathogens were eradicated after ceftazidime-avibactam treatment. One patient was admitted with traumatic brain injury and died due to progressive multiorgan failure. Another patient was admitted with joint pain, which worsened rapidly with septic shock and died of respiratory failure. The last case developed a polymicrobial infection, including carbape-nem-resistant *Acinetobacter baumannii* and cytomegalovirus, and died of multiorgan failure.

Side Effects

Diarrhea occurred in one patient treated with ceftazidime-avibactam, and relieved after discontinuation. No other adverse reactions were observed.

Discussion

Infections caused by CRO is a major threat to modern medicine, and treatment options are limited.^{27–29} Although ceftazidime-avibactam has been approved for complicated urinary tract and intra-abdominal infections caused by susceptible gram-negative microorganisms in children, data on its use in the treatment of CRO infections are limited. In this study, we analyzed the use of ceftazidime-avibactam in 38 children with CRO infections, and our findings provide valuable information on its efficacy in this population.

Our study demonstrated that ceftazidime-avibactam was associated with a successful clinical response rate of 84.0% in children with confirmed CRO infections, which was higher than the reported clinical success rate of polymyxins for managing infections caused by multidrug-resistant gram-negative organisms, including carbapenem-resistant strains. Previous retrospective studies evaluating the use of polymyxins in clinical settings reported clinical success rates of approximately 50%.^{30,31} In terms of safety, no serious safety signals were identified for ceftazidime-avibactam in our study, whereas adverse effects, particularly nephrotoxicity, were a major concern during polymyxin treatment, with a higher incidence in children.^{30,31} The all-cause 30-day mortality rate in our study was 20.0%, which is comparable to that of a recently published retrospective study that included 21 children with hematologic malignancies infected with a carbapenem-resistant gram-negative organism and treated with ceftazidime-avibactam, and reported an overall mortality rate of 20%.²³ However, the mortality rate of children infected with multidrug-resistant gram-negative organisms and treated with polymyxins in several retrospective reports fluctuated between approximately 30% and 40%,^{31–33} which is higher than that observed in our study.

Of the 17 isolates tested, nine (52.9%) produced carbapenemase MBLs. This is consistent with previously reported data from China, which confirmed that New Delhi metallo-beta-lactamases accounted for 49.0% of the CRE isolates in children.³⁴ The distribution of carbapenemases in China differs from that in other regions, where *Klebsiella pneumoniae*

Age	Sex	Comorbidity	Infection Source	Species	Carbapenemase	Therapy	Dosing	Duration (Days)	Microbiological Eradication	Comments
9 mo	F	НМ	Pneumonia	Klebsiella pneumoniae	MBL	CAZ-AVI+ aztreonam	0.46g q8h	12	Yes	Admitted with fever and myelosuppression died due to respiratory failure
5 y	F	НМ	Bloodstream	Escherichia coli	MBL	CAZ-AVI+ aztreonam	1.25g q8h	18	Yes	Admitted with AML M5, had chemotherap died due to multiorgan failure
9 y	М	Trauma	Pneumonia Bloodstream	Klebsiella pneumoniae	Not tested	CAZ-AVI	2.5g q8h	4	No	Admitted with a traumatic brain injury an died due to progressive multiorgan failur
ll y	F	НМ	Bloodstream	Escherichia coli	MBL	CAZ-AVI+ aztreonam	2.3g q8h	8	Not tested	Admitted with joint pain, rapid worsenin with septic shock, died due to respirator failure
l6 y	М	HSCT	Bloodstream	Klebsiella pneumoniae	SBL	CAZ-AVI+ tigecycline	2.5g q8h	10	No	Developed polymicrobial infections and died due to septic shock and multiorgan failure

Abbreviations: AML, acute myeloid leukemia; CAZ-AVI, ceftazidime-avibactam; F, female; HM, hematologic malignancies; HSCT, hematopoietic stem cell transplant; M, male; mo, months; MBL, metallo- β -lactamases; SBL, serine β -lactamases; y, years.

carbapenemases are the most common carbapenemases identified in carbapenemase-producing *Enterobacteriaceae* isolates that infect children in the United States.³⁵ It is important to note that infections caused by carbapenem-resistant MBL-producing isolates are associated with mortality rates > 30%, with the highest risk of death among carbapenem-resistant isolates.³⁶ Therefore, it is essential to highlight the properties of MBLs as they are not inhibited by avibactam, which limits the use of ceftazidime-avibactam as monotherapy.

The combination of ceftazidime-avibactam and aztreonam has been shown to be an effective regimen for treating MBL-producing CRE, with a reported reduction in mortality risk of approximately 60%.³⁷ This approach is based on the fact that aztreonam is not degraded by MBLs, whereas avibactam effectively inhibits other β -lactamases that hydrolyze aztreonam.³⁸ Accordingly, aztreonam was administered as targeted therapy in 80% of the cases in which isolates possessed MBLs in our study. Although three deaths were reported in these patients, clinical response and microbiological eradication were observed in two cases, in which death was not directly attributed to infection. Nonetheless, infection with MBL-producing *Enterobacterales* may increase the risk of mortality, and the combination of ceftazidime-avibactam and aztreonam may be a suitable therapeutic option.

Approximately of 40% patients received ceftazidime-avibactam combined with carbapenems in our study. Results from clinical experience have indicated that ceftazidime-avibactam combined with another in vitro non-susceptible antimicrobial, such as carbapenems, could significantly decrease the 30-day mortality rate for critically ill patients with carbapenem-resistant *Klebsiella pneumoniae*.³⁹ Our previous study has also confirmed that use of carbapenems was as an independent predictor of decreased mortality in children with carbapenem-resistant *Klebsiella pneumoniae* bacteremia.⁴⁰ In the present study, no one died among patients who received ceftazidime-avibactam combined with carbapenems, but we could not make a qualitative comparison due to the small sample size. Further clinical studies are needed to well define the potential use of ceftazidime-avibactam in combination with carbapenems in children with CRO infections.

Approximately 35% of patients who received ceftazidime-avibactam in our study were treated empirically, mostly for bloodstream infections. A retrospective study from India have also revealed that ceftazidime-avibactam was often used empirically in critically ill patients with suspected hospital-acquired infections in clinical settings.⁴¹ These patients had a high risk of CRO infections, presenting with one or more risk factors such as CRO colonization, prior carbapenem therapy in the past 3 months, and ICU admission.^{42–44} As expected, we observed a clear mortality benefit in patients empirically treated with ceftazidime/avibactam. However, the results are challenging to interpret because the majority of cases were in medical wards and not in the ICU. The question remains whether the benefit is meaningful or diluted by less severe underlying diseases. Furthermore, it should be emphasized that we evaluated the benefit of empiric therapy in terms of short-term mortality; however, we did not explore its impact on the long-term risk of ceftazidime-avibactam resistance, infection recurrence, or hospital readmission.

One major limitation of our study was the small sample size, which prevented us from performing stratification analyses to estimate potential confounding factors that may contribute to death. Another important limitation is the retrospective nature of our study, which limited our ability to collect data on clinical and demographic variables that were not recorded at the time. Third, it was a single-center study with the inherent shortcomings, and more patients from different regions and countries are warranted. Thus, caution should be exercised when interpreting our findings and further studies are required to confirm our results.

Conclusion

In summary, this retrospective study identified the clinical characteristics of children infected with suspected or confirmed CRO and their outcomes following ceftazidime-avibactam treatment. Our results suggest that ceftazidime-avibactam provides clinically important benefits in terms of survival, clinical response rate in children with confirmed CRO infection. MBL-producing CRE isolates were common and were likely associated with a higher 30-day mortality rate. Moreover, no death occurred in children who empirically treated with ceftazidime-avibactam. These findings highlight the potential efficacy of ceftazidime-avibactam for the treatment of pediatric CRO infections.

Data Sharing Statement

All data analyzed during this study are included in this published article.

Acknowledgments

This analysis was conducted as part of routine antimicrobial surveillance.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

References

- 1. Ezzeddine Z, Ghssein G. Towards new antibiotics classes targeting bacterial metallophores. *Microb Pathog.* 2023;182:106221. doi:10.1016/j. micpath.2023.106221
- Logan LK, Renschler JP, Gandra S, et al. Carbapenem-resistant Enterobacteriaceae in children, United States, 1999–2012. Emerg Infect Dis. 2015;21(11):2014–2021. doi:10.3201/eid2111.150548
- 3. Logan LK, Gandra S, Mandal S, et al. Multidrug- and carbapenem-resistant Pseudomonas aeruginosa in children, United States, 1999–2012. *J Pediatric Infect Dis Soc.* 2017;6(4):352–359. doi:10.1093/jpids/piw064
- Logan LK, Gandra S, Trett A, Weinstein RA, Laxminarayan R. Acinetobacter baumannii resistance trends in children in the United States, 1999– 2012. J Pediatric Infect Dis Soc. 2019;8(2):136–142. doi:10.1093/jpids/piy018
- 5. Caselli D, Cesaro S, Fagioli F, et al. Incidence of colonization and bloodstream infection with carbapenem-resistant Enterobacteriaceae in children receiving antineoplastic chemotherapy in Italy. *Infect Dis.* 2016;48(2):152–155. doi:10.3109/23744235.2015.1087647
- 6. Montagnani C, Prato M, Scolfaro C, et al. Carbapenem-resistant Enterobacteriaceae infections in children: an Italian Retrospective Multicenter Study. *Pediatr Infect Dis J.* 2016;35(8):862–868. doi:10.1097/INF.000000000001188
- Alvares PA, Arnoni MV, da Silva CB, Safadi MAP, Mimica MJ. Carbapenem-resistant Gram-negative bloodstream infections in critically ill children: outcome and risk factors in a tertiary teaching hospital in South America. J Hosp Infect. 2019;101(2):188–189. doi:10.1016/j. jhin.2018.10.001
- Chiotos K, Tamma PD, Flett KB, et al. Increased 30-day mortality associated with carbapenem-resistant Enterobacteriaceae in children. Open Forum Infect Dis. 2018;5(10):ofy222. doi:10.1093/ofid/ofy222
- Dong F, Zhang Y, Yao K, et al. Epidemiology of carbapenem-resistant Klebsiella pneumoniae bloodstream infections in a Chinese Children's Hospital: predominance of New Delhi Metallo-beta-Lactamase-1. *Microb Drug Resist.* 2018;24(2):154–160. doi:10.1089/mdr.2017.0031
- 10. Nabarro LEB, Shankar C, Pragasam AK, et al. Clinical and bacterial risk factors for mortality in children with carbapenem-resistant Enterobacteriaceae bloodstream infections in India. *Pediatr Infect Dis J.* 2017;36(6):e161–e166. doi:10.1097/INF.00000000001499
- 11. Logan LK, Bonomo RA. Metallo-beta-Lactamase (MBL)-producing Enterobacteriaceae in United States Children. Open Forum Infect Dis. 2016;3 (2):ofw090. doi:10.1093/ofid/ofw090
- 12. Maltezou HC, Kontopidou F, Katerelos P, Daikos G, Roilides E, Theodoridou M. Infections caused by carbapenem-resistant Gram-negative pathogens in hospitalized children. *Pediatr Infect Dis J.* 2013;32(4):e151–e154. doi:10.1097/INF.0b013e3182804b49
- Diaz A, Ortiz DC, Trujillo M, Garces C, Jaimes F, Restrepo AV. Clinical characteristics of carbapenem-resistant Klebsiella pneumoniae infections in ill and colonized children in Colombia. *Pediatr Infect Dis J.* 2016;35(3):237–241. doi:10.1097/INF.00000000000987
- 14. Taoufik L, Amrani Hanchi A, Fatiha B, Nissrine S, Mrabih Rabou MF, Nabila S. Emergence of OXA-48 Carbapenemase Producing Klebsiella pneumoniae in a Neonatal Intensive Care Unit in Marrakech, Morocco. *Clin Med Insights Pediatr.* 2019;13:1179556519834524. doi:10.1177/ 1179556519834524
- 15. Madney Y, Aboubakr S, Khedr R, et al. Carbapenem-Resistant Enterobacteriaceae (CRE) among children with cancer: predictors of mortality and treatment outcome. *Antibiotics*. 2023;12(2):405. doi:10.3390/antibiotics12020405
- Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by Klebsiella pneumoniae Carbapenemase-producing K. pneumoniae. *Clin Infect Dis.* 2019;68(3):355–364. doi:10.1093/cid/ciy492
- 17. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia. *Antimicrob Agents Chemother*. 2017;61(8):10–128. doi:10.1128/aac.00883-17
- van Duin D, Lok JJ, Earley M, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis. 2018;66(2):163–171. doi:10.1093/cid/cix783
- 19. Almangour TA, Ghonem L, Aljabri A, et al. Ceftazidime-avibactam versus colistin for the treatment of infections due to carbapenem-resistant Enterobacterales: a multicenter cohort study. *Infect Drug Resist*. 2022;15:211–221. doi:10.2147/IDR.S349004
- 20. Ji Z, Sun K, Li Z, Cheng W, Yang J. Carbapenem-resistant Klebsiella pneumoniae osteomyelitis treated with ceftazidime-avibactam in an infant: a case report. *Infect Drug Resist.* 2021;14:3109–3113. doi:10.2147/IDR.S320056
- 21. Wang W, Wang R, Zhang Y, et al. Ceftazidime-avibactam as salvage therapy in pediatric liver transplantation patients with Infections caused by carbapenem-resistant enterobacterales. *Infect Drug Resist*. 2022;15:3323–3332. doi:10.2147/IDR.S369368
- 22. Iosifidis E, Chorafa E, Agakidou E, et al. Use of Ceftazidime-avibactam for the treatment of extensively drug-resistant or Pan drug-resistant Klebsiella pneumoniae in neonates and children <5 years of age. *Pediatr Infect Dis J.* 2019;38(8):812–815. doi:10.1097/INF.0000000002344

- 23. Perruccio K, Rosaria D, Amico M, et al. Ceftolozane/Tazobactam and Ceftazidime/Avibactam: an Italian Multi-center retrospective analysis of safety and efficacy in children with hematologic malignancies and multi-drug resistant gram-negative bacteria infections. *Pediatr Infect Dis J*. 2022;41(12):994–996. doi:10.1097/INF.00000000003716
- 24. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0; 2020. Available from: http://www.eucast.org. Accessed August 30, 2023.
- Humphries R, Bobenchik AM, Hindler JA, Schuetz AN. Overview of changes to the clinical and laboratory standards institute performance standards for antimicrobial susceptibility testing, M100, 31st edition. J Clin Microbiol. 2021;59(12):e0021321. doi:10.1128/JCM.00213-21
- Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. In: CLSI Supplement M100-S28 [S].
 28th ed. Wayne PA: Clinical and Laboratory Standards Institute; 2018:112–122.
- 27. Iovleva A, Doi Y. Carbapenem-Resistant Enterobacteriaceae. Clin Lab Med. 2017;37(2):303-315. doi:10.1016/j.cll.2017.01.005
- 28. Sheu CC, Chang YT, Lin SY, Chen YH, Hsueh PR. Infections caused by carbapenem-resistant Enterobacteriaceae: an update on therapeutic options. *Front Microbiol.* 2019;10:80. doi:10.3389/fmicb.2019.00080
- 29. Sokhn ES, Salami A, El Roz A, Salloum L, Bahmad HF, Ghssein G. Antimicrobial susceptibilities and laboratory profiles of Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis isolates as agents of urinary tract infection in Lebanon: paving the way for better diagnostics. *Med Sci.* 2020;8(3):32. doi:10.3390/medsci8030032
- 30. Jia X, Yin Z, Zhang W, Guo C, Du S, Zhang X. Effectiveness and nephrotoxicity of intravenous polymyxin B in carbapenem-resistant gram-negative bacterial infections among Chinese children. *Front Pharmacol.* 2022;13:902054. doi:10.3389/fphar.2022.902054
- Ustundag G, Oncel EK, Sahin A, Keles YE, Aksay AK, Ciftdogan DY. Colistin treatment for multidrug-resistant gram-negative infections in children: caution required for nephrotoxicity. Sisli Etfal Hastan Tip Bul. 2022;56(3):427–434. doi:10.14744/SEMB.2021.69851
- 32. Sahbudak Bal Z, Kamit Can F, Yazici P, et al. The evaluation of safety and efficacy of colistin use in pediatric intensive care unit: results from two reference hospitals and review of literature. J Infect Chemother. 2018;24(5):370–375. doi:10.1016/j.jiac.2017.12.017
- 33. Siddiqui NU, Qamar FN, Jurair H, Haque A. Multi-drug resistant gram negative infections and use of intravenous polymyxin B in critically ill children of developing country: retrospective cohort study. *BMC Infect Dis.* 2014;14:626. doi:10.1186/s12879-014-0626-9
- 34. Han R, Shi Q, Wu S, et al. Dissemination of Carbapenemases (KPC, NDM, OXA-48, IMP, and VIM) among carbapenem-resistant Enterobacteriaceae isolated from adult and children patients in China. *Front Cell Infect Microbiol*. 2020;10:314. doi:10.3389/fcimb.2020.00314
- Pannaraj PS, Bard JD, Cerini C, Weissman SJ. Pediatric carbapenem-resistant Enterobacteriaceae in Los Angeles, California, a high-prevalence region in the United States. *Pediatr Infect Dis J.* 2015;34(1):11–16. doi:10.1097/INF.00000000000471
- 36. Falcone M, Tiseo G, Carbonara S, et al. Mortality attributable to bloodstream infections caused by different carbapenem-resistant Gram negative bacilli: results from a nationwide study in Italy (ALARICO Network). *Clin Infect Dis.* 2023;76(12):2059–2069.
- 37. Falcone M, Daikos GL, Tiseo G, et al. Efficacy of Ceftazidime-avibactam plus aztreonam in patients with bloodstream infections caused by Metallo-beta-lactamase-producing enterobacterales. *Clin Infect Dis.* 2021;72(11):1871–1878. doi:10.1093/cid/ciaa586
- 38. Shields RK, Doi Y. Aztreonam combination therapy: an answer to Metallo-beta-Lactamase-producing gram-negative bacteria? *Clin Infect Dis.* 2020;71(4):1099–1101. doi:10.1093/cid/ciz1159
- 39. Zheng G, Zhang J, Wang B, et al. Ceftazidime-avibactam in combination with in vitro non-susceptible antimicrobials versus ceftazidime-avibactam in monotherapy in critically ill patients with carbapenem-resistant Klebsiella pneumoniae infection: a retrospective cohort study. *Infect Dis Ther.* 2021;10(3):1699–1713. doi:10.1007/s40121-021-00479-7
- Meng H, Yang J, Niu M, Zhu H, Zhou Y, Lu J. Risk factors and clinical outcomes of carbapenem-resistant Klebsiella pneumoniae bacteremia in children: a retrospective study. Int J Antimicrob Agents. 2023;106933. doi:10.1016/j.ijantimicag.2023.106933
- 41. Radha S, Warrier AR, Wilson A, Prakash S. Use of ceftazidime-avibactam in the treatment of clinical syndromes with limited treatment options: a retrospective study. *Cureus*. 2023;15(1):e33623. doi:10.7759/cureus.33623
- 42. Lin Q, Wang Y, Yu J, et al. Bacterial characteristics of carbapenem-resistant Enterobacteriaceae (CRE) colonized strains and their correlation with subsequent infection. *BMC Infect Dis.* 2021;21(1):638. doi:10.1186/s12879-021-06315-0
- 43. Dickstein Y, Edelman R, Dror T, Hussein K, Bar-Lavie Y, Paul M. Carbapenem-resistant Enterobacteriaceae colonization and infection in critically ill patients: a retrospective matched cohort comparison with non-carriers. J Hosp Infect. 2016;94(1):54–59. doi:10.1016/j.jhin.2016.05.018
- 44. Daikos GL, Vryonis E, Psichogiou M, et al. Risk factors for bloodstream infection with Klebsiella pneumoniae producing VIM-1 metallo-betalactamase. J Antimicrob Chemother. 2010;65(4):784–788. doi:10.1093/jac/dkq005

Infection and Drug Resistance

Dovepress

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/infection-and-drug-resistance-journal

Infection and Drug Resistance 2023:16