ORIGINAL ARTICLE

The Comparative Efficacy of Ceftazidime–Avibactam with or without Aztreonam vs Polymyxins for Carbapenem-resistant Enterobacteriaceae Infections: A Prospective Observational Cohort Study

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Received on: 02 September 2023; *Accepted on:* 07 October 2023; *Published on:* 30 November 2023

Abstract

Background: Carbapenem-resistant enterobacteriaceae (CRE) is associated with high mortality in critically ill patients, with limited treatment options. This study aims to compare clinical response, microbiological response, and mortality in patients treated with ceftazidime–avibactam with or without aztreonam (CAZ–AVI + AZT) and colistin or polymyxin B (polymyxins) in CRE infections.

Materials and methods: This single-center prospective observational study included adult patients with CRE infections treated with CAZ–AVI+AZT or polymyxins between January 2022 and December 2022 at a Tertiary Care Medical Center in India. The clinical response, microbiological response, and mortality were compared between the two groups using a Cox multivariate regression model adjusted for the baseline SOFA score and comorbidities.

Results: A total of 89 patients were enrolled, with 59 (66%) patients receiving CAZ–AVI + AZT and 30 receiving polymyxins. Baseline demographics and clinical characteristics were similar between the two groups. The Cox multivariate regression analysis showed a statistically significant difference in clinical failure on day 14 with the CAZ–AVI + AZT group vs polymyxins (HR = 0.78, 95% CI 0.63–0.95, $p = 0.018$). There was no difference in microbiological failure (HR = 1.08, 95% CI 0.66–1.77, $p = 0.76$), microbiological relapse (HR = 0.75, 95% CI 0.36–3.02, $p = 0.62$), and hospital mortality (HR = 1.04, 95% CI 0.75–1.43, $p = 0.796$) between the two groups.

Conclusion: Treatment with ceftazidime–avibactam with or without aztreonam for CRE infections associated with a better clinical response compared with polymyxins monotherapy but without any difference in microbiological response or mortality.

Keywords: Aztreonam, Carbapenem-resistant enterobacterales, Carbapenem-resistant enterobacteriaceae, Cohort study, Ceftazidime–avibactam, Colistin, Intensive care unit, Observational study, Polymyxin B, Prospective.

Indian Journal of Critical Care Medicine (2023): 10.5005/jp-journals-10071-24577

Highlights

- Ceftazidime–avibactam with or without aztreonam therapy associated with better clinical response at day 14.
- Ceftazidime–avibactam with or without aztreonam therapy is not associated with lower mortality than polymyxins.

Introduction

Carbapenem-resistant Enterobacteriaceae (CRE) refers to Enterobacterales that exhibit resistance to at least one of the carbapenem antibiotics, namely ertapenem, meropenem, doripenem, or imipenem, or that produce carbapenemase – an enzyme conferring resistance to carbapenem antibiotics.[1] The prevalence of CRE has risen in recent times due to the inappropriate use of antibiotics. These organisms are notorious for causing a wide array of nosocomial infections. Within this group of pathogens, antimicrobial resistance can stem from inherent characteristics or be acquired over time.[2] Infection with CRE strains has been associated with prolonged hospital stay, increased mortality rate, and elevated direct or indirect healthcare expenses.[3–5] Available treatment options for such infections are limited and include drugs like ceftazidime–avibactam, ceftolozane–tazobactam, meropenem–vaborbactam, imipenem–cilastatin–relebactam, plazomicin, eravacycline, and cefiderocol.[6,7] Although colistin has traditionally been a commonly used agent, ceftazidime–avibactam may emerge as a viable alternative to colistin.[8–12]

Avibactam, a non-β-lactam β-lactamase inhibitor, deactivates specific β-lactamases through a reversible covalent mechanism, safeguarding ceftazidime from degradation by certain β-lactamases, excluding metallo-beta-lactamases (MBLs). Notably, aztreonam

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How to cite this article: Vijayakumar M, Selvam V, Renuka MK, Rajagopalan RE. The Comparative Efficacy of Ceftazidime–Avibactam with or without Aztreonam vs Polymyxins for Carbapenem-resistant Enterobacteriaceae Infections: A Prospective Observational Cohort Study. Indian J Crit Care Med 2023;27(12):923–929.

Source of support: Nil

Conflict of interest: None

remains stable against MBLs and is being developed with the premise that it can evade MBLs, while avibactam protects against concurrently produced serine beta-lactamases.[8] The combination of aztreonam and avibactam shows promise in augmenting the antibacterial activity of beta-lactam agents. Given that the aztreonam/avibactam combination was unavailable during the study period, a combination of ceftazidime–avibactam with aztreonam (CAZ–AVI + AZT) was employed. Although the majority of studies conducted in Western populations have focused on *Klebsiella pneumoniaee* carbapenemase (KPC)-producing CRE strains as the predominant pathogens, Indian populations have exhibited a prevalence of New Delhi metallo-beta-lactamase (*NDM*) and oxacillinase (*OXA-48*) producing organisms.[12,13]

Comparatively, fewer studies have explored the effectiveness of CAZ–AVI + AZT vs colistin or polymyxin for treating CRE infections. However, the existing literature on this subject is notably limited and predominantly comprises retrospective studies.[14] This study aims to assess the efficacy of CAZ–AVI + AZT in comparison to polymyxins for the treatment of CRE-induced infections and their subsequent outcomes.

Materials and Methods

This prospective single-center cohort study was conducted from January 2022 to December 2022. The study enrolled patients who tested positive for CRE through culture and had received either ceftazidime–avibactam with or without aztreonam or polymyxins as part of their treatment regimen. Patients with polymicrobial blood cultures, those on combination therapy involving ceftazidime–avibactam with or without aztreonam or polymyxins, and those who passed away within 48 hours of initiating antibiotic therapy were excluded from the study. Ethical approval for the study was obtained from the Institutional Ethics Committee before commencement, and the trial was registered with CTRI under the Trial Acknowledgement Number REF/2021/12/049884.

Microbiological Diagnostics

Appropriate cultures were collected from the suspected infection site. For blood isolates and other specimens, organisms were identified using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI ToF). The GeneXpert system, which employs PCR technology, was utilized to detect the presence of carbapenem-resistant genes (such as *NDM*, *OXA-48*, Imipenemase (IMP-1), and KPC) in samples that exhibited carbapenem resistance. Antimicrobial susceptibility testing was conducted using the VITEK 2 automated systems. Minimum inhibitory concentrations (MICs) were determined following ISO standards.[15] The interaction between CAZ–AVI and AZT was assessed through a double-disk sandwich diffusion method.[8]

Antibiotic Therapy

The antibiotic treatment regimen was determined by the attending physician, taking into consideration the results of culture sensitivity testing and the specific Carbapenemase gene present. Pre-emptive antibiotic therapy was started based on MALDI ToF and Xpert Carba-R report within 24–48 hours, and definitive therapy was started based on culture and sensitivity report within 48–72 hours. Within the CAZ–AVI + AZT treatment group, patients identified with the *OXA-48* gene were administered CAZ–AVI, while those found with the *NDM* gene received a combination of CAZ–AVI and AZT. The administration of CAZ–AVI involved 3-hour infusion every 8 hours, with a dosage of 2.5 grams (comprising 2 grams of ceftazidime and 500 milligrams of avibactam). Simultaneously, AZT was infused over 3 hours every 8 hours, at a dose of 2 grams. Dosages for CAZ–AVI and AZT were adjusted in patients with impaired renal function, determined by their creatinine clearance levels.[15,16]

In the subgroup of patients receiving polymyxins, those diagnosed with pneumoniae and bloodstream infections (BSI) were treated with polymyxin-B, while colistin was administered for urinary tract infections. Colistin dosing involved a 1-hour infusion, with a loading dose of 300 mg CBA followed by a maintenance dose of 300 mg CBA split into two doses. Dosage adjustments were made based on the patient's creatinine clearance. For polymyxin B, an infusion over 1 hour was performed, with a loading dose of 2.5 mg/kg, followed by a maintenance dose of 1.5 mg/kg administered in two divided doses every 12 hours for all patients.[17] The treatment duration was typically set at 7 days, although extensions were granted if clinically necessary as per the physician's judgment.

Patient demographic data, encompassing age, gender, underlying health conditions, the number of patients initially treated with pre-emptive antibiotics, therapy duration, the number of patients undergoing source control procedures, infection origin, microorganisms involved, and the specific carbapenemase genes present, were meticulously documented. Upon the initiation of antibiotics, the Charlson comorbidity index[18] and sequential organ failure assessment (SOFA) score were calculated on day 1, followed by subsequent calculations on days 3, 5, and 7. Patient follow-up was extended to 30 days to monitor discharges and in-hospital mortality since the onset of the infection. Furthermore, all blood cultures obtained during the 30-day antibiotic treatment period were recorded to assess microbiological treatment outcomes, failures, and potential relapses.

Outcome Variables

The primary study outcomes encompassed clinical success on day 14 and the microbiological response. Clinical success was determined by the patient's survival status, hemodynamic stability (systolic blood pressure >90 mm Hg without requiring vasopressor support), and an enhancement in SOFA score. Specifically, for a baseline SOFA score >3, a minimum 30% improvement in score was necessary, while for a SOFA score <3, a reduction of at least 1 point was required. Patients not meeting all these success criteria were categorized as experiencing clinical failure by day 14.

The microbiological response category encompassed both microbiological failure and microbiological relapse. Microbiological failure was characterized by the recurrence of bacteria phenotypically identical to the initial isolates on or after day 7. Microbiological relapse, on the other hand, involved the recurrence of bacteria phenotypically identical to the initial isolate after a previous negative culture within 30 days.

Secondary outcome measures included mortality rates at both the 14-day and 30-day. Other secondary outcome variables were recorded, such as the number of days free from mechanical ventilation, the duration of stay in the ICU and the hospital, days free from the use of vasopressors, and instances of complications arising from antibiotic treatment, including cases of renal failure. Renal failure was defined following KDIGO criteria, with assessment taking place 48 hours after the initiation of the study drug.

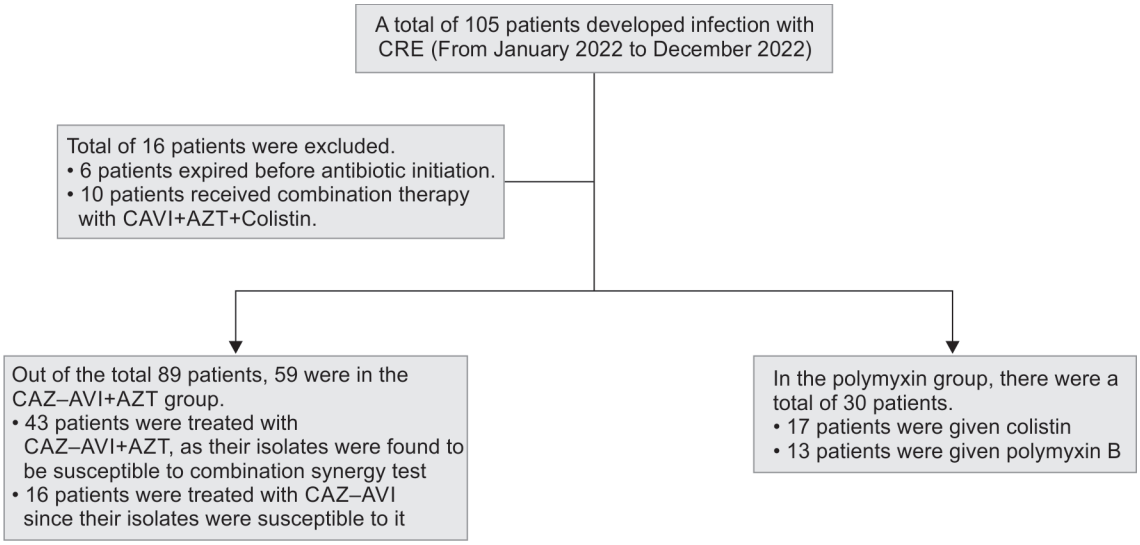


Fig. 1: STROBE chart

Statistical Analysis

All patients who met the inclusion criteria for the study's designated period were incorporated into the analysis. Categorical data were presented as absolute numbers alongside relative frequencies, and a comparison between treatment groups was conducted using either the Pearson Chi-square test or Fisher's exact test, depending on the scenario. Continuous variables were represented as mean and standard deviations or median and interquartile ranges (IQRs) based on the distribution of the data. These variables were subjected to comparison utilizing either the *t*-test or the Mann–Whitney *U*-test, as deemed appropriate for the situation. To ascertain crude and adjusted hazard ratios for mortality, a Cox multivariate regression model was employed. The model's adjustments encompassed the baseline SOFA score and prevailing comorbidities. Hazards ratios were computed, complete with confidence intervals, corresponding to diverse survival functions. To assess statistical significance, a nonparametric log-rank test was applied, with a significance level set at $p < 0.05$. All statistical analyses were executed using IBM SPSS software package version 23.0.

Results

Throughout the study duration, a total of 105 patients encountered infections caused by CRE. Among these, 6 patients who succumbed within 48 hours of initiating antibiotic treatment were excluded, along with an additional 10 patients who were administered a combination of CAZ–AVI+ AZT and colistin. Consequently, the study comprised 89 patients, out of which 59 individuals were treated with the CAZ AVI+ AZT regimen for either *OXA 48* or *NDM* infections, while the remaining 30 patients were assigned to the colistin antibiotic group. In the CAZ AVI+ AZT cohort, 43 patients were administered a combination of ceftazidime–avibactam with aztreonam to combat *NDM* infections, and 16 patients were exclusively administered ceftazidime avibactam to counter *OXA 48* organisms. In contrast, within the colistin group, 13 patients received polymyxin B, while 17 patients received colistin treatment (Fig. 1).

Descriptive Analysis

The demographic details of the study participants have been outlined in Table 1. Baseline demographic factors and clinical characteristics were found to be comparable between the two groups as depicted in Table 1. The average age of the cohort was 55.82 ± 15.47 years, with males constituting 66 individuals (74.2%) and medical patients accounting for 65 individuals (73%). Almost all patients received empiric antibiotics. Out of these, 44 patients (49.4%) received pre-emptive antibiotic treatment, while 16 patients (18%) underwent source control procedures. The initial SOFA score at the commencement of antibiotic therapy was comparable [(6 vs 9); $p = 0.09$]. The mean Charlson comorbidity index was nearly identical [(3.94 vs 3.07); $p = 0.83$]. There was no statistically significant distinction in the treatment duration [(8+/– 4 vs 8+/– 4); $p = 0.76$].

Among the 89 isolates, the prevailing genetic profile encountered in the cohort was *NDM*, identified in 70 cases (79%), among which 25 patients (27%) were found to harbor the *OXA-48* gene. Only the *NDM* gene was isolated in 52% of cases ($n = 45$). Additionally, 18 patients (20%) exhibited only the *OXA-48* gene, while 1 patient was isolated with IMP-1. Importantly, none of the patients were found to carry the VIM or KPC genes. *Klebsiella pneumoniaee* was the most frequently detected organism [66% ($n = 58$)], followed by *E. coli* [20% ($n = 18$)]. The majority of patients exhibited secondary bacteremia from an unidentified source [(37%), $n = 33$], as highlighted in Table 2 and Figure 2.

Outcome Analysis

The primary outcome measures encompassed clinical response and microbiological response. Notably, a statistically significant difference in clinical failure emerged on day 14 when comparing the CAZ AVI+ AZT group with the colistin group (HR = 0.78, 95% CI 0.63–0.95, $p = 0.018$), as depicted in Figure 3. However, no notable distinction was observed in terms of microbiological failure (HR = 1.08, 95% CI 0.66–1.77, $p = 0.76$) and microbiological relapse (HR = 0.75, 95% CI 0.36–3.02, $p = 0.62$). Also, there was no significant difference in other secondary outcomes like hospital mortality (HR = 1.04, 95% CI 0.75–1.43, $p = 0.796$), ventilator-free days (18 vs 18, $p = 0.98$), vasopressor-free days (20 vs 17, $p = 0.36$), ICU length of stay (12 vs 11.5, $p = 0.84$), hospital length of stay (18 vs 15, $p = 0.38$), and complications such as renal failure (13.6% vs 16.7%, $p = 0.695$) between the two groups (Table 3).

Table 1: Demographic data

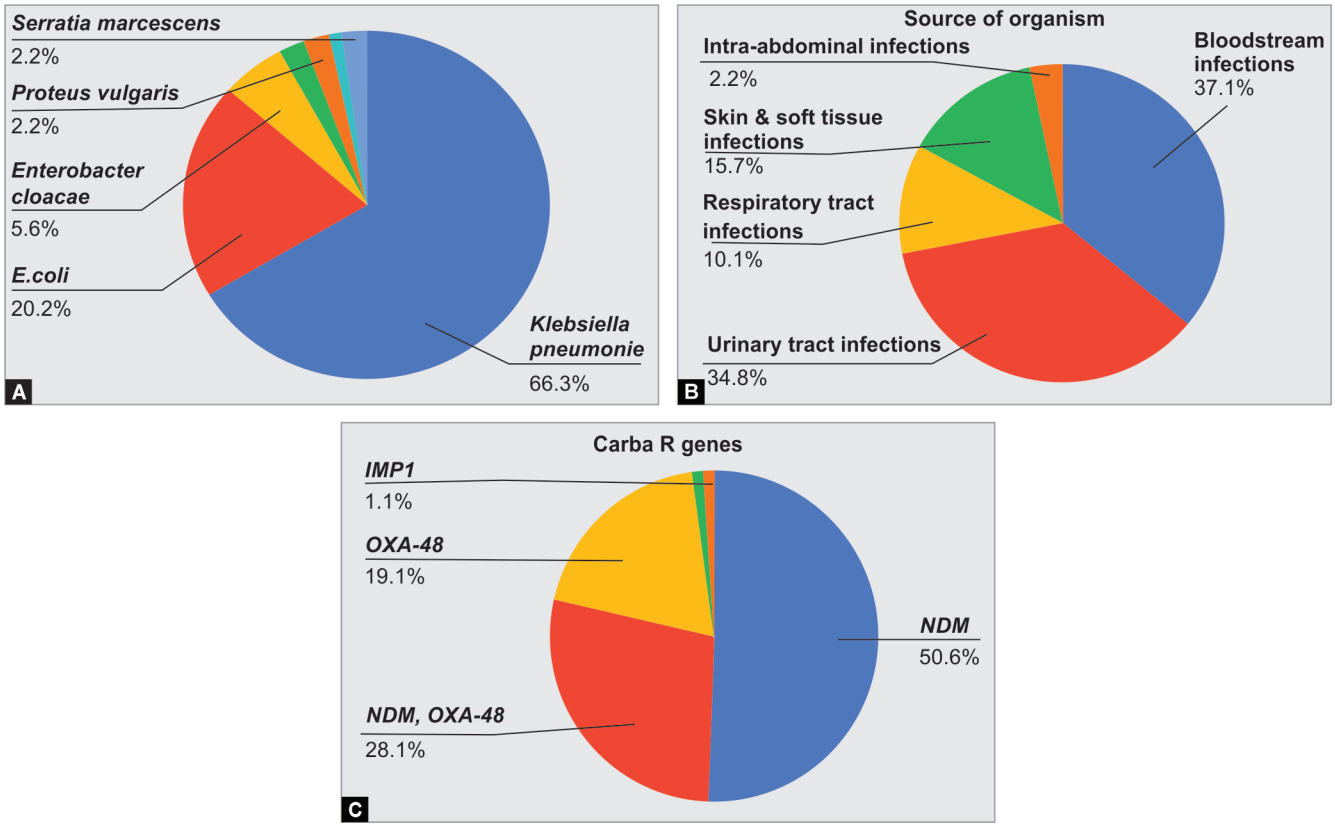
Characteristic	*Overall (N = 89)*	*CAZ–AVI ± AZT (N = 59)*	*Colistin group (N = 30)*	*p-value*
Age – year (mean ± SD)	55.82 ± 15.4	57.2 ± 15.6	53.2 ± 15.2	0.433
Sex – *n* (%)				
Male	66 (74.2%)	44 (74.6%)	22 (73.3%)	0.899
Female	23 (25.8%)	15 (25.4%)	8 (26.7%)	
Type of ICU				
Medical – *n* (%)	65 (73%)	41 (69.5%)	24 (80%)	0.291
Surgical – *n* (%)	24 (27%)	18 (30.5%)	6 (20%)	
Comorbidities – *n* (%)				
Diabetes	44 (49.4%)	31 (52.5%)	13 (43.3%)	0.411
Hypertension	34 (38.2%)	25 (42.4%)	9 (30.0%)	0.256
COPD	8 (9.0%)	6 (10.2%)	2 (6.7%)	0.585
CVA	6 (6.7%)	5 (8.5%)	1 (3.3%)	0.361
CAD	17 (19.1%)	13 (22.0%)	4 (13.3%)	0.324
CKD	14 (15.7%)	7 (11.9%)	7 (23.3%)	0.160
CLD	7 (7.9%)	2 (3.4%)	5 (16.7%)	0.028
Malignancy	7 (7.9%)	6 (10.2%)	1 (3.3%)	0.257
Charlson comorbidity index – median (IQR)[#]	4 (1–6)	4 (2–5)	3 (1–6)	0.855
SOFA score on the day of antibiotic initiation	7 (4–11)	6 (4–9)	9 (4–11)	0.096
Source control* – *n*(%)	16 (18.0%)	11 (18.6%)	5 (16.7%)	0.818
Pre-emptive antibiotic – *n*(%)	44 (49.4%)	31 (52.5%)	13 (43.3%)	0.411
Duration of antibiotic therapy – mean ± SD	8 ± 4	8 ± 4	8 ± 4	0.761

CAZ–AVI + AZT, ceftazidime–avibactam with or without aztreonam group, CKD, chronic kidney disease; CLD, chronic liver disease; Colistin group, colistin, or polymyxin B; COPD, chronic obstructive airway disease; CVA, cerebrovascular accident; IQR, interquartile range; *n*, number of patients; SD, standard deviation; *Source control-removal of infected line or catheter, incision and drainage of pus, laparotomy for intra-abdominal abscess, [#]Charlson comorbidity index range from 0 to 41, higher scores represent lower estimated 10-year survival. A score of 4 represents 10-year survival of 53%

Table 2: Microbiological data

	Overall (N = 89)	*CAZ AVI ± AZT (N = 59)*	*Colistin group (N = 30)*
Organisms – *n* (%)			
Klebsiella pneumoniae	58 (66%)	39 (66%)	19 (63%)
Escherichia coli	18 (20%)	12 (20%)	6 (20%)
Enterobacter cloacae	5 (5.6%)	3 (5%)	2 (7%)
Serratia marcescens	3 (3.4%)	2 (3%)	1 (3.3%)
Citrobacter freundi	2 (2%)	1 (2%)	1 (3.3%)
Proteus vulgaris	2 (2%)	1 (2%)	1 (3.3%)
Providencia rettgeri	1 (1%)	1 (2%)	0 (0%)
Carba R gene – *n* (%)			
NDM and *OXA 48*	25 (28.1%)	19 (32.2%)	6 (20.0%)
NDM	45 (50.6%)	27 (45.8%)	18 (60%)
OXA 48	18 (20.2%)	13 (22.0%)	5 (16.7%)
IMP1	1 (1.1%)	0 (0.0%)	1 (1.1%)
Source – *n* (%)			
Bloodstream infection	33 (37.1%)	19 (32.2%)	14 (46.6%)
Respiratory tract	9 (10.1%)	4 (6.8%)	5 (16.7%)
Urinary tract	31 (34.8%)	25 (42.4%)	6 (20.0%)
Skin and soft tissue	14 (15.7%)	10 (17%)	4 (13.3%)
Intra-abdominal	2 (2.2%)	1 (1.7%)	1 (3.3%)

CAZ–AVI ± AZT, ceftazidime avibactam with or without aztreonam; IMP, imipenemase; *n*, number of patients; *n* (%), the number of patients with percentage; *NDM*, New Delhi metallo-beta-lactamase1; *OXA 48*, oxacillinase 48



Figs 2A to C: Microbiological data

Table 3: Outcome data

		HR (95% CI)	*p-value*
Primary outcome			
• Clinical failure on day 14	CAZ–AVI ± AZT	0.78 (0.63–0.95)	0.018
• Microbiological failure	CAZ–AVI ± AZT	1.08 (0.66–1.77)	0.76
• Microbiological relapse	CAZ–AVI ± AZT	0.75 (0.36–3.02)	0.62
• Mortality – *n* (%)	CAZ–AVI ± AZT	1.04 (0.75–1.43)	0.71
Secondary outcome	*CAZ–AVI ± AZT (N = 59)*	*Colistin group (N = 30)*	*p-value*
• Length of ICU stay – mean ± SD	12 ± 11	11.5 ± 10.8	0.843
• Length of hospital stay – mean ± SD	18 ± 18	14.6 ± 14	0.387
• Mechanical-ventilation-free days – mean ± SD	18.1 ± 13.5	18 ± 14	0.982
• Vasopressor-free days – mean ± SD	20.1 ± 13.2	17.4 ± 13.7	0.369
• Days to outcome – mean ± SD	16.9 ± 17.2	14.3 ± 14.1	0.324
Complications			
Renal failure – *n* (%)	8 (13.6)	5 (16.7%)	0.695

CAZ–AVI + AZT, ceftazidime avibactam with or without aztreonam; ICU, intensive care unit; IQR, interquartile range; *n*, number of patients; *n* (%), the number of patients with percentage; Renal failure definition refers methods section. #SOFA, sequential organ failure assessment score, A score ranges 0 (best) to 24 (worst) scores; SD, standard deviation

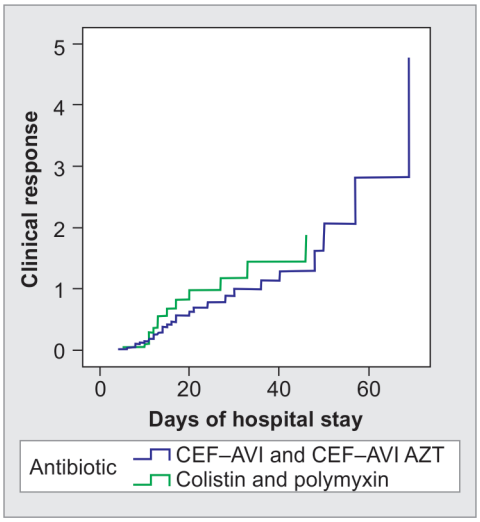


Fig. 3: Kaplan–Meier curve for trial patients treated with polymyxins and CAZ–AVI + AZT

Discussion

In this study, we investigated the clinical and microbiological responses in patients treated with CAZ–AVI + AZT vs colistin for CRE infections. Our findings revealed a statistically significant difference in clinical failure at day 14 between the CAZ–AVI + AZT group and the colistin group. This indicates that patients treated with CAZ–AVI + AZT had a lower risk of clinical failure compared to those treated with colistin. This result is particularly noteworthy as it demonstrates the potential superiority of CAZ–AVI + AZT over colistin as a treatment option for CRE infections. In contrast, there was no statistically significant difference in microbiological failure or microbiological relapse between the two groups indicating that CAZ–AVI + AZT and colistin are equally effective in eradicating the causative pathogens.

The clinical response favored CAZ–AVI + AZT in various matched case–control studies. In a prior multinational observational study by Falcone M et al.,[10] comparing CAZ–AVI + ATM to other alternative antibiotics (OAAs) for MBL-producing Enterobacterales-induced BSI, a superior clinical response with CAZ–AVI + ATM was demonstrated. Another retrospective study, mainly covering *OXA-48* and *NDM* cases, compared CAZ–AVI to colistin for CRE bacteremia, revealing better clinical success with CAZ–AVI.[13] Our study's clinical response aligns with these prior findings.

The association between treating CRE infections with CAZ–AVI + ATM and improved survival remains contentious. Our study revealed insignificant differences in mortality between the two treatment groups. In contrast, a prospective observational study focusing solely on bacteremia patients showed a lower mortality rate with the CAZ–AVI + ATM combination.[10] This contrast might stem from several factors: first, our study encompassed a heterogeneous infection pattern, with only a third of patients displaying bacteremia. Second, our study mainly dealt with *NDM* and *OXA-48* isolates, whereas the previous study predominantly featured KPC and VIM-1 cases. Third, our study employed colistin monotherapy in contrast to the colistin-based combination therapy in the control group of the previous study, possibly influencing the outcomes.

Meta-analysis of 5 randomized controlled trials (RCTs) which compared with colistin monotherapy vs combination therapy against carbapenem-resistant gram-negative bacteria infections concluded no difference in overall mortality, infection-related mortality, and microbiologic response.[19] An open-label RCT (AIDA trial) that compared colistin alone vs colistin plus meropenem for the treatment of severe infections caused by carbapenem-resistant gram-negative bacteria, combination therapy was not associated with improved clinical success and mortality. *Post-hoc* analysis of the study, which included CRE and pseudomonas infection, seems to suggest a trend toward reductions in 28-day mortality with combination therapy but was underpowered to assess significant differences in these subgroups.[20] A more recent RCT overcome study confirms the same finding.[21] Another retrospective multicenter study comparing CAZ–AVI + ATM and colistin monotherapy (Hakeam HA et al.),[11] primarily involving *NDM* and *OXA-48* infections, showed similar mortality outcomes as our study. Further evaluation is required to assess the efficacy of colistin-based combination therapy for CRE infections.

There was no difference in complication of treatment between the two groups. Though nephrotoxicity is a known complication of colistin, there was no difference in the nephrotoxicity between the groups. This is probably due to half of the patients in our study received polymyxin-B in the polymyxins group, which has less nephrotoxicity.

The current study possesses several strengths. Firstly, it is among the few studies with a substantial number of participants. Secondly, the interpreters and analyzers of the data remained blinded during group analysis. Thirdly, considering the limited data on managing CRE infections in the Indian population, this study provides valuable insights. However, there are certain limitations to acknowledge. Primarily, this study was observational and conducted at a single center, potentially limiting the generalizability of our findings to a global context. Secondly, antibiotic selection was based on individual clinical judgment, resulting in dissimilarities among group members. Thirdly, our study may have been underpowered to demonstrate a mortality benefit. Despite these limitations, the findings underscore the importance of selecting appropriate antibiotics for effectively managing the challenging and widespread occurrence of carbapenem-resistant organisms.

Conclusion

Ceftazidime avibactam with or without the aztreonam group showed a statistically significant clinical response compared to the polymyxin monotherapy for carbapenemase-producing gram-negative organisms. However, there was no difference in survival benefit, microbiological response, and side effects between the two groups.

Acknowledgments

Dr Baby Sailaja K, Dr Janarthanan S, Dr A Sumanth Reddy, Dr Hemalatha RV for reviewing the paper, and Mr R Vasanthakumar for helping in data collection.

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