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ORIGINAL RESEARCH

Ceftazidime-Avibactam as a Salvage Treatment for Severely Infected Immunosuppressed Children

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Background: Multidrug-resistant Gram-negative bacteria (MDR-GNB) are becoming increasingly common around the world, with carbapenems frequently serving as a last resort but being threatened by the growing incidence of carbapenemase-producing bacteria. Ceftazidime-avibactam (CAZ/AVI) is a potential agent against MDR-GNB but with limited clinical experience, particularly in critically ill immunosuppressed children.

Methods: This study analyzed the use of CAZ/AVI as salvage treatment in severely infected immunosuppressed children from September 2019 to July 2022. Patients with confirmed GNB infection who received CAZ/AVI were matched with patients who received other antibiotics.

Results: Twenty-five critically ill immunosuppressed children treated with CAZ/AVI were included. The majority had hematologic diseases. All patients presented with sepsis in all 30 courses. Septic shock presented in 36.7% of these courses. The primary sites of infection included bloodstream infection (20.0%), skin and skin structure infection (20.0%), intra-abdominal infection (13.3%) and hospital-acquired pneumonia (10.0%). Twelve of the 25 (48.0%) patients had positive microbiological cultures, mainly *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, including 5 carbapenem-resistant GNB-infected cases. Fifteen (50.0%) courses presented clinical improvement. For the initial course of each patient, the clinical response rate of the GNB recovered group was significantly higher than that of the group without GNB recovery (66.7% vs 23.1%, $P = 0.047$). The 14-day and 30-day mortality rates were 24.0% and 28.0%, respectively, which were significantly correlated with the absence of GNB recovery ($P = 0.004$ and 0.024, respectively) and hospital-acquired pneumonia as the primary site of infection ($P = 0.001$ and 0.006, respectively). There was no significant difference in major outcomes between patients who received CAZ/AVI and matched patients who received other antibiotics.

Conclusion: CAZ/AVI could be considered a salvage strategy for immunosuppressed children with confirmed GNB infection. Caution should be taken when CAZ/AVI is applied to these patients in the absence of GNB recovery.

Keywords: gram-negative bacteria, hematological disease, hematopoietic stem cell transplantation, adverse events

Introduction

Antibiotic resistance causes approximately 35,000 deaths and $55 billion in healthcare costs each year in the United States.[1] In the WHO European region, it was estimated that 541,000 deaths were associated with antibiotic-resistant bacteria in 2019.[2] Antibiotic use is associated with the selection and colonization of multidrug-resistant Gram-negative bacteria (MDR-GNB), which is the most concerning type of antibiotic-resistant bacteria.[1,3] It was reported that the prevalence of MDR-GNB carriage varied from 3.64% to 50.62%, depending on the setting, region, and period.[4–6] According to a systematic review, the overall prevalence of antimicrobial-resistant GNB carriage in hospitalized patients was 13.8%, with an 11.0% rate of progression to infection.[7] Another systematic review found that patients colonized with MDR-GNB had a higher incidence (14%) of infection at a 30-day median follow-up, with carbapenem-resistant GNB having the highest incidence (19%).[8] Among GNB bloodstream infections (BSIs), approximately 33.6–39.0% of the organisms were MDR, which strongly predicted septic shock and increased the risk of mortality.[9–11] Notably, patients with malignant diseases, immunosuppressant use, and organ transplantation are especially

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vulnerable to MDR-GNB infections, with carbapenem-resistant *Enterobacterales* (CRE) and extended spectrum β-lactamase-producing bacteria colonization rates of 21.7% and 19.2%, respectively, resulting in high mortality rates, particularly for BSIs (40% to 100%).[12,13]

The emergence of antibiotic resistance has led to the widespread use of carbapenems. However, monitoring data from the China Antimicrobial Surveillance Network demonstrated that carbapenem-resistant GNB prevalence increased significantly between 2005 and 2021, from 3% to 23.1% for carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and from 31.0% to 71.5% for carbapenem-resistant *Acinetobacter baumannii* (CRAB).[14] These isolates are usually extensively drug-resistant or pandrug-resistant, with limited antimicrobial therapy options, and result in a significant healthcare burden and high mortality.[15]

Ceftazidime-avibactam (CAZ/AVI) is a novel combination of the third-generation cephalosporin ceftazidime and β-lactamase inhibitor avibactam, which exhibits high in vitro activity against many GNBs expressing Ambler class A, class C, some class D enzymes, and many drug-resistant *Pseudomonas aeruginosa* (PA) isolates but not those carrying class B metallo-β-lactamases.[16,17] The Food and Drug Administration and European Medicines Agency approved its use in adults in 2015, and in 2019, the FDA approved its use for the treatment of complicated intra-abdominal infections (IAI) and complicated urinary tract infections in children ≥3 months. The post-marketing experience of CAZ/AVI has also proven to be a valuable option for the treatment of infections with CRE and other MDR-GNB in adults.[18–20] Several case studies of adults with hematologic diseases and organ transplantation also demonstrated CAZ/AVI efficacy against MDR-GNB infections.[18,21–23] However, some clinical results did not provide sufficient support for its use.[24] The pediatric population has little experience with CAZ/AVI. Only two case series of pediatric patients with hematologic diseases and liver transplantation demonstrated successful CAZ/AVI treatment for MDR-GNB and CRE infections.[25,26] The accumulation of more cases will help to improve the experience of using CAZ/AVI. Meanwhile, many critically ill and immunosuppressed children were unable to obtain a positive GNB culture, and it is unclear whether CAZ/AVI is an effective and safe empirical salvage option. A recent review on CAZ/AVI for MDR-GNB infection in adult hematological cancer patients also called for additional research to assess the empirical use of CAZ/AVI in this vulnerable population.[27]

In this study, we assessed CAZ/AVI application in a tertiary children's hospital in eastern China to investigate its efficacy and safety as a salvage treatment for severely infected immunosuppressed children.

Materials and Methods

Data Collection

This was a single-center, retrospective case series study. Patients who received CAZ/AVI during September 2019 to July 2022 for at least 48 h were included. The inclusion criteria were: (1) age <18 years; and (2) treatment of CAZ/AVI for at least 48 h. The exclusion criteria were: (1) patients who receive CAZ/AVI treatment for less than 48 h; (2) fail to continuation of CAZ/AVI due to against advice discharge; and (3) inappropriately prescribed CAZ/AVI when evidence of non-susceptibility was present by commercialized antimicrobial susceptibility tests. Clinical information of these patients was collected according to electronic medical records.

CAZ/AVI was given at a standard dose of 50 mg/kg ceftazidime/12.5 mg/kg avibactam to a maximum dose of 2000 mg ceftazidime/500 mg avibactam intravenously every 8 h (by 2 h IV infusion), with adjustments made for one infant aged ≥3 months to < 6 months (40 mg/kg ceftazidime/10 mg/kg avibactam, q8 h) and a patient with previously existing renal impairment (estimated glomerular filtration rate ≥30 to <50 mL/min/1.73 m^2) (25 mg/kg ceftazidime/6.25 mg/kg avibactam to a maximum dose of 1000 mg ceftazidime/250 mg avibactam, q8 h), according to the manufacturer's recommendations (AVYCAZ [ceftazidime and avibactam]. Revised: 3/2019). This study was approved by the Ethics Committee of The Children's Hospital of Zhejiang University School of Medicine (Reference No. 2022-IRB-170, July 17, 2022). Due to the retroactive nature of the study, the Ethics Committee authorized permission to waive the requirement for written informed consent. The study adhered to the Declaration of Helsinki and maintained the patient data confidential.

We summarized the demographic and comorbidity profiles, pediatric sequential organ failure assessment (pSOFA) score on the first day, seventh day, and fourteenth day of CAZ/AVI therapy, when available, clinical and microbiological infection features, laboratory markers including procalcitonin (PCT), high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, and IL-10 levels on the days nearest to the onset of CAZ/AVI therapy, prior or concomitant use of

antimicrobial therapies, CAZ/AVI treatment options (dosage, duration) and outcomes when applicable. Clinical response and 14-day, 30-day and 90-day all-cause mortality after the onset of CAZ/AVI administration were recorded.

Patients with confirmed GNB infection who received CAZ/AVI were matched in a 1:1 ratio to patients who received other antibiotics, hospitalized during September 2019 to July 2022. The matching criteria were as follows: (1) patients with hematological disease; (2) patients diagnosed with sepsis; (3) patients infected with the same GNB species (cases with only colonization of GNB were not included); (4) difference of pSOFA score on the first day of inclusion of the two groups within ± 3 points; and (5) age difference within ± 5 years. The main outcomes included clinical response and 14-day and 30-day all-cause mortality.

Safety Assessment

Adverse events (AEs) were collected from the onset of CAZ/AVI to 30 days after the last dose of CAZ/AVI and needed to fulfil the following criteria: (1) new symptoms, signs, diseases, and laboratory test results; (2) aggravation of previously existed symptoms, signs, diseases and laboratory test results; and (3) symptoms or abnormal signs during infusion of CAZ/AVI; with a special focus on AEs that were more frequently reported in the literature. AEs are listed in Table S1 and were analyzed according to the Naranjo score method for the probability of adverse drug reaction related to CAZ/AVI.[28]

Microbiological Investigation

Antimicrobial susceptibility tests were determined by a commercialized microdilution method (VITEK COMPACT, BioMérieux, France). Minimum inhibitory concentrations (MICs) were classified according to breakpoints established by the most recent Clinical and Laboratory Standards Institute guidelines of the corresponding year. Resistance to carbapenems in Enterobacterales was defined as an imipenem and/or meropenem MIC of ≥ 4 μg/mL or ertapenem MICs of ≥ 2 μg/mL. Due to the retrospective nature of this study, CAZ/AVI susceptibility was not conducted routinely in this center for the past years until most recently in one case, so in most of the included cases, only ceftazidime susceptibility was available. MIC breakpoints for ceftazidime for *K. pneumoniae*: susceptible, ≤ 4 μg/mL; intermediate, 8 μg/mL; resistant, ≥ 16 μg/mL. MIC breakpoints for ceftazidime for PA: susceptible, ≤ 8 μg/mL; intermediate, 16 μg/mL; resistant, ≥ 32 μg/mL.

Definitions

The definitions of sepsis and septic shock were presented in Table S2. Sepsis was defined as systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection, according to the definitions and criteria for sepsis published by the International Pediatric Sepsis Consensus Conference in 2005, which have been widely adopted by many studies over the past years.[29,30] Septic shock was defined as sepsis with cardiovascular dysfunction (including hypotension, need for treatment with a vasoactive medication, or impaired perfusion), according to the expert consensus for the diagnosis and management of septic shock (infectious shock) in children (2015) in China.[31]

Sepsis of unknown origin (SUO) was considered sepsis where the source of infection site and causative pathogen could not be identified. However, there are currently no established standard diagnostic criteria for SUO.

Children who have malignant illnesses, immunodeficiency, hemophagocytic lymphohistiocytosis, aplastic anemia, hematopoietic stem cell transplantation (HSCT), or solid organ transplantation, or who are receiving immunosuppressive medication, are considered immunosuppressed.

Prior antibiotic was defined as antibiotic covering GNB administered for a duration exceeding 72 h, with the last dose given within 72 h prior to the initiation of CAZ/AVI therapy. CAZ/AVI was considered salvage therapy when prior antibiotics covering GNB had proven ineffective or had to be discontinued due to severe adverse reactions.

Monotherapy refers to a single drug therapy against GNB, with or without the combined use of antibiotics against Gram-positive bacteria, such as vancomycin and linezolid, or a combination of antifungals or antiviral medications. Combination therapy was defined as the concomitant use of at least two antibiotics against GNB for at least 48 h.

Clinical response was characterized as follows: partial or complete resolution of signs and symptoms related to the infection and improvement of laboratory test results. Clinical failure was defined as the persistence or worsening of the symptoms of infection that required additional intervention and/or death due to infection. The microbiological response was defined as negative culture of the pretreatment etiologic pathogen after treatment.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the patients. Continuous data were expressed either as the mean ± standard deviation or median and interquartile range, and the independent *t*-test or Wilcoxon rank-sum test was used to compare continuous variables according to whether the distribution of the data was normal or nonnormal. Categorical variables are presented as numbers and percentages. Fisher's exact test (two-tailed) was used to compare categorical variables. For case-matched pairs, the Wilcoxon signed rank and McNemar tests were used to compare differences in characteristics and outcomes. A P value < 0.05 was considered statistically significant. Data analysis was performed by using IBM SPSS Statistics v.25.0. (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

As shown in Figure 1, a total of 27 patients were treated with CAZ/AVI from September 2019 to July 2022; among them, one was excluded for against advice discharge on the third day of CAZ/AVI treatment, and the other was excluded for inappropriate prescription of CAZ/AVI against CAZ/AVI-nonsusceptible GNB. A second course of one patient was excluded for a duration less than 48 h. Twenty-five critically ill and immunosuppressed patients were included in this study, with a total of 30 courses of CAZ/AVI therapy. The demographic and clinical data are shown in Table 1. The median age was 73 months, with a range from 5 months to 14 years. Twelve (48.0%) of the patients were male. Most (24/25) of the patients had hematologic diseases, including 12 cases of acute myeloid leukemia, 6 cases of acute lymphoblastic leukemia, 2 cases of juvenile myelomonocytic leukemia and 4 cases of aplastic anemia, 10 of whom received HSCT. One infant patient had congenital biliary atresia and received liver transplantation (1/25).

All patients presented with sepsis in each course (100.0%, 30/30), and 36.7% (11/30) of the courses presented with septic shock within several days before or after the onset of CAZ/AVI therapy (Table 1). On the first day of 30 CAZ/AVI courses, the median pSOFA score was 4 (4, 6) (n = 30), and the levels of PCT, IL-6, IL-10 and hsCRP were 1.1 (0.5, 3.2) ng/mL (n = 23), 239.9 (94.0, 919.3) pg/mL (n = 29), 13.0 (9.8, 35.4) pg/mL (n = 29) and 86.8 (34.7, 199.2) mg/L (n = 30), respectively. Seventeen of the 30 (56.7%) courses were associated with neutropenia status (absolute neutrophil count <500 mm^3). The primary sites of infection included BSI (6/30, 20.0%), skin and skin structure infection (SSSI) (6/30, 20.0%, including facial cellulitis, gluteal abscess and mouth cavity infection), IAI (4/30, 13.3%) and HAP (3/30, 10.0%).

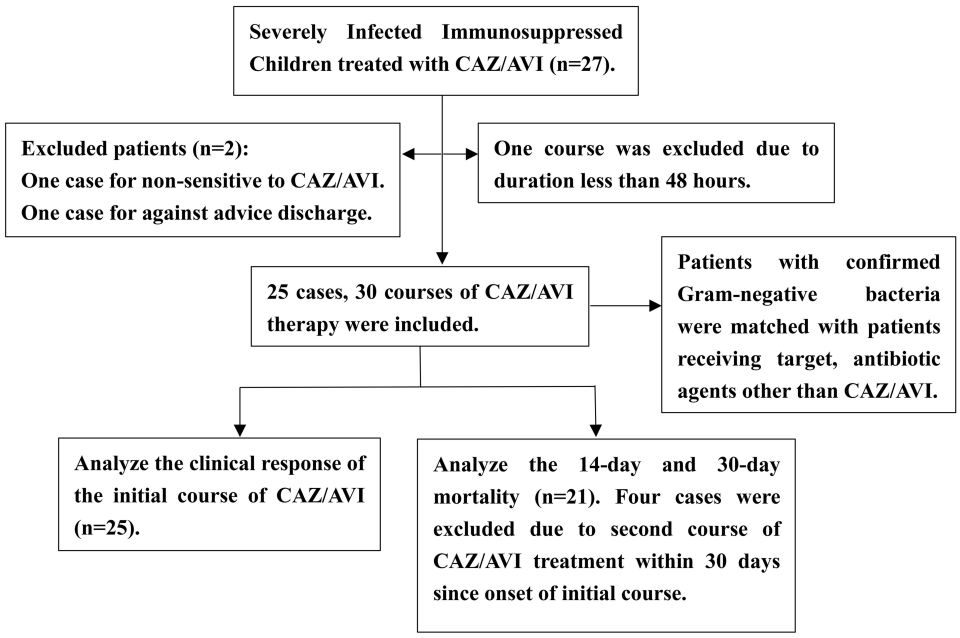

Figure 1 Flowchart of patients included and excluded for the study.

Table 1 Demographic and Clinical Data of Patients Treated by CAZ/AVI

No.	Underlying Disease	Sepsis	Septic Shock	pSOFA (Day 1)	pSOFA (Day 7)	pSOFA (Day 14)	Neutropenia	Primary Site of Infection	GNB and Specimen Origins	Prior Antibiotics	Concomitant Antibiotics	CAZ/AVI Duration (Day)	Improve After CAZ/AVI	Culture Turning Negative (Interval Days)	14-Day Result	30-Day Result	90-Day Result	Cause of Death
1	HM (JMML), HSCT	Yes	Yes	9	5	6	Yes	BSI	KP (blood); Ab (throat swab)	IMI, CPZ/SBT	POL	15	Yes	3d (KP); 3d (Ab)	Alive	Dead	–	GVHD
2	HM (AML), HSCT	Yes	No	4	2	6	Yes	SSSI	CRKP (blood)	PIP/TAZ, AMI	POL	7	Yes	2d	Alive	Alive	Alive	–
3	AA	Yes	No	4	NA	NA	No	BSI	KP (blood)	IMI	IMI	4	No	2d	Alive	Alive	Alive	–
4	HM (AML), HSCT	Yes	Yes	5	4	4	Yes	BSI	KP (blood)	POL	Monotherapy	11	No	2d	Alive	Alive	Dead	Pulmonary hemorrhage
5	AA, HSCT	Yes	No	5	5	6	Yes	SSSI	CRPA (pus)	CPZ/SBT	Monotherapy	8	Yes	NA	Alive	Alive	Dead	Pulmonary hemorrhage
6	HM (AML)	Yes	No	3	2	NA	Yes	SSSI	CRPA (pus)	MEM, CPZ/SBT	IMI	11	Yes	NA	Alive	Alive	Alive	–
7	HM (AML)	Yes	Yes	6	7	1	Yes	BSI	PA (blood, CSF, vaginal discharge)	TGC, AMI, POL	POL[a]	24	No	18d	Alive	Alive	Alive	–
8	HM (AML)	Ini: Yes	Ini: Yes	Ini: 4	2	1	Ini: Yes	Ini: SSSI	Ini: CRPA (blood, throat swab)	Ini: TGC, POL	Ini: AMI, MEM	Ini:16	Ini: Yes	Ini: 2d	Alive	Alive	Dead	ARDS, septic shock
		Sec: Yes	Sec: No	Sec: 6	4	14	Sec: Yes	Sec: SSSI	Sec: PA (blood, throat swab)	Sec: AMI, POL	Sec: AMI, POL (MEM)[b]	Sec: 14	Sec: No	Sec: 4d				
9	HM (AML)	Yes	No	4	3	0	No	BSI	PA (blood)	AMI, POL	POL	7	Yes	2d	Alive	Alive	Alive	–
10	HM (ALL)	Yes	Yes	6	13	7	Yes	SSSI	CRPA (blood, anal swab)	TGC, AMI, POL	LEV, TGC	7	No	2d	Alive	Alive	Alive	–
11	HM (AML)	Ini: Yes	Ini: No	Ini: 6	6	2	Ini: Yes	Ini: IAI	Ini: PA (blood)	Ini: TGC, POL	Ini: POL, AMI	Ini: 23	Ini: Yes	Ini: 2d	Alive	Alive	Alive	–
		Sec: Yes	Sec: No	Sec: 2	3	3	Sec: No	Sec: IAI	Sec: NA	Sec: AMI, PIP/TZA	Sec: MEM, MET	Sec: 13	Sec: Yes	Sec: NA				
12	HM (ALL)	Yes	Yes	4	0	0	Yes	BSI	PA (blood), Colonization of *Escherichia coli* (anal swab)	CPZ/SBT, TGC	AMI, POL	10	Yes	3d	Alive	Alive	Alive	–

(*Continued*)

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Table 1 (Continued).

No.	Underlying Disease	Sepsis	Septic Shock	pSOFA (Day 1)	pSOFA (Day 7)	pSOFA (Day 14)	Neutropenia	Primary Site of Infection	GNB and Specimen Origins	Prior Antibiotics	Concomitant Antibiotics	CAZ/AVI Duration (Day)	Improve After CAZ/AVI	Culture Turning Negative (Interval Days)	14-Day Result	30-Day Result	90-Day Result	Cause of Death
13	HM (AML), HSCT	Yes	Yes	13	NA	NA	Yes	HAP	NA	TGC, POL	POL	2	No	NA	Dead	–	–	Septic shock
14	HM (ALL)	Yes	Yes	5	4	4	Yes	SUO	NA	AMI, LEV	LEV	6	No	NA	Alive	Alive	Dead	Septic shock
15	HM (AML)	Ini: Yes	Ini: No	Ini: 4	4	3	Ini: No	Ini: SUO	Ini: NA	Ini: TGC, IMI	Ini: Monotherapy	Ini: 5	Ini: No	Ini: NA	alive	alive	alive	–
		Sec: Yes	Sec: No	Sec: 2	0	0	Sec: No	Sec: SUO	Sec: NA	Sec: TGC, IMI	Sec: IMI	Sec: 7	Sec: Yes	Sec: NA				
16	HM (ALL)	Yes	No	4	NA	0	Yes	SUO	NA	MEM	Monotherapy	4	Yes	NA	Alive	Alive	Alive	–
17	HM (AML)	Yes	No	8	4	15	Yes	SUO	NA	MEM	Monotherapy	9	No	NA	Dead	–	–	Gastrointestinal bleeding
18	HM (JMML), HSCT	Yes	No	4	NA	NA	No	IAI	NA	TGC, MEM	Monotherapy	2.5	No	NA	Dead	–	–	Recurrent infection
19	HM (AML), HSCT	Yes	No	4	NA	NA	No	HAP	NA	MEM	Monotherapy	5	No	NA	Dead	–	–	Pulmonary hemorrhage
20	AA, HSCT	Yes	No	7	6	7	Yes	IAI	NA	POL, MEM	MEM	7	No	NA	Dead	–	–	Recurrent infection
21	HM (AML), HSCT	Yes	No	3	2	1	No	SUO	NA	PIP/TZA	Monotherapy	11	No	NA	Alive	Alive	Alive	–
22	HM (ALL)	Yes	Yes	6	2	1	No	SUO	NA	POL, AMI	POL	10	Yes	NA	Alive	Alive	Alive	–
23	AA, HSCT	Ini: Yes	Ini: No	Ini: 6	4	4	Ini: Yes	Ini: SUO	Colonization of CRKP (anal swab)	Ini: AMI, TGC	Ini: TGC	Ini: 10	Ini: No	Ini: No	Alive	Alive	Alive	–
		Sec: Yes	Sec: No	Sec: 4	3	3	Sec: No	Sec: SUO		Sec: AMI, TGC	Sec: TGC	Sec: 5	Sec: Yes	Sec: No				
24	HM (ALL)	Ini: Yes	Ini: No	Ini: 0	0	0	Ini: No	Ini: SUO	Ini: NA	Ini: MEM, AMI, TGC	Ini: Monotherapy	Ini: 10	Ini: Yes	Ini: NA	Alive	Alive	Alive	–
		Sec: Yes	Sec: Yes	Sec: 3	0	0	Sec: No	Sec: SUO	Sec: NA	Sec: CPZ/SBT, MEM	Sec: TGC, FOM	Sec: 25	Sec: Yes	Sec: NA				
25	CBA, LT	Yes	Yes	5	13	NA	No	HAP	NA	CPZ/SBT	Monotherapy	8	No	NA	Dead	–	–	Recurrent infection

Notes: [a]POL was given through intravenous injection and lateral ventricular drainage tube. [b]POL was adjusted to MEM considering the nephrotoxicity possibly caused by POL.

Abbreviations: HM, Hematologic malignancy; ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; JMML, Juvenile myelomonocytic leukemia; HSCT, Hematopoietic stem cell transplantation; AA, Aplastic anemia; CBA, Congenital biliary atresia; LT, Liver transplantation; pSOFA, pediatric Sequential Organ Failure Assessment; BSI, Bloodstream infection; SSSI, Skin and skin structure infection; IAI, Intra-abdominal infection; HAP, Hospital acquired pneumonia; GNB, Gram-negative bacteria; PA, *Pseudomonas aeruginosa*; CRPA, Carbapenem-resistant *P; aeruginosa*; KP, *Klebsiella pneumoniae*; CRKP, Carbapenem-resistant *K; pneumoniae*; Ab, *Acinetobacter baumannii*; CSF, Cerebrospinal fluid; CAZ/AVI, Ceftazidime-avibactam; IMI, Imipenem-cilastatin; CPZ/SBT, Cefoperazone-sulbactam; PIP/TAZ, Piperacillin-tazobactam; POL, Polymyxin B; MEM, Meropenem; TGC, Tigecycline; AMI, Amikacin; LEV, Levofloxacin; MET, Metronidazole; FOM, Fosfomycin; SUO, Sepsis of unknown origin; NA, Not Available; GVHD, Graft-versus-host disease; ARDS, Acute respiratory distress syndrome; Ini, Initial course; Sec, Second course.

The remaining cases were considered SUO (11/30, 36.7%). Patient 11 underwent the first surgery due to acute gangrenous appendicitis and the second surgical intervention due to intestinal adhesion. Patient 7 underwent left lateral ventricular drainage, ventricular microscopic surgery and cerebellar hemisphere lesion resection due to secondary acute purulent meningitis, intracerebral hemorrhage and acute hydrocephalus.

Microbiological results

Twelve of 25 (48.0%) patients presented confirmed GNB infection (Tables 1 and 2). A total of 15 isolates are presented in Table 2. *K. pneumoniae* (KP) infection occurred in 4 courses, with 1 CRKP and 3 carbapenem-susceptible KP (CSKP). PA infection occurred in 9 courses, with 4 CRPA and 6 carbapenem-susceptible PA (CSPA) presented in 5 courses. In patient 7, CSPA isolates with increased MIC for ceftazidime (from 2 μg/mL to ≥ 64 μg/mL) were observed on the fifth day of CAZ/AVI infusion. In patient 8, the PA isolates had changed from CRPA to CSPA in different courses. Patient 1 had concurrent infection with carbapenem-resistant *Acinetobacter baumannii*. According to the susceptibility profiles composed of 14 KP and PA (Table 2), 5 (35.7%) were carbapenem-resistant, and 3 (21.4%) were non-susceptible to CAZ.

Treatment Options and Clinical Response Evaluation

Five patients received two courses of CAZ/AVI administration due to repeated infection (patient 8 with facial cellulitis, patient 11 with intestinal adhesion, patient 15, 23 and 24 with BSI), and the intervals were 44 days, 4 days, 15 days, 24 days and 21 days after the first course was discontinued, respectively. A total of 30 courses of CAZ/AVI were assessed, and all were salvage therapy after failure with prior antimicrobials against GNB (Table 1). Carbapenems (40.0%, 12/30), tigecycline (40.0%, 12/30), amikacin (36.7%, 11/30) and polymyxin B (33.3%, 10/30) were the most commonly used antibiotic prescriptions prior to CAZ/AVI. Ten (33.3%, 10/30) courses of CAZ/AVI were administered as monotherapy to GNB (Table 1), and twenty (66.7%, 20/30) courses were given with concomitant antibiotics to GNB, mainly polymyxin B (45.0%, 9/20), carbapenems (30.0%, 6/20), amikacin (20.0%, 4/20) and tigecycline (20.0%, 4/20). The median

Table 2 Susceptibility Testing Results of Isolates from 12 Patients Treated with CAZ/AVI

No.	Pathogen species	AMI	FEP	CAZ	TGC	CIP	LEV	CST	IMP	MEM	PIP/TAZ	CPZ/SBT	ESBL
1	KP	S	R	S	R	NA	R	NA	S	S	S	NA	+
2	CRKP	S	R	R[a]	R	NA	R	NA	R	R	R	NA	+
3	KP	S	S	I[b]	R	NA	R	NA	S	S	R	NA	+
4	KP	S	S	S	S	NA	R	NA	S	S	S	NA	–
5	CRPA	S	S	S	NA	R	R	S	R	R	S	NA	NA
6	CRPA	S	S	S	NA	S	S	S	R	R	S	NA	NA
7	PA	S	S	S	NA	S	S	S	S	S	S	S	NA
7[c]	PA	S	R	R	NA	S	S	S	S	S	R	R	NA
8_{Ini}	CRPA	S	S	S	NA	R	R	S	R	S	S	S	NA
8_{Sec}	PA	S	S	S	NA	S	S	S	S	S	S	S	NA
9	PA	S	S	S	NA	S	S	S	S	S	S	S	NA
10	CRPA	S	S	S	NA	S	S	I	R	R	S	S	NA
11_{Ini}[d]	PA	S	S	S	NA	S	S	S	S	S	S	S	NA
12	PA	S	S	S	NA	I	R	S	S	S	I	I	NA
No.	**Pathogen species**	**AMI**	**FEP**	**CAZ**	**TGC**	**SMZco**	**LEV**	**CST**	**IMP**	**MEM**	**PIP/TAZ**	**CPZ/SBT**	**CRO**
1[e]	Ab	NA	R	R	S	R	S	NA	R	R	R	S	R

Notes: [a]MIC ≥ 64 μg/mL. [b]MIC = 8 μg/mL. [c]Development of resistance to ceftazidime (MIC ≥ 64 μg/mL) in patient 7 during one courses of CAZ/AVI treatment, specimen origins contain blood, cerebrospinal fluid. [d]Patient 11 had positive culture of PA only in first course. [e]Patient 1 had concurrent infection of *Acinetobacter baumannii*;

Abbreviations: MIC, Minimum inhibitory concentrations; NA, not available (not tested); CAZ/AVI, Ceftazidime-avibactam; AMI, Amikacin; FEP, Cefepime; CAZ, Ceftazidime; TGC, Tigecycline; CIP, Ciprofloxacin; LEV, Levofloxacin; CST, Colistin; IMP, Imipenem; MEM, Meropenem; PIP/TAZ, Piperacillin-tazobactam; CPZ/SBT, Cefoperazone-sulbactam; CRO, Ceftriaxone Sodium; PA, *Pseudomonas aeruginosa*; CRPA, Carbapenem-resistant *P. aeruginosa*; KP, *Klebsiella pneumoniae*; CRKP, Carbapenem-resistant *K. pneumoniae*; Ab, *Acinetobacter baumannii*; SMZco, Compound sulfamethoxazole; +, positive; -, negative; Ini, Initial course; Sec, Second course; S, Susceptible; I, Intermediate Resistant.

duration of CAZ/AVI therapy was 8.5 (5.8, 11.5) days. Fifteen (50.0%, 15/30) courses presented clinical improvement, including 3 monotherapy and 12 combination therapy, mostly with polymyxin B (40.0%, 6/15). The vast majority of microbiological response days ranged from 2 to 4 days and were 18 days in patient 7 (Table 1).

To explore possible factors associated with clinical response, data from the initial 25 courses of the 25 patients were analyzed to avoid nonindependence of data from the second course of the individuals (Tables 3 and 4). Patients with confirmed GNB pathogens showed a better clinical response of 66.7% (8/12) compared to the group without GNB recovery (23.1%, 3/13) (P = 0.047). No significant differences in clinical response outcomes were found in other features, such as age, sex, first-day pSOFA score, CAZ/AVI therapy duration, neutropenia, clinical markers, including IL-6, IL-10 and hsCRP, underlying disease, types of primary infection, transplantation, septic shock, or treatment options (monotherapy or combination therapy).

The all-cause mortality rates at the 14-day, 30-day and 90-day observation timepoints after the onset of CAZ/AVI therapy were 24.0% (6/25), 28.0% (7/25) and 44.0% (11/25), respectively. Univariate analysis instead of multivariate logistic regression was used to explore factors associated with mortality in this study due to the small sample size. The 14-day mortality correlated significantly with the absence of confirmed GNB pathogens (100% vs 0%, compared with the GNB recovered group, P = 0.004) (Table 3), and with IAI and HAP as the primary sites of infection (100% vs 0%, compared with the BSI and SSSI groups, respectively, P = 0.001) (Table 4). The 30-day mortality was significantly associated with the absence of confirmed GNB pathogens (85.7% vs 14.3%, P = 0.024), a higher pSOFA score from the first day of CAZ/AVI therapy (7 vs 4, P = 0.041), a history of transplantation (85.7% vs 28.6%, P = 0.024) (Table 3) and HAP as the primary site of infection (100% vs 0%, compared with the SSSI group, P = 0.001) (Table 4). There were no significant differences between groups in other features, such as underlying disease, CAZ/AVI duration, inflammatory biomarkers, treatment options such as monotherapy or combined therapy.

Adverse Events

A summary of the AEs of patients receiving CAZ/AVI therapy is listed in Table S1. Hepatobiliary system disorder and hypokalemia were the most frequently occurring AEs. Specifically, hypokalemia is listed in the package insert of CAZ/AVI; it was considered a probable adverse drug reaction in patient 11, and the Naranjo score was 6. The lowest serum potassium concentration was 1.9 mmol/L in the first CAZ/AVI course, which was considered severe Grade 4 according to general guidelines of the Common Terminology Criteria for Adverse Events scale. We did not observe CAZ/AVI-related drug reactions in the hepatobiliary system or respiratory system or hypersensitivity reactions. During the CAZ/AVI treatment period, blood urea and creatinine levels increased in patient 5 and patient 8. The renal damage of patient 5 was considered to be caused by renal thrombotic microangiopathy after HSCT, a graft-versus-host disease. For patient 8, creatinine elevation was considered to be related to the nephrotoxicity of polymyxin B, as renal function was restored when polymyxin B was adjusted to meropenem (Table 1, Note [b]).

We excluded the second course of CAZ/AVI in patient 5. He was readmitted for seizure, syncope and cough 14 days after the first successful CAZ/AVI therapy. Seizure reoccurred at the beginning of a second episode of CAZ/AVI infusion despite an adjusted dose according to renal function, leading to discontinuation of this therapy. Seizures have been reported in patients treated with ceftazidime, particularly in those who had renal dysfunction, as mentioned by the drug manufacturers (AVYCAZ [ceftazidime and avibactam]. Revised: 3/2019). We could not rule out the underlying disease as the reason for seizures in patient 5, as it had occurred before the second episode of CAZ/AVI injection. The Naranjo score for estimating the probability of adverse effects is 0, defined as a "doubtful" causal relationship between CAZ/AVI and seizures in this individual. This patient died of pulmonary hemorrhage and severe pneumonia. No AEs were related to the outcome of death in patients with CAZ/AVI therapy.

Case-Matched Analysis

The characteristics and outcomes of the 12 case-matched pairs are shown in Tables 5 and S3. The majority of patients in the control group received antibiotics containing carbapenems. There were no significant differences in outcomes including clinical response, 14-day mortality and 30-day mortality.

Table 3 Univariate Analysis of Factors Associated with Clinical Response of CAZ/AVI Therapy and Mortality

Characteristics	n = 25		*P* value	n = 21		*P* value	n = 21		*P* value
	Clinical Response (Initial) (n = 11)	Clinical Failure (iniTial) (n = 14)		14-Day Survived (n = 15)	14-Day Died (n = 6)		30-Day Survived (n = 14)	30-Day Died (n = 7)	
Male sex	4 (36.4%)	8 (57.1%)	0.428	5 (33.3%)	5 (83.3%)	0.063	5 (35.7%)	5 (71.4%)	0.183
Age (months), median (P25, P75)	73 (66, 100)	70 (30, 147)	0.913	71 (41, 109)	40 (14, 109)	0.35	72 (43, 118)	41 (17, 93)	0.232
pSOFA, median (P25, P75)	4 (4, 6)	5 (4, 6.2)	0.195	4 (4, 6)	6 (4, 9.2)	0.159	4 (4, 5.2)	7 (4, 9)	0.041
Duration (days), median (P25, P75)	10 (7, 15)	7 (4.8, 10.2)	0.093	10 (7, 11)	6 (2.4, 8.2)	0.055	9 (6.8, 11)	7 (2.5, 9)	0.202
Clinical markers									
Neutropenia (<500 mm^3)	8 (72.7%)	8 (57.1%)	0.677	11 (73.3%)	3 (50.0%)	0.613	10 (71.4%)	4 (57.1%)	0.638
IL-6 (pg/mL), median (P25, P75)	272 (162, 1143)	179 (96, 1579)	0.702	240 (116, 514)	246 (96, 1772)	0.969	256 (103, 884)	162 (99, 696)	0.911
IL-10 (pg/mL), median (P25, P75)	14.6 (9.8, 39.2)	12.2 (6.8, 42.2)	0.642	14.6 (9.9, 39.2)	15.6 (5.8, 889.5)	0.586	13.2 (9.4, 33.5)	21.3 (5.9, 99.7)	0.941
hsCRP (mg/L), median (P25, P75)	87.6 (36.2, 204.6)	88.4 (32.7, 201.6)	0.956	87.6 (23.4, 204.6)	106.1 (50.2, 160.9)	0.815	91.7 (23.2, 207.1)	90.8 (55.5, 142.1)	0.881
Post-transplantation	3 (27.3%)	8 (57.1%)	0.227	5 (33.3%)	5 (83.3%)	0.063	4 (28.6%)	6 (85.7%)	0.024
Septic shock	4 (36.4%)	6 (42.8%)	1	8 (53.3%)	2 (33.3%)	0.635	7 (50.0%)	3 (42.8%)	1.000
GNB culture									
GNB recovered	8 (72.7%)	4 (28.6%)	0.047	11 (73.3%)	0 (0.0%)	0.004	10 (71.4%)	1 (14.3%)	0.024
No GNB recovered	3 (27.3%)	10 (71.4%)		4 (26.7%)	6 (100.0%)		4 (28.6%)	6 (85.7%)	
Treatment options									
Monotherapy	3 (27.3%)	7 (50.0%)	0.414	4 (26.7%)	4 (66.7%)	0.146	4 (28.6%)	4 (57.1%)	0.346
Combination therapy	8 (72.7%)	7 (50.0%)		11 (73.3%)	2 (33.3%)		10 (71.4%)	3 (42.8%)	

Notes: pSOFA, hsCRP at the first day of CAZ/AVI therapy was recorded. The result of IL-6, IL-10 level closest to the first day of CAZ/AVI therapy was recorded (within ± 2 days).

Abbreviations: CAZ/AVI, Ceftazidime-avibactam; pSOFA, pediatric Sequential Organ Failure Assessment; hsCRP, high-sensitivity C-reactive protein; IL-6, Interleukin-6; IL-10, Interleukin-10; GNB, Gram-negative bacteria.

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Table 4 Multi-Group Analysis of Outcomes with Bonferroni Adjustments

Characteristics	n = 25		*P* value	n = 21		*P* value	n = 21		*P* value
	Clinical Response (Initial) (n = 11)	Clinical Failure (Initial) (n = 14)		14-Day Survived (n = 15)	14-Day Died (n = 6)		30-Day Survived (n = 14)	30-Day Died (n = 7)	
Underlying diseases									
Acute myeloid leukemia	5 (41.7%)	7 (58.3%)	0.750	7 (70.0%)	3 (30.0%)	0.268	7 (70.0%)	3 (30.0%)	0.052
Acute lymphoblastic leukemia	4 (66.7%)	2 (33.3%)		5 (100.0%)	0 (0.0%)		5 (100.0%)	0 (0.0%)	
Juvenile myelomonocytic leukemia	1 (50.0%)	1 (50.0%)		1 (50.0%)	1 (50.0%)		0 (0.0%)	2 (100.0%)	
Aplastic anemia	1 (25.0%)	3 (75.0%)		2 (66.7%)	1 (33.3%)		2 (66.7%)	1 (33.3%)	
Congenital biliary atresia	0 (0.0%)	1 (100.0%)		0 (0.0%)	1 (100.0%)		0 (0.0%)	1 (100.0%)	
Primary site of infection									
Bloodstream infection	3 (50.0%)	3 (50.0%)	0.341	6^{a} (100.0%)	0 (0.0%)	0.001	5^{ab} (83.3%)	1 (16.7%)	0.006
Skin and skin structure infection	4 (80.0%)	1 (20.0%)		5^{ab} (100.0%)	0 (0.0%)		5^{b} (100.0%)	0 (0.0%)	
Intra-abdominal infection	1 (33.3%)	2 (66.7%)		0^{bc} (0.0%)	2 (100.0%)		0^{ab} (0.0%)	2 (100.0%)	
Hospital acquired pneumonia	0 (0.0%)	3 (100.0%)		0^{c} (0.0%)	3 (100.0%)		0^{a} (0.0%)	3 (100.0%)	
Sepsis of unknown origin	3 (37.5%)	5 (62.5%)		4^{abc} (80.0%)	1 (20.0%)		4^{ab} (80.0%)	1 (20.0%)	

Notes: [a]Indicate significant difference from group [b], group [c] and group [bc], but not group [ab] or group [abc]. [c]Indicate significant difference from group [a] and group [ab], but not group [bc] or group [abc].

Table 5 Characteristics in Case-Matched Study

Characteristics	CAZ/AVI Group (n = 12)	Control Group (n = 12)	*P* value
Age (months), median (P25, P75)	82.5 (50.0, 121.0)	72.0 (51.0, 97.8)	
pSOFA of day1, median (P25, P75)	4.0 (3.0, 5.8)	4.5 (4.0, 6.0)	
Gram-negative bacteria			
Carbapenem-resistant *Klebsiella pneumoniae*	1 (8.3%)	1 (8.3%)	
Carbapenem-susceptible *K. pneumoniae*	3 (25.0%)	3 (25.0%)	
Carbapenem-resistant *Pseudomonas aeruginosa*	4 (33.3%)	4 (33.3%)	
Carbapenem-susceptible *P. aeruginosa*	4 (33.3%)	4 (33.3%)	
Other characteristics			
Sex			
Male	4 (33.3%)	3 (25.0%)	1.000
Underlying diseases			
Hematologic malignancy	10 (83.3%)	10 (83.3%)	1.000
Aplastic anemia	2 (16.7%)	2 (16.7%)	1.000
Hematopoietic stem cell transplantation	4 (33.3%)	1 (8.3%)	0.250
Septic shock	6 (50.0%)	7 (58.3%)	1.000
Neutropenia	10 (83.3%)	10 (83.3%)	0.500
Site of infection (more than 1 site in some cases)			
Bloodstream infection	10 (83.3%)	10 (83.3%)	0.500
Skin and skin structure infection	3 (25.0%)	1 (8.3%)	0.500
Intra-abdominal infection	1 (8.3%)	1 (8.3%)	1.000
Intracranial infection	1 (8.3%)	1 (8.3%)	1.000
Treatment options including:			
Carbapenems	3 (25.0%)	9 (75.0%)	0.031
Amikacin	3 (25.0%)	4 (33.3%)	1.000
Piperacillin tazobactam	0 (0.0%)	2 (16.7%)	0.500
Tigecycline	1 (8.3%)	1 (8.3%)	1.000
Levofloxacin	1 (8.3%)	0 (0.0%)	1.000
Polymyxin B	6 (50.0%)	3 (25.0%)	0.375
Outcomes			
Clinical response	8 (66.7%)	10 (83.3%)	0.500
14-day Mortality	0 (0.0%)	2 (16.7%)	0.500
30-day Mortality	1 (8.3%)	2 (16.7%)	1.000

Note: Wilcoxon signed rank and McNemar test was used for statistical comparison for matched pairs, as appropriate.
Abbreviation: CAZ/AVI, Ceftazidime-avibactam.

Discussion

Clinical practice of CAZ/AVI therapy against life-threating GNB infections in critically ill and immunosuppressed pediatric patients is scarce.[17] In this study, all of the patients were hospitalized in the intensive care units or Hematology and Oncology wards, the majority had hematologic diseases, 11 were posttransplantation, all presented with sepsis, the median pSOFA score on the first day of CAZ/AVI onset was 4 points, reported to be a threshold to discriminate mortality in China;[32] all failed with prior antibiotics against GNB. Forty-eight percent of them obtained positive microbiological cultures, and the main pathogen isolates were PA and KP.

The clinical response rates were 50.0% (15/30) of all courses, which were not as encouraging as previous pediatric studies (75.0% to 100.0% response).[10,22,33–38] One explanation for the lower clinical response is that we did not exclude cases without GNB recovery; among them, 23.1% (3/13) had a clinical response (Table 3). Meanwhile, patients with confirmed GNB pathogens showed a better clinical response regardless of whether the pathogen was susceptible to CAZ/AVI in vitro. This is in line with a previous single-center retrospective study that compared empirical CAZ/AVI therapy to targeted therapy in adult patients, and found that the empirical therapy group had a lower clinical response rate (25.0% vs 77.8%).[39] For children with cancer or post-HSCT who are clinically unstable and have a risk of antibiotic resistance, situations are more complicated

across institutions and countries with different local epidemiologies of pathogens, and the treatment options remain even less. The empirical use of CAZ/AVI in our study was based on the failure of guideline-recommended carbapenems and other prior antibiotics, including polymyxin B, amikacin and tigecycline. However, as salvage therapy in our study, the efficacy of the group without GNB recovery was not satisfactory. In addition, the lower clinical response of all courses might be partially explained by potentially non-infectious reasons, the immunocompromised status and multiple comorbidities of our patients, whose lives were also threatened by infection of multiple pathogens (invasive fungal diseases, virus infections, etc).

CAZ/AVI performed well in 8 adult hematologic patients with acute leukemia, multiple myeloma, lymphoma, myeloproliferative disease and confirmed CRE (6 isolates of KP, 1 isolate of *Klebsiella oxytoca*, 1 isolate of *Escherichia coli*).[23] In our study, four of five children with isolates of carbapenem-resistant GNB (1 CRKP, 4 CRPA) achieved clinical response, and all of them had SSSI as the primary site of infection, offering supportive experience of CAZ/AVI as preserved salvage therapy for treating confirmed CRE or CRPA infection in immunosuppressed children with SSSI.

The combined use of antibiotics in research has made it difficult to evaluate the specific efficacy of certain regimens. Monotherapy in one clinical trial achieved more than 95.0% clinical response in the Phase 2 trial for pediatric complicated urinary tract infections[38] and was supportively reported in reports of CRKP infection.[22,36,40] Some recent studies of adults, including two meta-analyses and two multicenter studies, compared CAZ/AVI monotherapy to combination therapy for infections due to GNB and showed a similar effect on mortality, microbiological cure rates or clinical response.[41–43] In contrast, other studies showed that the combination of two or more active drugs was associated with lower mortality, especially in patients with severe infections.[44,45] In our study, the clinical response seemed higher in the combination group than in the monotherapy group, but there was no statistical significance.

Three of the KP or PA isolates from our patients were resistant to ceftazidime (Table 2). The exact MIC of CAZ/AVI was unknown, as our observation is retrospective, and susceptibility tests were not routinely conducted in our center. CAZ/AVI nonsusceptible GNB occurring during antimicrobial treatment have also been reported.[33,46] We observed an increase in ceftazidime MIC (from 2 μg/mL to ≥ 64 μg/mL) in patient 7, who was infected with PA, during CAZ/AVI therapy, suggesting that we need to be cautious of drug resistance in the process of application, although the mechanism was unknown. Empirical use of CAZ/AVI in patient 2 with ceftazidime-nonsusceptible CRKP infection achieved a clinical response. The clinical effect might be partially explained by avibactam, which could restore ceftazidime efficacy against most ceftazidime-nonsusceptible GNB.[17,33,47] Nevertheless, in patient 2, we could not rule out the possible efficacy of polymyxin B, as it, along with CAZ/AVI, was used concomitantly.

In this study, the overall 14-day and 30-day mortality rates were 24.0% and 28.0%, respectively, since the onset of CAZ/AVI. The outcomes of other studies of CAZ/AVI therapy against GNB infections have been highly variable. A report showed a 30-day mortality rate of 25.0% in 8 adult hematologic patients infected by CRE.[23] All 5 patients with carbapenem-resistant GNB-infected SSSI treated with CAZ/AVI survived for 30 days in our study. The 14-day and 30-day mortality correlated significantly with HAP as the primary site of infection, compared to SSSI. No comparable data exist for CAZ/AVI therapy in severely infected immunosuppressed children with mainly hematologic diseases and complex comorbidities. We could not draw conclusions given the small sample size and univariate analysis. However, an adult study investigating CAZ/AVI therapy on CRE infection also showed the highest mortality rate in patients with pneumonia (56.2%).[43] The limited experience suggested that children with HAP as the primary site of infection may not benefit from empirical use of CAZ/AVI treatment. The 30-day mortality was significantly associated with a history of transplantation and a higher pSOFA score from the first day of CAZ/AVI therapy, but the significance was absent in the 14-day mortality analysis. These inconsistent results may reflect that the original features have varying impacts over time.

Regarding AEs, a Phase 1 study reported that 18.8% of the single dose CAZ/AVI infusion led to mild to moderate AEs in children, mostly gastrointestinal symptoms and one case of sinus tachycardia.[48] A phase 2 trial of children with cIAI reported that 10.4% of the CAZ/AVI group had AEs possibly related to the drug, which included nausea, vomiting, dizziness, diarrhea, rash, dermatitis diaper, and one case of severe psychiatric disorder – anxiety; hypokalemia occurred in 2 of 61 patients receiving a combination of CAZ/AVI and metronidazole and was considered a treatment-emergent AE.[32] In our study, hypokalemia was one of the most common AEs, and in Patient 11, it was considered a probable severe reaction related to CAZ/AVI, which highlights the importance of being cautious during subsequent applications. Nephrotoxicity and seizure were considered unrelated to CAZ/AVI. However, the natural history of underlying conditions, such as chemotherapies,

comorbidities, and the concomitant use of other therapies for the vast majority of our patients, may lead to nonspecific laboratory changes and clinical symptoms indistinguishable from adverse drug reactions. Overall, CAZ/AVI is generally safe for children, and the majority of side effects are nonserious.[22,34,35,37,40]

The number of case matches was too small to meet the demand of conditional logistic regression to adjust for covariates. Well-designed, comparable, multicenter studies, or prospective randomized controlled trials are needed to better define the role of CAZ/AVI compared with other strategies such as a higher dose of meropenem therapy in immunosuppressed pediatric population with severe infection.

This study had some limitations. First, it is a retrospective, single-center observational study and therefore, bias existed in the interpretation of the results. The statistical analysis was exploratory, and the causal relationship needs to be further confirmed through prospective multicenter studies. Second, the phenotype or genotype of carbapenemase enzymes were not routinely detected in the past in our hospital until recently. Finally, the effect of previous antibiotics with different types and durations before the onset of CAZ/AVI, nonuniversalization of metagenome next-generation sequencing, and uncontrolled potential infection of other pathogens may also limit the analysis. Despite these limitations, our study provides real-world evidence for the efficacy and safety of CAZ/AVI in children with immunocompromised states.

Conclusions

CAZ/AVI could be used as a salvage therapeutic choice for immunosuppressed children with GNB recovered. We provided supportive experience in CAZ/AVI treatment of CRKP- or CRPA-related SSSI after careful evaluation. Caution should be taken when CAZ/AVI is applied to immunosuppressed children with severe conditions without GNB recovery or those children with HAP as the primary site of infection.

Key Messages

1. The clinical response rate of CAZ/AVI therapy for immunosuppressed children with sepsis was significantly higher in the GNB recovered group than in the group without GNB recovery ($P = 0.047$).
2. The 14-day and 30-day mortality of these patients were significantly correlated with the absence of confirmed GNB pathogens ($P = 0.004$ and 0.024, respectively) and hospital-acquired pneumonia as the primary site of infection (compared with the skin and skin structure infection group, $P = 0.001$ and 0.006, respectively).

Data Sharing Statement

All datasets used during the current study are available from the corresponding author upon reasonable request.

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Disclosure

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