Efficacy of Ceftazidime-Avibactam on the Carbapenem Resistant Strains of Enterobacteriaceae and Pseudomonas Aeruginosa - a Retrospective Study

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KEYWORDS

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ABSTRACT

Background: Carbapenem-resistant Enterobacterales (CRE) and Pseudomonas aeruginosa (CRPA) are a big challenge in clinical practice because of restricted choices in treatment. Ceftazidime-avibactam (CZA) is considered a possible alternative, but its effectiveness depends on the mechanism of resistance. The susceptibility of carbapenem-resistant isolates to CZA is assessed in this study in a tertiary care hospital.

Methods: This was a retrospective observational study done between October 2023 and March 2024 in a tertiary care facility at Jamshedpur, India. Data were retrieved from the microbiology laboratory with emphasis on culture and antimicrobial resistance patterns of carbapenem-resistant Enterobacterales and P. aeruginosa. Antimicrobial susceptibility testing (AST) was done by Vitek2 compact system, and susceptibility to CZA was determined following CLSI guidelines (2023-2024).

Results: Out of 107 carbapenem-resistant isolates, Klebsiella pneumoniae (n=69, 63.89%) was the most common, followed by Escherichia coli (n=17, 15.74%) and P. aeruginosa (n=21, 19.44%). In total, 22 isolates (20.56%) were sensitive to CZA, with Klebsiella pneumoniae having the highest susceptibility (30.43%) and E. coli having minimal susceptibility (5.88%). All P. aeruginosa isolates were resistant to CZA.

Conclusion: CZA is moderately effective against CRE, especially Klebsiella pneumoniae, but not against CRPA. The results emphasize the importance of continued surveillance, antimicrobial stewardship, and novel treatment approaches against carbapenem-resistant infections. Research into combination therapies and new agents is essential to combat emerging resistance.

I. INTRODUCTION

Carbapenem-resistant Enterobacteriaceae (CRE) and Pseudomonas aeruginosa are a topic of serious concern in current healthcare, causing disproportionately high morbidity and mortality, particularly in critically ill and immunocompromised patients. Emergence and spread of these multidrug-resistant organisms have been driven, largely, by excess and unwarranted use of antibiotics, rendering carbapenems—the drugs of last resort—ineffective in most cases (Alraddadi et al., 2019) [1]. Increasing endemicity of these resistant organisms has emphasized the need for developing alternative treatment strategies to treat CRE- and carbapenem-resistant Pseudomonas aeruginosa (CRPA)-caused severe infections.

Ceftazidime-avibactam (CAZ-AVI), a novel β-lactam/β-lactamase inhibitor combination, is a long-awaited agent to treat infections caused by these resistant organisms. Ceftazidime is a third-generation cephalosporin with activity against Gram-negative bacteria, while avibactam is a non-β-lactam β-lactamase inhibitor that effectively rescues ceftazidime's activity against class A, C, and some class D β-lactamases, such as Klebsiella pneumoniae carbapenemase (KPC) and some oxacillin uses (OXA-48-like) (Krapp et al., 2017) [2]. This novel mechanism of action has rendered CAZ-AVI an interesting therapeutic option to treat CRE- and CRPA-caused infections, particularly where carbapenems have become ineffective.

Different studies have shown the efficacy of CAZ-AVI as a treatment regimen for CRE infection, including bloodstream infection, pneumonia, urinary tract infection, and complicated intra-abdominal infections (Tsolaki et al., 2020; Hu et al., 2024) [5, 6]. Clinical trials and retrospective studies have shown improved clinical outcomes and lower mortality rates among patients treated with CAZ-AVI compared to standard therapies like polymyxins and colistin, which are known to induce severe nephrotoxicity (Chen et al., 2024) [8]. CAZ-AVI has also been used as salvage therapy in critically ill patients with severe infection, with excellent pathogen clearance and patient survival rates (Temkin et al., 2017; Tumbarello et al., 2019) [4, 7].

Despite being effective, resistance to CAZ-AVI has been reported, most significantly with KPC-producing Klebsiella pneumoniae isolates. Genomic studies have reported different mechanisms of resistance to CAZ-AVI, including bla_KPC-2 gene mutations and outer membrane porin changes, leading to reduced susceptibility to CAZ-AVI (Giddins et al., 2018) [3]. Development of resistance emphasizes the importance of continued monitoring and judicious use of CAZ-AVI to preserve its efficacy against severe infection caused by CRE and CRPA.

The prospective retrospective study to be conducted at the current time will evaluate the efficacy of CAZ-AVI in the treatment of carbapenem-resistant Enterobacteriaceae and Pseudomonas aeruginosa infections. Through clinical outcomes evaluation, microbiological response, and resistance patterns, the study aims to illuminate the real-world efficacy of CAZ-AVI and its role in the treatment of multidrug-resistant Gram-negative infections.

II. METHODS

Study Design and Setting

This was a single-center, retrospective observational study conducted at TATA Main Hospital, Jamshedpur, Jharkhand, India. The study duration was from October 2023 to March 2024, during which clinical microbiology data were examined to determine the effectiveness of ceftazidime-avibactam (CZA) against carbapenem-resistant Enterobacterales (CRE) and carbapenem-resistant Pseudomonas aeruginosa (CRPA).

Data Collection and Study Population

The study used microbiological culture data and antimicrobial susceptibility test results, ensuring that no patient identifiers were present to ensure confidentiality and data privacy. Bacterial isolates included in the study were isolated from different clinical specimens like blood, urine, pus, sputum, endotracheal secretions, bronchoalveolar lavage (BAL), and other body fluids. Only Gram-negative bacterial isolates of the Enterobacterales family and Pseudomonas aeruginosa that were carbapenem-resistant (imipenem and/or meropenem) were included. Duplicate isolates from the same patient with the same resistance pattern were not included in the study to ensure data integrity. Carbapenem-resistant Acinetobacter baumannii isolates were also not included in the analysis.

Microbiological Analysis

The bacterial isolates were processed in the microbiology laboratory according to standard operating procedures. Identification and antimicrobial susceptibility testing (AST) were conducted using the automated Vitek2 compact system (Biomerieux, India). The AST profile of Enterobacterales was determined using the n-405 AST card, while the n-406 AST card was used for Pseudomonas aeruginosa. Isolates with imipenem or meropenem resistance, or both, were further tested for susceptibility to ceftazidime-avibactam using the n-407 AST card. The susceptibility results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines for 2023 and 2024.

Ethical Considerations

Since this study was microbiological data-based and not patient-related data, ethical approval was waived. Sufficient precautions were taken to protect against data confidentiality, and all the study procedures complied with institutional and national standards for ethics on research involving microbiological and epidemiological data.

This approach facilitated thorough assessment of carbapenem-resistant Enterobacterales and Pseudomonas aeruginosa antimicrobial susceptibility patterns, which provided valuable insights on the clinical value of ceftazidime-avibactam in a real-life hospital environment.

III. RESULTS

Microbiological Profile of Carbapenem-Resistant Isolates

A total of 107 carbapenem-resistant Gram-negative bacterial isolates were studied over the study period. Of these, Klebsiella spp. were the most common isolates (n = 69), followed by Pseudomonas aeruginosa (n = 21) and Escherichia coli (n = 17). The isolate distribution is depicted in Table 1 and Figure 1.

Susceptibility to Ceftazidime-Avibactam

Among the 107 carbapenem-resistant isolates, only 22 (20.56%) were sensitive to ceftazidime-avibactam. The maximum rate of susceptibility was seen in Klebsiella spp. (30.43%, 21/69), followed by E. coli (5.88%, 1/17), whereas all Pseudomonas aeruginosa isolates (0/21) were resistant to ceftazidime-avibactam. The susceptibility pattern is given in detail in Table 2 and Figure 2.

Antimicrobial Susceptibility of Pseudomonas aeruginosa

All 21 Pseudomonas aeruginosa isolates were resistant to both meropenem and ceftazidime-avibactam but susceptible to colistin. The resistance pattern of Pseudomonas aeruginosa isolates is explained in Table 3.

Table 1: Distribution of Carbapenem-Resistant Bacterial Isolates

Organism	Number of Isolates (n)	Percentage (%)
Klebsiella spp.	69	64.48
Pseudomonas aeruginosa	21	19.62
Escherichia coli	17	15.88
Total	107	100

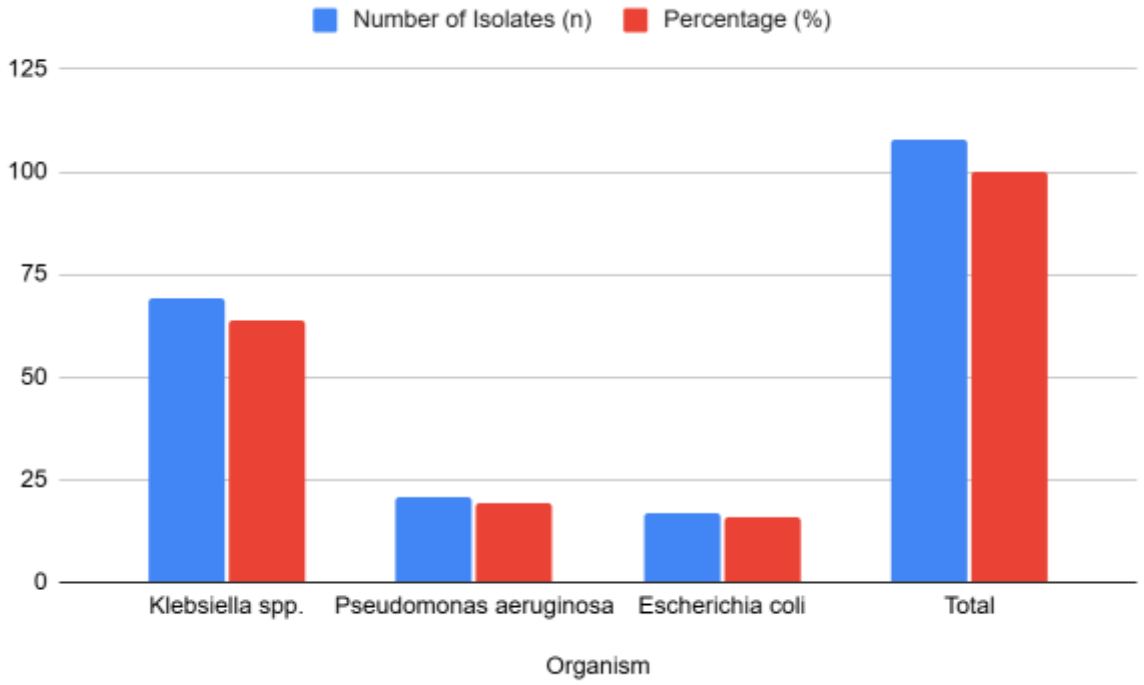

Figure 1: Bar graph representing the distribution of carbapenem-resistant isolates

Table 2: Susceptibility of Carbapenem-Resistant Isolates to Ceftazidime-Avibactam

Organism	Total Isolates (n)	Ceftazidime-Avibactam Sensitive (n)	Sensitivity Rate (%)
Klebsiella spp.	69	21	30.43
Pseudomonas aeruginosa	21	0	0.00

Escherichia coli	17	1	5.88
Total	107	22	20.56

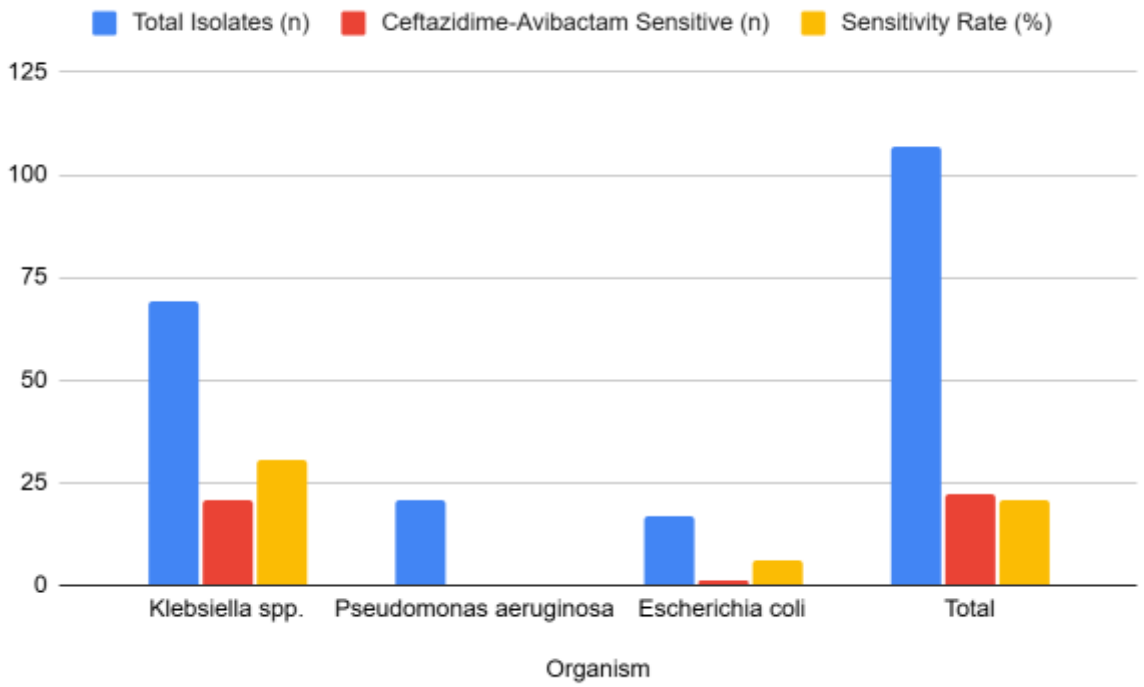

Figure 2: Bar chart depicting ceftazidime-avibactam susceptibility among carbapenem-resistant isolates

Table 3: Antimicrobial Susceptibility Pattern of Pseudomonas aeruginosa Isolates

Organism	Colistin (CS)	Ceftazidime-Avibactam (CZA)	Meropenem (MEM)
Pseudomonas aeruginosa (MDRO)	I	R	R
Pseudomonas aeruginosa (MDRO)	I	R	R
Pseudomonas aeruginosa (MDRO)	I	R	R
Pseudomonas aeruginosa (MDRO)	I	R	R
Pseudomonas aeruginosa (MDRO)	I	R	R

Pseudomonas aeruginosa (MDRO)	I	R	R
Pseudomonas aeruginosa (MDRO)	I	R	R
Pseudomonas aeruginosa (MDRO)	I	R	R
Pseudomonas aeruginosa (MDRO)	I	R	R
Pseudomonas aeruginosa (MDRO)	I	R	R

- ***I (Intermediate)***
- ***R (Resistant)***

The results reveal an alarming pattern of resistance in Pseudomonas aeruginosa since all the isolates were resistant to ceftazidime-avibactam. On the other hand, Klebsiella spp. was found to be most sensitive, which reflects its possible responsiveness to ceftazidime-avibactam treatment. The research emphasizes the need for ongoing antimicrobial monitoring and rational use of antibiotics to counteract the development of carbapenem resistance.

IV. DISCUSSION

The results of this study yield essential information on the effectiveness of ceftazidime-avibactam (CZA) against carbapenem-resistant Enterobacterales (CRE) and Pseudomonas aeruginosa (CRPA) in a tertiary care institution. The sensitivity rate to CZA was overall 20.56%, of which Klebsiella spp. was found to be the most susceptible (30.43%), followed by Escherichia coli (5.88%), while all isolates of Pseudomonas aeruginosa were found to be resistant. These findings indicate the limited but clinically significant action of CZA against CRE, but also its failure against CRPA.

The comparatively high sensitivity of Klebsiella spp. to CZA in this work is consistent with earlier observations, indicating that CZA is still a viable therapeutic agent against carbapenem-resistant Klebsiella pneumoniae (CRKP) infections. Castón et al. (2020) [9] found that CZA demonstrated excellent efficacy in the treatment of infections due to KPC-producing K. pneumoniae, with clinical efficacy depending on the severity of the infection and bacterial burden (Castón et al., 2020) [9]. Also, Lima et al. (2022) proved CZA effective against OXA-48-producing K. pneumoniae bacteremia, though mechanisms of resistance like porin mutations and efflux pumps might abate its effectiveness (Lima et al., 2022) [14]. The rate of susceptibility seen in the current study (30.43%) is similar to that reported by some earlier studies but less than others, which have reported CZA sensitivity rates of up to 70% in some clinical environments (Guimarães et al., 2019) [15]. Heterogeneity in rates of susceptibility can be due to differences in local patterns of antimicrobial resistance, local stewardship policies for antibiotics, and prevalence of certain carbapenemase enzymes.

The low susceptibility of E. coli to CZA (5.88%) reported in this research is alarming because CZA was deemed a plausible substitute for carbapenem-resistant E. coli infections treatment.

Prior work indicated that CZA effectiveness against CRE largely depends on the co-existence of carbapenemase enzymes like KPC, OXA-48, and NDM. A paper by Eren-Kutsoylu et al. (2024) indicated developing resistance to CZA among carbapenem-resistant K. pneumoniae prior to its clinical use, emphasizing the danger of prior resistance mechanisms (Eren-Kutsoylu et al., 2024) [10]. This reiterates the necessity for ongoing surveillance and molecular typing of the resistance determinants to maximize the use of CZA.

One of the notable results of this research is the total resistance of Pseudomonas aeruginosa against CZA. This concurs with previous research that has indicated poor activity of CZA against CRPA, especially those that produce metallo-beta-lactamases (MBLs) like NDM and VIM. Zhen et al. (2024) reported that CZA was of limited efficacy against CRPA in hematological patients with bacteremia, highlighting the necessity for alternative therapeutic approaches (Zhen et al., 2024) [12]. Also, van Duin et al. (2018) compared CZA with colistin in the treatment of CRE infections and established that though CZA was more effective in comparison to CRE, its effectiveness against CRPA was much lower (van Duin et al., 2018) [11]. This pattern of resistance can be attributed to the capacity of Pseudomonas aeruginosa to upregulate efflux pumps as well as modify porin channels, reducing beta-lactam–beta-lactamase inhibitor combinations' efficacy considerably.

Considering the suboptimal effectiveness of CZA against CRPA and the increasing resistance in Klebsiella pneumoniae, maximizing antimicrobial therapy with combination regimens and alternative drugs is essential. Ackley et al. (2020) contrasted the effectiveness of meropenem-vaborbactam (MVB) and CZA in treating CRE infections and concluded that MVB showed better outcomes in some patient groups (Ackley et al., 2020) [13]. These results indicate that although CZA is still a valuable agent for the treatment of CRE infections, its application should be based on antimicrobial susceptibility testing and alternative therapy consideration in the event of resistance.

The results of this research underscore the dynamic nature of antimicrobial resistance and the need for regional surveillance to inform empirical antibiotic therapy. The comparatively high resistance rate seen in CRPA isolates necessitates immediate action on antimicrobial stewardship and infection control practices to stem the rise of resistance. Additional molecular definition of resistance determinants, including whole-genome sequencing, might offer greater understanding of the underlying genetic mechanisms for CZA resistance. Future investigations should also evaluate combination regimens and new antimicrobial agents as a means to counter the increasingly serious threat posed by carbapenem resistance in Gram-negative bacteria.

V. CONCLUSION

The results of the current research highlight the minimal activity of ceftazidime-avibactam (CZA) against carbapenem-resistant Pseudomonas aeruginosa (CRPA) with strong moderate activity against carbapenem-resistant Enterobacterales (CRE), such as Klebsiella pneumoniae. As its general sensitivity rate stands at 20.56%, CZA is still an available drug to use against some CRE infections, yet the lack of effect on CRPA calls for pressing urgency for novel treatment protocols. The total resistance seen in P. aeruginosa emphasizes the need for sustained monitoring, antimicrobial stewardship, and more investigation into combination regimens or new agents. Due to the emerging resistance trends, directed antimicrobial susceptibility testing should inform clinical practice to maximize treatment results and avoid the increasing threat of multidrug-resistant Gram-negative disease.

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