REALITY DATA ON THE USE AND EFFECTIVENESS OF CEFTAZIDIME - AVIBACTAM

Dao Nguyen Van[1], Hai Duong Thanh[1]

Ceftazidime - avibactam (CAZ-AVI), a novel cephalosporin, has proven activity against multidrug-resistant Enterobacterales and P. aeruginosa, and it has only been used in Vietnam in recent years.

Objectives: This study aimed to describe the usage pattern and treatment effectiveness of CAZ-AVI.

Subjects and methods: A retrospective observational study was conducted at Vinmec Times City International Hospital. Adult patients treated with CAZ-AVI for more than 48 hours from September 2021 to June 2023 were enrolled. Data on clinical characteristics, microbiology, and antibiotic regimens were collected, and outcomes such as microbiological and clinical effectiveness were analyzed.

Results: A total of 61 patients were included, with an average age of 64.9 years, and 78.7% were male. All patients had at least one risk factor for multidrug-resistant Gram-negative bacteria. The most common infections were pneumonia (54%), urinary tract infections (20%), and abdominal infections (15%). Septic shock occurred in 16% of patients. Out of 61 patients, 39 (63.9%) had positive culture, yielding a total of 51 isolates, primarily Klebsiella pneumoniae (45.1%) and Pseudomonas aeruginosa (21.5%). Carbapenem and CAZ-AVI resistance rates among Gram-negative bacteria were 86.7% and 48.8%, respectively. Among the 36 carbapenem-resistant strains tested for sensitivity to CAZ-AVI, the resistance rate was 58.3%.

CAZ-AVI was used empirically in 37.7% of cases, and combination therapy was employed in 65.6% of patients to treat multi drug resistant isolates. The most commonly used antibiotics in combination therapy were aminoglycosides, tigecycline, fluoroquinolones, and colistin. The average duration of treatment was 10.7 ± 5.2 days.

Overall, microbiological cure was achieved in 38.5% of cases, while 43.6% experienced microbiological failure. Clinical improvement was observed in 77% of patients, and the 30-day mortality rate was 16.4%. There were no significant differences in microbiological or clinical outcomes between patients with ceftazidime-avibactam-resistant and -sensitive isolates.

Conclusions: This study provides important real-world evidence on the use and effectiveness of CAZ-AVI in treating infections caused by multidrug-resistant Gram-negative bacteria. Despite high resistance rates, the drug showed promising clinical improvement, though microbiological failure remains a concern.

Keywords: Ceftazidim-avibactam, multidrug-resistant, gram-negative, infection, real-world evidence.

INTRODUCTION

Ceftazidime-avibactam (CAZ-AVI) is a combination of a third-generation cephalosporin ceftazidime and a novel, non-β-lactam β-lactamase inhibitor avibactam. Avibactam binds reversibly to β-lactamases, efficiently inactivating β-lactamase enzymes and preventing the hydrolysis of ceftazidime by broad-spectrum beta-lactamase enzymes, including ESBLs, carbapenemases (KPC and OXA-48), and AmpC. As a result, the drug is effective against multi-drug resistant

(1) Vinmec Times City International Hopspital

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Responsibility for the scientific content of the article: *Hai Duong Thanh, Vinmec Times City International Hospital*

Tel: 0983961510. Email: phar.duonghai@gmail.com

Enterobacterales and *P. aeruginosa*, including carbapenems resistant isolates. The drug is reserved for severe infections caused by multi-drug resistant bacteria that do not respond to standard treatment. This study was conducted to investigate reality data on the use and treatment effectiveness of CAZ-AVI.

SUBJECTS AND METHODS

Study Population: Adult patients treated with CAZ-AVI for more than 48 hours between September 2021 and June 2023 were included in the study.

Study design: A retrospective observational study was conducted at Vinmec Times City International Hospital. Data were collected from the time of hospital admission until discharge through the abstraction of hospital medical records.

Data collection: Collected data included patient characteristics, clinical and microbiological characteristics of the infection, antibiotic regimens and treatment outcomes. Treatment outcomes was evaluated in terms of both microbiological and clinical cure. Microbiological cure was defined as the absence of the initial pathogen in cultures obtained after 7 days of treatment and continuing until the end of the treatment course. Microbiological failure was defined as the isolation of the same pathogen at least 7 days after the initiation of CAZ-AVI treatment.

Clinical outcome is assessed on day 7, at the end of the treatment course, and for 30-day mortality. Clinical outcomes are independently evaluated by a clinician specializing in intensive care. Clinical improvement is defined as resolution of signs and symptoms of infection, hemodynamic stability, no need for vasopressors, decrease in infection markers (CRP, PCT, blood count). Clinical failure is defined as clinical worsening of signs and symptoms of infections or requiring escalation of antibiotics.

Cases with insufficient information (due to missing clinical notes, missing laboratory results, transfer to another facility) are categorized as unable to be evaluated.

Data analysis: Descriptive statistics were performed using SPSS Statistics 27. Continuous variables were summarized using the number of observations, mean, standard deviation (SD), median, and range, as appropriate. Categorical data were presented as frequency counts and percentages.

RESULTS

A total of 61 patients were enrolled in the study, predominantly male. All patients had at least one risk factor for infection with multi-drug resistant Gram-negative bacteria, 100% had received intravenous antibiotics within the 90 days prior to enrollment, and 86.9% had previously used carbapenem.

Table 1. The common characteristics of the patients

Characteristic	Mean ± SD	Median, IQR	Frequency (%, N = 61)
Male (n, %) (N = 61)	64.9 ± 21.9		
Age (years) (N = 61)	85.2 ± 40.2		
GFR (ml/min/1.73 m²) (N = 61)	15.9 ± 4.5		
APACHE II Score (N = 30)		3 (2 - 5)	
SOFA Score (N = 51)	5.6 ± 2.8		
Charlson Score (N = 61)			
Comorbidities			
Diabetes			18 (29.5%)
Heart Failure			6 (9.8%)
Chronic Kidney Disease			6 (9.8%)
Chronic Liver Disease			6 (9.8%)

Characteristic	Mean ± SD	Median, IQR	Frequency (%, N = 61)
COPD			9 (14.8%)
Malignancy			29 (47.5%)
Type of infection			
Septic shock			10 (16%)
Pneumonia			33 (54%)
Bloodstream			17 (28%)
Abdominal Infection			9 (15%)
Urinary Tract Infection			12 (20%)
Skin and Soft Tissue Infection			6 (10%)
Febrile Neutropenia			5 (8.2%)
Risk Factors for Multi-drug resistant Bacteria			
Intravenous Antibiotics within 90 days			61 (100%)
Carbapenem Use within 90 days			53 (86.9%)
Previous ICU Admission			39 (63.9%)
Length of Hospital Stay > 30 days			48 (78.7%)
History of Isolation of Multi drug Resistant Bacteria			40 (65.6%)
Hemodialysis			9 (14.8%)
Mechanical Ventilation			22 (36.1%)
Length of Hospital Stay (days)		31 (16 - 50,7)	
Length of ICU Stay (days)		19 (10 - 39)	

Remarks: All 61 patients had microbiological culture. Among them, 47 patients (77%) had blood cultures, while 32 patients (52.4%) had lower respiratory tract samples, followed by urine and abdominal drainage samples.

A total of 39 patients (63.9%) had positive cultures, with 12 patients (19.6%) having two or more isolates. In total, 51 isolates were identified, of which 43 were tested for susceptibility to CAZ-AVI. The frequency of isolates and their resistance to carbapenem and CAZ-AVI are presented in Table 2.

Table 2. The frequency of isolated bacterial species and the level of antibiotic resistance

Bacteria	Frequency (%, N = 51)	Resistance rate
Klebsiella pneumoniae	23 (45.1%)	Carbapenem: 22/23 CAZ-AVI: 14/21
Enterobacterales khác	8 (15.6%)	Carbapenem: 5/8 CAZ-AVI: 1/8
Pseudomonas aeruginosa	11 (21.5%)	Carbapenem: 9/11 CAZ-AVI: 4/10

Bacteria	Frequency (%, N = 51)	Resistance rate
Stenotrophomonas maltophilia	4 (7.8%)	
Acinetobacter baumanii	3 (5.9%)	Carbapenem: 3/3 CAZ-AVI: 1/3
Others	2 (3.9%)	

Remarks: *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were the two most commonly isolated species in this study. The carbapenem resistance rate among the tested Gram-negative isolates was 86.7% (39/45), accouting for to 63.9% of the total patient population. The resistance rate to CAZ-AVI among the tested isolates was 48.8% (21/43), accounting for 33.3% of all patients.

The carbapenem resistance rates for *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were 95.6% (22/23) and 81.8% (9/11), respectively. The resistance rates to CAZ-AVI for *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were 63.6% (14/21) and 40.0% (4/10), respectively. Among the 36 carbapenem-resistant isolates, the resistance rate was 58.3% (21/36).

CAZ-AVI was used in the initial empirical treatment regimen for 23 patients (37.7%), of whom 17 (74%) received combination therapy, including metronidazole for anaerobic coverage and vancomycin for MRSA coverage. Only 6 patients (26%) were treated with combination therapy specifically targeting multi-drug resistant Gram-negative bacteria. The use of monotherapy in other patients was primarily due to a lack of response to carbapenem or had a history of infection with carbapenem-resistant pathogens.

A total of 38 patients (62.3%) received targeted therapy. Among these, 21 patients (55%) had isolates resistant to CAZ-AVI. Within this group, CAZ-AVI was used as monotherapy in 15 patients, including 12 patients with CAZ-AVI resistant isolates, due to the absence of susceptibility testing data at the time of treatment initiation.

Commonly used in combination with CAZ-AVI for resistant Gram-negative infections included aminoglycosides, tigecycline, and fluoroquinolones. Colistin in combination only for the treatment of *Acinetobacter baumanii*. Details are presented in Table 3.

Table 3. The characteristics of CAZ-AVI (ceftazidim-avibactam) use in the study

Characteristics	Frequency (%, N = 61)
Empirical treatment	23 (37.7%)
Targeted treatment	38 (62.3%)
Monotherapy regimen	21 (34.4%)
Combination therapy regimen	40 (65.6%)
Combination therapy for Gram-negative bacteria	24 (39.3%)
Types of antibiotics used in combination: Aminoglycoside Tigecycline Fluoroquinolon Colistin Others (sulbactam, cotrimoxazole, fosfomycin)	 9 6 5 3 7
Total duration of antibiotic use (mean ± SD), days	10.7 ± 5.2

Outcomes: Only 31 patients had adequate microbiological results before and during treatment. Among the total of 39 patients with positive culture, microbiological cure and failure rates were observed at 38.4% and 41.1%, respectively.

A total of 58 out of 61 patients were evaluated for clinical response, with 77% showing improvement by the end of treatment. The 30-day mortality rate in the study was 16.4%.

There were no differences in microbiological and clinical response between the CAZ-AVI - resistant and susceptible group (p = 0.322 and 0.395, respectively). Table 4.

Table 4. The treatment outcomes of the patients in the study

Microbiological efficacy	Frequency (%, N = 39)
Cure	15 (38.4%)
Failure	16 (41.1%)
Undetermined	8 (20.5%)
Clinical outcome	Frequency (%, N = 61)
Response on day 7 Improvement Failure Undetermined	 44 (72.1%) 12 (19.7%) 5 (8.2%)
End of treatment Improvement Failure Undetermined	 47 (77%) 11 (18%) 3 (5%)
30-day mortality (N = 61)	10 (16.4%)

DISCUSSIONS

This observational retrospective study provides real-world clinical data on infected patients who received ceftazidime-avibactam for at least 48 hours. The majority of patients were male, elderly. All patients in the study were at high risk for multidrug-resistant bacteria due to a history of extensive broad-spectrum antibiotic use, including carbapenems, and prolonged hospital stays. These factors influenced the selection of CAZ-AVI for treatment. Patients had a significant comorbidity burden, with a mean Charlson score of 5.6 ± 2.8, and a substantial proportion had conditions associated with immune deficiency, such as hematological malignancies. This further complicated treatment.

Among the patients who received CAZ-AVI, 63.9% had positive culture, which is significantly lower than the 91.5% reported in the EZTEAM study across 11 countries in Europe and Latin America6. The predominant isolate was Klebsiella pneumoniae (45.1%), followed by *Pseudomonas aeruginosa* (21.5%).

Notably, the rate of carbapenem-resistant Gram-negative bacteria was very high, with 83.7% of isolates being resistant. CAZ-AVI is recommended for treating these challenging pathogens. The carbapenem resistance rates were similar to data from the United States, European countries, and Spain, ranging from 57.1% to 89.9%[1,2,6]. However, the resistance rates of CAZ-AVI for *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* reached 63.6% and 40.0%, respectively, significantly higher than the 7.8% observed in the EZTEAM study[6].

In this study, CAZ-AVI was primarily selected after the isolation of multidrug-resistant Gram-negative bacteria (80.8% carbapenem-resistant). It was also used to treat CAZ-AVI-resistant isolates due to a lack of available appropriate agents, and susceptibility testing for CAZ-AVI was not conducted at the time of treatment. CAZ-AVI was employed for empirical treatment in 37.7% of patients, indicating that it was selected based on the patients' resistance risk factors rather than on susceptibility results. Among the 62.3% of patients receiving targeted treatment, 55% had isolated

bacteria that were resistant to CAZ-AVI, primarily due to the lack of susceptibility results and effective alternatives. These findings highlight the critical need for timely antibiotic susceptibility testing and emphasize the urgent challenges of antibiotic resistance and the shortage of clinically effective antibiotics.

In this study, 39.3% of patients received combination regimens to treat multidrug-resistant Gram-negative infections. Common combinations included aminoglycosides, tigecycline, fluoroquinolones, and colistin. This choice of combination antibiotics is similar to real-world data from a study by Jorgensen SCJ and colleagues in the United States[3]. However, clinical efficacy evidence for these combinations remains limited.

The study found that 77% of patients showed clinical improvement by the end of treatment, and 72.1% improved after seven days. These results demonstrate the clinical efficacy of CAZ-AVI, especially in the context of patients at high risk for multidrug-resistant Gram-negative infections. When compared to randomized controlled trials such as RECAPTURE and REPROVE, the cure rates were 68.8% for hospital-acquired pneumonia and 90.3% for complicated urinary tract infections, respectively[4,7]. Unlike these two trials, most patients in our study had a high prevalence of carbapenem-resistant bacteria, complicating treatment and resulting in a markedly lower cure rate. These results are consistent with findings from Shields et al., where the cure rate was only 59%. This implies that carbapenem resistance may also influence the efficacy of CAZ-AVI.

Among the 39 patients with isolated bacteria, the microbiological cure rate was only 38.5%, which is relatively lower than expected. The high rate of microbiological failure can be attributed to the significant levels of resistance observed in the study, including a notable proportion of resistance to CAZ-AVI. The 30-day mortality rate for patients in the study was 16.4%, similar to the 17.2% reported by Jorgensen SCJ and colleagues[3].

Our study did not find any differences in microbiological and clinical efficacy between patients infected with CAZ-AVI-susceptible and-resistant isolates. These results may partly reflect the challenges in treating multidrug-resistant bacteria, as even patients with infections caused by susceptible pathogens did not achieve significant treatment outcomes. However, further analysis of data, such as combination regimens and source control, is needed to clarify this issue.

Limitations of the study: While this study provides valuable real-world clinical treatment data, the retrospective data collection may introduce inaccuracies and limit the information. The small sample size restricts the ability to detect significant differences between subgroups categorized by infection type or antibiotic combination regimens. Furthermore, the assessment of clinical efficacy by treating physicians may be subject to personal biases. The lack of a control group comparing CAZ-AVI with other antibiotic therapies limits the ability to draw definitive conclusions regarding its effectiveness.

CONCLUSIONS

This study provides important information on the current use and effectiveness of ceftazidime-avibactam in treating patients with suspected or confirmed infections caused by multidrug-resistant Gram-negative bacteria, particularly carbapenem-resistant isolates. The findings indicate that CAZ-AVI is effective in the clinical management of these infections. To optimize its use in clinical settings, it is essential to develop specific guidelines for antibiotic stewardship. Furthermore, additional research with larger sample sizes is needed to clarify the role of CAZ-AVI in various infections and pathogens, facilitating the selection of appropriate antibiotic therapies.

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