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Effectiveness of Ceftazidime-Avibactam versus Colistin against Carbapenem-Resistant *Enterobacteriaceae- A* Retrospective Study

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ABSTRACT

Background: This study compared the efficacy of ceftazidime-avibactam (CAZ-AVI with colistin for treating carbapenem-resistant *Enterobacteriaceae* (CRE) infections.
Materials & Methods: This retrospective study included 120 patients with a confirmed CRE infection and information on causative bacteria and their susceptibility pattern. Patients were divided into two groups: those receiving CAZ-AVI and/or aztreonam (n=53) and those receiving colistin (n=67) for at least seven days. The colistin group was further subdivided into those who switched to CAZ-AVI due to poor outcomes. Patient data, including demographics, clinical history, microbiological data, Charlson comorbidity index, and outcomes, were collected and analyzed. Mann-Whitney U, Chi-square, and Fisher's exact tests were used to compare the groups. $P< .05$ was considered statistically significant.
Findings: The findings revealed comparable clinical characteristics, there were no major differences in mean duration of hospitalization, intensive care unit (ICU) admission, and Charlson scores between the two groups. The CAZ-AVI group required a significantly longer duration of antibiotic treatment ($p= .018$) and more source control measures ($p= .009$). *Klebsiella pneumoniae* was the predominant causative pathogen in both groups, with NDM and OXA48 carbapenem resistance genes being the most common. Toxicity ($p= .001$) and mortality ($p= .049$) were significantly higher in the colistin group. Higher improvement was observed among the CAZ-AVI group and higher mortality among the colistin group ($p= .049$).
Conclusion: CAZ-AVI could serve as an alternative to colistin for treating CRE infections. Further research is necessary to confirm these findings and provide evidence-based guidelines for managing CRE infections in India.

Keywords: Carbapenem-resistant *Enterobacteriaceae*, Ceftazidime, Colistin, Drug resistance, Microbial, Outcomes

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Introduction

Antimicrobial resistance is a serious public health concern that reduces the effectiveness of drugs against different pathogenic microorganisms. Infections due to drug-resistant pathogens have resulted in 700,000 deaths worldwide and are predicted to cause up to 10 million deaths by 2050 [1]. Considering the highest mortality rates due to infectious diseases in South Asia, the status of antibiotic resistance is worrisome in India. Antibiotic resistance of *Escherichia coli* and *Klebsiella pneumoniae* to carbapenems along with other antimicrobials is the cause of a 50% case-fatality rate among hospital-acquired infection cases [1, 2].

Carbapenems are considered as the most effective beta-lactam class of broad-spectrum antibiotics. Beta-lactamase-resistant bacteria are said to show the least resistance to them. However, the rapid spread of carbapenem resistance, mostly among Gram-negative bacteria, poses serious global health concerns [3].

Among Gram-negative bacteria, carbapenem-resistant *Enterobacteriaceae* (CRE) are of great concern due to their ability to produce carbapenemases, which hydrolyse carbapenems and render them ineffective. CRE infection is determined by three carbapenemase groups: Class A *K. pneumoniae* carbapenemases (KPC), Class B metallo-beta-lactamases such as New Delhi metallo-lactamases (NDM), and Class D oxacillin-hydrolyzing carbapenemases (OXA) [4].

Studies have shown that polymyxins (colistin) as first-line agents traditionally used to treat CRE infections lead to 40-60% treatment failure and 20-50% nephrotoxicity [5]. As a novel beta-lactamase inhibitor, ceftazidime-avibactam (CAZ-AVI) has shown promising activity against KPC and OXA carbapenemases and has recently been approved as a frontline agent for treating CRE infections. This drug has been prescribed for complicated urinary tract infections, hospital-acquired pneumonia, and ventilator-associated pneumonia, with promising results [6]. Additionally, a combination of aztreonam and CAZ-AVI has been shown to notably reduce clinical treatment failure and mortality rates by acting against NDM and other metallo-lactamases [7].

In-vitro studies conducted in India have suggested the use of CAZ-AVI as an alternative to traditional treatments, but many studies have not confirmed its efficacy in Indian scenarios [8, 9].

Objectives: This retrospective study aimed to compare the effectiveness of CAZ-AVI and colistin in the treatment of CRE infections by assessing the treatment outcomes of patients.

Materials and Methods

Study design and population: This retrospective study involved 120 patients diagnosed positive for CRE infection between January 2020 and January 2021. The study was approved by the Institutional Human Ethics Committee (IHEC, Reference No. PSG/IHEC/2021/Appr/Exp/057) on April 1, 2021. Since this research was a retrospective study, the need for informed consent was waived off by the ethics committee; however, all patient data (if available) were analyzed after anonymization.

The study population included patients with CRE infection, admitted to a tertiary care hospital in Coimbatore, India.

The inclusion criteria were as follows: a) patients above 18 years of age b) with a confirmed CRE infection and information about the causative bacteria at the species level and their susceptibility pattern to predefined antibiotics, c) who received either colistin or CAZ-AVI and/or aztreonam (i.e., zavicefta and/or azenem) for at least

seven days. In patients with multiple episodes, only the first episode of bacteremia per patient was included in analysis. Infants, children, pregnant women, and any patient without laboratory-confirmed CRE infection and those treated for less than seven days were excluded from the study.

Data collection: The patients' data were then divided into two groups based on the treatment strategies; the first group consisted of patients who received CAZ-AVI and/or aztreonam (commercially available forms of zavicefta or azenem), and the second group consisted of patients who received colistin. The colistin group was further demarcated to separate patients who initially received colistin but switched to CAZ-AVI and aztreonam due to poor outcomes and renal toxicity.

Collected patient data included demographics, clinical history, blood and urine reports, swab reports, tracheal aspirate and other respiratory fluid sample data, Charlson comorbidity index score, [10] infecting organism, and carbapenem resistance gene sequence data from Xpert Carba-R assay (Cepheid). The Xpert Carba-R assay, performed on GeneXpert® systems, is a qualitative in vitro diagnostic test designed to detect and differentiate bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{OXA48}, and bla_{IMP} gene sequences associated with carbapenem-non-susceptibility using automated real-time polymerase chain reaction (PCR). Data related to the need for surgical intervention, ventilation, toxicity status, discharge, and follow-up at the next outpatient visit (two weeks after discharge) were also obtained for analysis.

Statistical analysis: Data was analyzed using Statistical Package for Social Sciences (SPSS) software Version 24.0. Categorical variables were represented as frequency and percentage. Continuous variables were presented as mean ± standard deviation (SD)/ median (min, max). The normality of data was assessed using Kolmogorov–Smirnov test. Mann-Whitney U test was used to assess the differences between the two groups. Pearson's Chi-square test verified the relationship between the characteristics in the two groups. When this test did not meet its requirements (n > 20, all expected values in the table are greater than 1, and at least 80% are greater than or equal to 5), Fisher's exact test was used. A *p*-value of <.05 was considered statistically significant.

Findings

Hospitalization data and clinical characteristics: During the study period, a total of 120 patient records were deemed eligible for inclusion in the study. The mean (±SD) age of the patients was 56.2 (±13.1) years, and they were predominantly male (76.7%, n=92). The mean duration of hospitalization, intensive care unit (ICU) admission, and antibiotic administration was 28.2 (±16.7), 11.9 (±11.9), and 10.1 (±3.6) days, respectively. The mean Charlson comorbidity score was 3.7(±2.7), indicating a high risk of mortality [10].

Based on the treatment strategies provided, 55.8% (n=67) of the patients were in the colistin group, and 44.2% (n=53) were in the CAZ-AVI group. Table 1 outlines the differences between these two groups. No major differences were observed between the two groups with respect to the mean duration of hospitalization, ICU admission, and Charlson scores; however, the duration of antibiotic administration was found to be significantly higher in the CAZ-AVI group (p= 0.018). In the subgroup of patients who switched from colistin to CAZ-AVI, the mean duration of hospitalization, ICU admission, and antibiotic administration was 33.0 (±21.6), 16.8 (±15), and 8.9 (±2.6) days, respectively. This subgroup had a high mean Charlson score of 4.8 (±2.8) (Table 2).

Table 1) Differences in hospitalization parameters and comorbidity index between ceftazidime-avibactam (CAZ-AVI) and colistin groups

Group	Age (Years)	Duration of Hospitalization (Days)	Duration of ICU Stay (Days)	Charlson Score	Duration of Antibiotic Administration (Days)
Colistin group (n = 67)	57.2 ± 13.0	28.7 ± 15.6	12.5 ± 12.2	3.6 ± 2.4	9.3 ± 2.6
CAZ-AVI group (n = 53)	55.0 ± 13.3	27.5 ± 18.2	11.2 ± 11.7	3.8 ± 3.1	11.1 ± 4.3
p-value	.423[M]	.318[M]	.599[M]	.940[M]	.018[M*]

Abbreviations: CAZ-AVI: ceftazidime-avibactam, ICU: intensive care unit, M: Mann-Whitney U-test, * indicates significance at $p < .05$.

Table 2) Distribution of duration of hospitalization and intensive care unit (ICU) stay along with other parameters among the colistin and ceftazidime-avibactam (CAZ-AVI) groups and the subgroup of colistin to CAZ-AVI

Group	Age (Years)	Duration of Hospitalization (Days)	Duration of ICU Stay (Days)	Charlson Score	Duration of Antibiotic Administration (Days)
Colistin group (n = 67)	57.2 ± 13.0	28.7 ± 15.6	12.5 ± 12.2	3.6 ± 2.4	9.3 ± 2.6
CAZ-AVI group (n = 53)	55.0 ± 13.3	27.5 ± 18.2	11.2 ± 11.7	3.8 ± 3.1	11.1 ± 4.3
Colistin to CAZ-AVI (n=18)	59.0 ± 11.7	33.0 ± 21.6	16.8 ± 15.0	4.8 ± 2.8	8.9 ± 2.6

Abbreviations: CAZ-AVI: ceftazidime-avibactam, ICU: intensive care unit

The clinical characteristics of the patients and the differences between both groups are listed in Table 3. Most of the characteristics like the presence of comorbidities, previous hospitalization history, previous surgery, immunodeficiency, and previous colonization were similar in both groups. Similarly, no abnormalities were observed in blood culture, urine, wound swab, tracheal aspirate, pus, broncho-alveolar lavage, pleural and ascitic fluid, and sputum in the majority of patients in both groups.

Bacteriological profile and carbapenem resistance: The bacterium causing infection in most patients in both groups was *K. pneumoniae* (88.3%, n=106). Xpert Carba-R assay was not done for 46 patients (38.3%). Most patients with completed Carba-R assays co-carried bla_{NDM} and bla_{OXA48} (26.7%, n=32) carbapenem resistance genes, and 23.3% of them carried only bla_{OXA48} genes (n=28). Also, four (3.3%) patients were Carba-R negative (Table 3).

K. pneumoniae was the most common infection-causing bacterium among patients in the colistin to zavicefta subgroup (n=16), and the majority of patients in this subgroup were positive for bla_{OXA48} carbapenemase resistance gene (n=11) (Table 4).

Source control measures, treatment characteristics, and outcomes: Overall, patients were treated with colistin (55.8%, n=67), zavicefta and azenem (45.8%, n=55), and only zavicefta (13,3%, n=16), regardless of groups (Table 4).

Among source control measures, surgical

Table 3) Distribution of clinical characteristics, bacteriological profile, Carba-R gene profile, and outcomes between the ceftazidime-avibactam (CAZ-AVI) and colistin groups

Characteristics		Total Patients N=120 N (%)	Colistin Group N=67 N (%)	CAZ-AVI Group N=53 N (%)	Chi-Square Test
Gender	Female	28 (23.3)	18 (64.3)	10 (35.7)	X^2=1.06 *df*=1 *p*= .304[P]
	Male	92 (76.7)	49 (53.3)	43 (46.7)	
Comorbidities	No	10 (8.3)	5 (50.0)	5 (50.0)	*P*= .748[F]
	Yes	110 (91.7)	62 (56.4)	48 (43.6)	
Previous hospitalization	No	42 (35.0)	26 (61.9)	16 (38.1)	X^2= 0.97 *df* = 1 *p* = .326[P]
	Yes	78 (65.0)	41 (52.6)	37 (47.4)	
Previous surgery	No	102 (85.0)	60 (58.8)	42 (41.2)	X^2= 2.47 *df* = 1 *p* = .116 [P]
	Yes	18 (15.0)	7 (38.9)	11 (61.1)	
Immunodeficiency	No	103 (85.8)	60 (58.3)	43 (41.7)	X^2= 1.73 *df* = 1 *p* = .189 [P]
	Yes	17 (14.2)	7 (41.2)	10 (58.8)	
Immunosuppressant use	No	93 (77.5)	58 (62.4)	35 (37.6)	X^2= 7.15 *df* = 1 *p* = .007*[P]
	Yes	27 (22.5)	9 (33.3)	18 (66.7)	
Previous colonization	No	92 (76.7)	51 (55.4)	41 (44.6)	X^2= 0.03 *df* = 1 *p* = .873[P]
	Yes	28 (23.3)	16 (57.1)	12 (42.9)	
Blood culture	No	79 (65.8)	45 (57.0)	34 (43.0)	X^2= 0.12 *df* = 1 *p* = .730[P]
	Yes	41 (34.2)	22 (53.7)	19 (46.3)	
Urine	No	88 (73.3)	53 (60.2)	35 (39.8)	X^2= 2.58 *df* = 1 *p* = .108[P]
	Yes	32 (26.7)	14 (43.8)	18 (56.2)	
Wound swab	No	105 (87.5)	60 (57.1)	45 (42.9)	X^2= 0.58 *df* = 1 *p* = .445[P]
	Yes	15 (12.5)	7 (46.7)	8 (53.3)	
Tracheal aspirate	No	82 (68.3)	42 (51.2)	40 (48.8)	X^2= 2.24 *df* = 1 *p* = .135[P]
	Yes	38 (31.7)	25 (65.8)	13 (34.2)	
Pus	No	93 (77.5)	55 (59.1)	38 (40.9)	X^2= 1.83 *df* = 1 *p* = .176[P]
	Yes	27 (22.5)	12 (44.4)	15 (55.6)	
Broncho-alveolar lavage	No	115 (95.8)	64 (55.7)	51 (44.3)	*P*=1.00[F]
	Yes	5 (4.2)	3 (60.0)	2 (40.0)	
Pleural fluid	No	117 (97.5)	67 (57.3)	50 (42.7)	*P*= .083[F]
	Yes	3 (2.5)	-	3 (100.0)	
Ascitic fluid	No	117 (97.5)	67 (57.3)	50 (42.7)	*P*= .083[F]
	Yes	3 (2.5)	-	3 (100.0)	
Sputum	No	106 (88.3)	62 (58.5)	44 (41.5)	X^2= 2.60 *df* = 1 *p* = .107[P]
	Yes	14 (11.7)	5 (35.7)	9 (64.3)	

Organism	*E.coli*	7 (5.8)	3 (42.9)	4 (57.1)	*P*= .90[9]F
	Klebsiella pneumoniae	106 (88.3)	60 (56.6)	46 (43.4)	
	Others	7 (5.8)	4 (57.1)	3 (42.9)	
Carba-R assay	bla_{KPC} positive	1 (0.8)	1 (100)	-	-
	bla_{KPC} + bla_{OXA48} co-production	1 (0.8)	-	1 (100)	
	bla_{NDM} positive	8 (6.7)	1 (12.5)	7 (87.5)	
	bla_{NDM} + bla_{OXA48} co-production	32 (26.7)	5 (15.6)	27 (84.4)	
	Carba-R negative	4 (3.3)	2 (50.0)	2 (50.0)	
	Carba-R not done	46 (38.3)	45 (97.8)	1 (2.2)	
	bla_{OXA48} positive	28 (23.3)	13 (46.4)	15 (53.6)	
Surgical intervention	No	68 (56.7)	45 (66.2)	23 (33.8)	X^2= 6.81 *df* = 1 *p* = .009*[P]
	Yes	52 (43.3)	22 (42.3)	30 (57.7)	
Inotropes	No	48 (40.0)	25 (52.1)	23 (47.9)	X^2= 0.46 *df* = 1 *p* = .499[P]
	Yes	72 (60.0)	42 (58.3)	30 (41.7)	
Ventilation	No	49 (40.8)	24 (49.0)	25 (51.0)	X^2= 1.58 *df* = 1 *p* = .209[P]
	Yes	71 (59.2)	43 (60.6)	28 (39.4)	
Foley	No	16 (13.3)	12 (75.0)	4 (25.0)	X^2= 2.75 *df* = 1 *p* = .097[P]
	Yes	104 (86.7)	55 (52.9)	49 (47.1)	
Central line	No	37 (30.8)	21 (56.8)	16 (43.2)	X^2= 0.02 *df* = 1 *p* = .892[P]
	Yes	83 (69.2)	46 (55.4)	37 (44.6)	
Colistin	No	53 (44.2)	-	53 (100)	-
	Yes	67 (55.8)	67 (100)	-	
Zavicefta	No	104 (86.7)	65 (62.5)	39 (37.5)	X^2= 14.06 *df* = 1 *p* = .001*[P]
	Yes	16 (13.3)	2 (12.5)	14 (87.5)	
Zavicefta+colistin	No	65 (54.2)	51 (78.5)	14 (21.5)	X^2= 29.45 *df* = 1 *p* = .001*[P]
	Yes	55 (45.8)	16 (29.1)	39 (70.9)	
Toxicity	No	106 (88.3)	53 (50.0)	53 (50.0)	*P*= .001*
	Yes	14 (11.7)	14 (100)	-	
Discharge status	Death	31 (25.8)	22 (71.0)	9 (29.0)	X^2= 3.88 *df* = 1 *p* = .049*[P]
	Improved	89 (74.2)	45 (50.6)	44 (49.4)	
Follow-up	No	71 (59.2)	47 (66.2)	24 (33.8)	X^2= 7.57 *df* = 1 *p* = .006*[P]
	Yes	49 (40.8)	20 (40.8)	29 (59.2)	

Abbreviations: d.f: degrees of freedom, [P]: Pearson's Chi-square test, [F]: Fischer's exact test, CAZ-AVI: ceftazidime-avibactam, bla_{KPC}- beta-lactamase *K. pneumoniae* carbapenemase gene, bla_{NDM}- beta-lactamase New Delhi metallo-lactamases gene, bla_{OXA}- beta-lactamase oxacillin-hydrolyzing carbapenemase genes, *indicates significance at *p*< .05, - indicates none reported

Table 4) Distribution of clinical characteristics, bacteriological profile, *Carba-R* gene profile, and outcomes between the ceftazidime-avibactam (CAZ-AVI) and colistin groups and the colistin to CAZ-AVI subgroup

Characteristics		Total Patients, N=120 N (%)	Colistin Group N=67 N (%)	CAZ-AVI Group N=53 N (%)	Colistin to CAZ-AVI Subgroup N=18 N (%)
Gender	Female	28 (23.3)	15 (53.6)	10 (35.7)	3 (10.7)
	Male	92 (76.7)	34 (37.0)	43 (46.7)	15 (16.3)
Comorbidities	No	10 (8.3)	3 (30.0)	5 (50.0)	2 (20.0)
	Yes	110 (91.7)	46 (41.8)	48 (43.6)	16 (14.5)
Previous hospitalization	No	42 (35.0)	20 (47.6)	16 (38.1)	6 (14.3)
	Yes	78 (65.0)	29 (37.2)	37 (47.4)	12 (15.4)
Previous surgery	No	102 (85.0)	44 (43.1)	42 (41.2)	16 (15.7)
	Yes	18 (15.0)	5 (27.8)	11 (61.1)	2 (11.1)
Immunodeficiency	No	103 (85.8)	47 (45.6)	43 (41.7)	13 (12.6)
	Yes	17 (14.2)	2 (11.8)	10 (58.8)	5 (29.4)
Immunosuppressant use	No	93 (77.5)	47 (50.5)	35 (37.6)	11 (11.8)
	Yes	27 (22.5)	2 (7.4)	18 (66.7)	7 (25.9)
Previous colonization	No	92 (76.7)	36 (39.1)	41 (44.6)	15 (16.3)
	Yes	28 (23.3)	13 (46.4)	12 (42.9)	3 (10.7)
Blood culture	No	79 (65.8)	34 (43.0)	34 (43.0)	11 (13.9)
	Yes	41 (34.2)	15 (36.6)	19 (46.3)	7 (17.1)
Urine	No	88 (73.3)	42 (47.7)	35 (39.8)	11 (12.5)
	Yes	32 (26.7)	7 (21.9)	18 (56.2)	7 (21.9)
Wound swab	No	105 (87.5)	44 (41.9)	45 (42.9)	16 (15.2)
	Yes	15 (12.5)	5 (33.3)	8 (53.3)	2 (13.3)
Tracheal aspirate	No	82 (68.3)	31 (37.8)	40 (48.8)	11 (13.4)
	Yes	38 (31.7)	18 (47.4)	13 (34.2)	7 (18.4)
Pus	No	93 (77.5)	41 (44.1)	38 (40.9)	14 (15.1)
	Yes	27 (22.5)	8 (29.6)	15 (55.6)	4 (14.8)
Broncho-alveolar lavage	No	115 (95.8)	47 (40.9)	51 (44.3)	17 (14.8)
	Yes	5 (4.2)	2 (40.0)	2 (40.0)	1 (20.0)

Pleural fluid	No	117 (97.5)	49 (41.9)	50 (42.7)	18 (15.4)
	Yes	3 (2.5)	-	3 (100.0)	-
Ascitic fluid	No	117 (97.5)	49 (41.9)	50 (42.7)	18 (15.4)
	Yes	3 (2.5)	-	3 (100.0)	
Sputum	No	106 (88.3)	46 (43.4)	44 (41.5)	16 (15.1)
	Yes	14 (11.7)	3 (21.4)	9 (64.3)	2 (14.3)
Organism	*E.coli*	7 (5.8)	3 (42.9)	4 (57.1)	-
	Klebsiella pneumoniae	106 (88.3)	44 (41.5)	46 (43.4)	16 (15.1)
	Others	7 (5.8)	2 (28.6)	3 (42.9)	2 (28.6)
Carba-R assay	bla_{KPC} positive	1 (0.8)	-	-	1 (100)
	bla_{KPC} + bla_{OXA48} co-production	1 (0.8)	-	1 (100)	-
	bla_{NDM} positive	8 (6.7)	1 (12.5)	7 (87.5)	-
	bla_{NDM} + bla_{OXA48} co-production	32 (26.7)	2 (6.2)	27 (84.4)	3 (9.4)
	Carba-R negative	4 (3.3)	1 (25.0)	2 (50.0)	1 (25.0)
	Carba-R not done	46 (38.3)	43 (93.5)	1 (2.2)	2 (4.3)
	bla_{OXA48} positive	28 (23.3)	2 (7.1)	15 (53.6)	11 (39.3)
Surgical intervention	No	68 (56.7)	34 (50.0)	23 (33.8)	11 (16.2)
	Yes	52 (43.3)	15 (28.8)	30 (57.7)	7 (13.5)
Inotropes	No	48 (40.0)	18 (37.5)	23 (47.9)	7 (14.6)
	Yes	72 (60.0)	31 (43.1)	30 (41.7)	11 (15.3)
Ventilation	No	49 (40.8)	17 (34.7)	25 (51.0)	7 (14.3)
	Yes	71 (59.2)	32 (45.1)	28 (39.4)	11 (15.5)
Foley	No	16 (13.3)	11 (68.8)	4 (25.0)	1 (6.2)
	Yes	104 (86.7)	38 (36.5)	49 (47.1)	17 (16.3)
Central line	No	37 (30.8)	15 (40.5)	16 (43.2)	6 (16.2)
	Yes	83 (69.2)	34 (41.0)	37 (44.6)	12 (14.5)
Colistin	No	53 (44.2)	-	53 (100)	-
	Yes	67 (55.8)	49 (73.1)	-	18 (26.9)
Zavicefta	No	104 (86.7)	49 (47.1)	39 (37.5)	16 (15.4)
	Yes	16 (13.3)	-	14 (87.5)	2 (12.5)
Zavicefta+colistin	No	65 (54.2)	49 (75.4)	14 (21.5)	2 (3.1)
	Yes	55 (45.8)	-	39 (70.9)	16 (29.1)
Toxicity	No	106 (88.3)	39 (36.8)	53 (50.0)	14 (13.2)
	Yes	14 (11.7)	10 (71.4)	-	4 (28.6)
Discharge status	Death	31 (25.8)	17 (54.8)	9 (29.0)	5 (16.1)
	Improved	89 (74.2)	32 (36.0)	44 (49.4)	13 (14.6)
Follow-up	No	71 (59.2)	34 (47.9)	24 (33.8)	13 (18.3)
	Yes	49 (40.8)	15 (30.6)	29 (59.2)	5 (10.2)

Abbreviations: CAZ-AVI: ceftazidime-avibactam, *blaKPC*- beta-lactamase *K. pneumoniae* carbapenemase gene, *blaNDM*- beta-lactamase New Delhi metallo-lactamases gene, *blaOXA*- beta-lactamase oxacillin-hydrolyzing carbapenemase genes; - indicates none reported

intervention was required in 43.3% (n=52) of patients, which was found to be significantly higher among the CAZ-AVI group (57.7%, n=30; *p*= .009). The need for inotropes (*p*= .499), ventilation (*p*= .209), foley (*p*= .097), and central line (*p*= .892) was not significantly different between groups (Table 3).

Regarding the outcomes assessed, toxicity was observed among 14 patients only in the colistin group (*p*= .001). Discharge status was significantly different between the two groups, with higher improvement in the CAZ-AVI group and higher mortality in the colistin group (*p*= .049). Follow-up was significantly higher among the CAZ-AVI group (59.2%, n=29; *p*= .006). Also, five patients in the colistin to CAZ-AVI subgroup did not survive (Table 4).

Discussion

Due to the increasing burden of antimicrobial resistance in India, newer and improved antibiotics that work well against resistant pathogens are the need of the hour. Despite the widespread use of previously approved antibiotic classes, carbapenems are still effective against *Enterobacteriaceae*, while last-resort treatment using colistin has resulted in treatment failure and high mortality rates, apart from nephrotoxicity [3, 5]. CAZ-AVI has recently grabbed attention as an alternative to colistin for treating CRE infections; however, its efficacy in the Indian context has been less explored [6, 9].

In the present study, CAZ-AVI was found to be a noteworthy alternative to colistin in the treatment of CRE infections in different aspects. Demographics and baseline clinical characteristics like gender, age, comorbidities, previous surgeries, immunodeficiency, and other laboratory parameters were comparable in both CAZ-AVI and colistin groups. It was found that patients receiving CAZ-AVI had a significantly longer antibiotic treatment duration than those treated with colistin. This finding is in contrast with other studies reporting comparable treatment durations for both groups [11–14]. Additionally, in the present study, the need for surgical intervention was significantly higher among the CAZ-AVI group. These contradicting results could be due to the presence of patients with severe course of the disease among the CAZ-AVI group, hence requiring extended treatment courses and source control measures [15]. However, the number of patients using immunosuppressants was significantly higher in the CAZ-AVI group. Immunosuppression has previously been reported as an independent risk factor for mortality in CRE infections [16].

The current study found *K. pneumoniae* as the predominant Gram-negative infection-causing bacterium. Among the different carbapenemase resistance genes assessed, co-expression of bla_{NDM} and bla_{OXA48} genes, and bla_{OXA48} genes alone were observed in most of the patients. This finding agrees with the results of other studies conducted in India.[8, 17, 18]

Finally, patient outcomes in the present study revealed that patients in the colistin group had significantly higher toxicity and mortality rates, compared to the CAZ-AVI group where most of the patients were discharged successfully. Several studies have suggested better efficacy and safety of CAZ-AVI compared to polymyxins like colistin. This is predominantly attributed to the lower mortality rates in patients treated with CAZ-AVI, projecting it as a suitable alternative to standard colistin therapy [6, 11, 17–19]. In addition, in the present study, due to severe complications including renal toxicity, 18 patients from the colistin group were switched to CAZ-AVI treatment, which demonstrated lower toxicity and mortality compared to the colistin group. This highlights the need for timely

identification of toxicity status and initiation of appropriate antibiotic treatment for favourable outcomes. Furthermore, the cost-effectiveness of CAZ-AVI compared to colistin[20] should propel the use of the former treatment regimen among patients with CRE infections.

Limitations: The retrospective study design and limited sample size could lead to selection bias, limiting the generalizability of the findings. Further, this study did not consider long-term outcomes such as antibiotic resistance during follow-up or mortality.

Conclusion

The study provides evidence for CAZ-AVI as a suitable alternative to standard colistin therapy against CRE infections. Future research with larger sample sizes, prospective designs, and long-term follow-up is necessary to validate these findings and refine treatment strategies for CRE infections.

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Consent to participate: The need for informed consent was waived off by the ethics committee as this research was a retrospective study. However, all patient data (if available) were analysed after anonymization.

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Author's contributions: NG Data Collection, Monitoring, Lab report interpretation , final manuscript review. KSN Concept, data interpretation , design , final drafting. EM Data collection, monitoring , interpretation , final drafting. DN Design and final drafting. MA Concept , statistical analysis and interpretation , final drafting.

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