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ORIGINAL RESEARCH

Ceftazidime-Avibactam versus Colistin for the Treatment of Infections Due to Carbapenem-Resistant Enterobacterales: A Multicenter Cohort Study

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Background: The aim of this study was to compare the safety and effectiveness of ceftazidime-avibactam (CAZ-AVI) to colistin-based regimen in the treatment of infections caused by carbapenem-resistant Enterobacterales (CRE).

Methods: This was a retrospective, multicenter, observational cohort study of inpatients who received either CAZ-AVI or intravenous colistin for treatment of infections due to CRE. The study was conducted in 5 tertiary care hospitals in Saudi Arabia. Main study outcomes included in-hospital mortality, clinical cure at end of treatment, and acute kidney injury (AKI). Univariate analysis and multivariate logistic regression model were conducted to assess the independent impact of CAZ-AVI on the clinical outcome.

Results: A total of 230 patients were included in this study: 149 patients received CAZ-AVI and 81 patients received colistin-based regimen. Clinical cure (71% vs 52%; P = 0.004; OR, 2.29; 95% CI, 1.31–4.01) was significantly more common in patients who received CAZ-AVI. After adjusting the difference between the two groups, treatment with CAZ-AVI is independently associated with clinical cure (adjusted OR, 2.75; 95% CI, 1.28–5.91). In-hospital mortality (35% vs 44%; P = 0.156; OR, 0.67; 95% CI, 0.39–1.16) was lower in patients who received CAZ-AVI but the difference was not significant. AKI (15% vs 33%; P = 0.002; OR, 0.37; 95% CI, 0.19–0.69) was significantly less common in patients who received CAZ-AVI.

Conclusion: CAZ-AVI is associated with higher rate of clinical cure and lower rate of AKI compared to colistin. Our findings support the preferential use of CAZ-AVI over colistin-based regimen for treating these infections.

Keywords: ceftazidime-avibactam, colistin, colistimethate sodium, carbapenem-resistant Enterobacterales

Background

As the antimicrobial resistance catastrophe aggravates, carbapenem resistance in Gram-negative microorganisms creates a particular clinical concern, as carbapenems have long been judged the most effective against multidrug-resistant (MDR) Gram-negative pathogens.[1] Carbapenem-resistant Enterobacterales (CRE) are considered an urgent threat on human health in the United States (US) according to the Centers for Disease Control and Prevention (CDC).[2] In 2017, a global priority pathogen list was published by the World Health Organization (WHO) in which CRE were designated a critical priority for research and development.[3]

Infections due to CRE have been growing in many countries of the world while the optimal management is limited by a paucity of effective therapeutic options. Before 2015, intravenous (IV) colistin was among the few frontline regimens

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for the treatment of infections due to CRE. However, the use of IV colistin was limited by suboptimal pharmacokinetics,[4,5] high rate of nephrotoxicity,[6,7] dosing complexity, and concerns regarding the accuracy of in vitro susceptibility testing.[8,9]

In 2015, the US Food and Drug Administration approved ceftazidime-avibactam (CAZ-AVI) for the treatment of complicated intra-abdominal infections (cIAIs), complicated urinary tract infections (cUTIs) and later for hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP).[10] Avibactam is a novel non-β-lactam β-lactamase inhibitor that retains ceftazidime activity against CRE expressing *Klebsiella pneumoniae carbapenemase* (KPCs), certain oxacillinase including OXA-48, but not against metallo-β-lactamases (MBL).[1]

The US FDA approved CAZ-AVI for the previously mentioned indications after non-inferiority was successfully demonstrated to the best available therapy, which were carbapenems for infections caused by ceftazidime-resistant Enterobacterales in Phase 2 and 3 clinical trials.[11–15] Hence, individuals whose infections were caused by CRE were excluded from these trials. Therefore, these trials are not reflective of patients most in need of CAZ-AVI given that the key characteristic of this novel agent is its potential activity against CRE. Data comparing the use of CAZ-AVI versus IV colistin for the treatment of infections caused by CRE are limited. The available data focused on strains that produced bla_{KPC} and little knowledge is currently available regarding the outcomes of CAZ-AVI compared to colistin against bla_{OXA-48} producing strains, the most common gene encoding for carbapenemase-producing *K pneumoniae* in the Kingdom of Saudi Arabia.[16]

Hence, the aim of this study was to compare the safety and effectiveness of CAZ-AVI to IV colistin in treating infections caused by CRE.

Method

Setting and Study Design

This was a retrospective, multicenter, observational cohort study of inpatients who received either CAZ-AVI or intravenous (IV) colistin for the treatment of infections due to CRE between June 2015 and December 2020. The study was conducted at King Saud University Medical City (KSUMC), a 1500-bed tertiary care academic medical center, Riyadh, Saudi Arabia; King Fahad Medical City (KFMC), a 1200-bed tertiary care hospital, Riyadh, Saudi Arabia; King Faisal Specialist Hospital and Research Center (KFSHRC), a 500-bed tertiary care hospital, Jeddah, Saudi Arabia; King Abdulaziz Medical City (KAMC), a 750-bed tertiary care hospital Jeddah, Saudi Arabia; and Security Forces Hospital (SFH), a 250-bed hospital, Makkah, Saudi Arabia. Records were computerized and electronically retrieved. Eligible patients were hospitalized adults, aged ≥ 18 years, who developed an infection due to CRE and were treated with either CAZ-AVI or IV colistin for at least 48 hours. Patients were excluded if the infecting isolate was non-susceptible to the study drug being investigated, they received overlapping therapy of CAZ-AVI and IV colistin for more than 48 hours, or if polymicrobial or concomitant infections existed and were not properly managed. Proper management referred to appropriate, in vitro active antibiotic coverage of the etiologic microorganisms. Only cases of infection rather than colonization as reported by treating clinicians were included. If multiple episodes of CRE infections occurred in the same patient, only the first episode was included. Primary endpoints included overall in-hospital mortality and clinical cure at end of treatment. Secondary endpoints included acute kidney injury (AKI), microbiologic eradication, infection-related mortality, 30-day readmission, 30 and 90-day recurrence, length of hospital and intensive-care unit (ICU) stay from the onset of CRE infection, and duration of mechanical ventilation. The total daily dose of IV colistin was 9 million international unit (MIU) given as a loading dose followed by at least 9 MIU given in divided doses with dosage adjustment for renal impairment. One MIU of colistin = 80 mg of the prodrug colistimethate sodium (CMS) = 33.3 mg of colistin base activity. This dose was given to most patients, but small variations occurred between institutions. CAZ-AVI was administered intravenously at a dose of 2.5 grams every 8 hours and adjusted per renal function. Ethical approvals had been granted from the Institutional Review Boards of all participating hospitals.

Data Collection

For all included patients, the following data were collected: demographic characteristics of included patients, study drug, dosing regimen, site of infection, time to active antibiotic (any antibiotic with in vitro susceptibility), time to study drug

(CAZ-AVI or IV colistin), duration of therapy, etiologic pathogen, type of CRE gene, susceptibility to study drugs, concurrent antibiotics and the susceptibility data, existence of polymicrobial infections, serum creatinine before and after treatment, comorbid conditions, Charlson comorbidity index (CCI), immune status, indwelling devices, mechanical ventilation, hospital setting, Acute Physiology and Chronic Health Evaluation (APACHE II) score, presence of septic shock, infectious diseases consultation, and length of hospital stay. Clinical effectiveness, microbiological, and safety outcomes were recorded and assessed.

Microbiological Testing

Identification and antimicrobial susceptibility testing of the causative Enterobacterales to commonly used antibiotics were performed using automated systems depending on the hospital own protocols: VITEK 2 system (bioMerieux, Craponne, France), MicroScan WalkAway 96 plus (Beckman Coulter, Inc., Brea, CA, USA), or BD Phoenix M50 (Becton Dickinson Diagnostic Systems, Sparks, MD, USA). The automated systems displayed the identity of the microorganisms with the percentage of assurance and susceptibility to 15–20 antimicrobials (susceptible, intermediate, or resistant). The susceptibility of these microorganisms to colistin was tested using commercial broth microdilution [(ComASP™ Colistin (Liofilchem® srl, Roseto degli Abruzzi, Italy)]. The susceptibility to CAZ-AVI was performed using E-test method. In the case of confirmed CRE isolates, GeneXpert (Xpert®Carba-R; Cepheid, Sunnyvale, CA, USA) was used to detect and differentiate bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, and $bla_{\text{OXA-48}}$ genes. Colistin minimum inhibitory concentration (MIC) for Enterobacterales isolates were classified using European Committee on Antimicrobial Susceptibility Testing breakpoints. Isolates were designated as being susceptible to colistin if the MIC was ≤2 mg/L; otherwise, they were considered as resistant.[17] The study was conducted before the application of the most recent Clinical and Laboratory Standards Institute (CLSI) standards, in which the susceptible category for colistin was eliminated.[8] CRE definition and CAZ-AVI breakpoints used were following the guidelines from CLSI.[18]

Definitions

APACHE II is a severity score and mortality estimation tool routinely used in critically ill patients.[19] CCI is a widely used measure of comorbidity to predict 1-year mortality of medical inpatients.[20] Sepsis was defined as suspected/documented infection plus in SOFA score of at least 2 from baseline.[21] Septic shock was defined as sepsis with persisting hypotension requiring vasopressors and a serum lactate level >2 mmol/L despite adequate volume resuscitation.[21]

Per the CDC, CRE was defined as Enterobacterales resistant to at least one carbapenem antibiotic or producing a carbapenemase enzyme.[22]

Clinical cure was defined as resolution of signs and symptoms of infection with the study drug without therapy needing to have been modified due to failure or toxicity while clinical failure was defined as persistence or worsening of the signs and symptoms of infection from the baseline to the end of treatment. Laboratory and radiologic outcomes were included in the assessment of the clinical cure including resolution of fever, decrease or lack of progression of radiographic abnormalities, improvement or normalization of arterial blood gas, and improvement or return to baseline of the white blood cells, C-reactive protein, and procalcitonin, when applicable.

In-hospital mortality was defined as death due to any cause during same hospitalization. We consider this mortality as infection-related if patients had ongoing unequivocal clinical and/or biochemical signs of infection at the time of their death.

Microbiologic eradication was defined as no growth while microbiologic failure was defined as persistence of positive cultures of the etiologic pathogen irrespective of clinical outcome of the infection (assessed only in patients with repeated cultures). Indeterminate was listed when no microbiologic evaluation available.

Recurrence of infection was defined as positive cultures of same species, and susceptibility pattern as the index culture isolate after evidence of at least one negative growth of microorganisms.

Polymicrobial infection was defined as isolation of more than one microbial species during the same episode of infection.

"RIF" components of RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria were used to evaluate renal function as long-term assessment was not conducted.[23] Patients were judged to have AKI if

any of the previous categories was met during the treatment course. We also included whether patients received RRT due to AKI.

Statistical Analysis

Descriptive statistics were used to summarize variables. Categorical variables were presented in numbers and percentages while continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). The $\chi 2$ test or Fisher exact test were used to compare categorical variables while the independent *t*-test or Wilcoxon rank-sum test were used to compare continuous variables depending on normality of the data. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated for all associations that emerged. Analyses were performed with the level of significance set at $P < 0.05$. Variables emerging from univariate analysis with statistical significance were included in the multivariate logistic regression model to identify independent factors of the primary outcome. All statistical analyses were performed using STATA 15.1 (StataCorp LP, College Station, Texas, USA).

Results

A total of 230 patients were included in this study: 149 patients received CAZ-AVI and 81 patients received colistin-based regimen. The mean age was 58 ± 18 years and 143 (62%) were male. Most common comorbid conditions included hypertension (n = 137; 60%), diabetes (n = 118; 51%), endocrine disorder (n = 69; 30%), and cerebrovascular diseases (n = 63; 27%). The median (IQR) CCI was 5 (3–7). A total of 146 (65%) were in the ICU, 111 (48%) were on mechanical ventilation. The most common infection was hospital-acquired pneumonia (n = 60; 26%), followed by UTI (n = 44; 19%), wound infection (n = 37; 16%), intraabdominal infection (n = 30; 13%) and ventilator-associated pneumonia (n = 22; 10%). A total of 60 (26%) of patients presented with bacteremia.

Klebsiella pneumoniae was the most common isolated pathogen (n = 201; 87%). Type of carbapenemase was reported for 73 (49%) and 37 (46%) isolates in CAZ-AVI and colistin groups, respectively. Around 98% in both arms were $bla_{\text{OXA-48}}$, while only 1 bla_{KPC} reported in each arm. In CAZ-AVI arm, 116 (78%) isolates were susceptible to CAZ-AVI while in colistin arm, 62 (76%) isolates were susceptible to colistin. The rest of the included isolates had unidentified susceptibility. Patient was excluded if the isolate was identified as non-susceptible to the study drug being investigated. Polymicrobial infection presented in 103 (45%) patients. In CAZ-AVI arm, median (IQR) time to active therapy and time to study drug were 48 hours (20–79) and 60 hours (48–99), respectively, which were longer than median times in colistin arm: 43 hours (32–67) and 57 hours (24–90), respectively. The differences, however, were not statistically significant. Combination therapy was more commonly used in colistin arm (70% versus 23%; $P < 0.001$). The isolates were in vitro susceptible to at least one combination agent in 28% of the cases in colistin arm.

The two groups were matched in demographics and baseline characteristics. There was higher incidence of chronic heart failure and peripheral vascular diseases in CAZ-AVI arm. Median CCI was higher in CAZ-AVI group. In addition, median baseline serum creatinine was higher in CAZ-AVI group. More details about demographics and clinical characteristics of the two groups are shown in Table 1.

Clinical cure (71% vs 52%; P = 0.004; OR, 2.29; 95% CI, 1.31–4.01) was significantly more common in patients who received CAZ-AVI than in patients who received colistin-based regimen. In-hospital mortality (35% vs 44%; P = 0.156; OR, 0.67; 95% CI, 0.39–1.16) and infection-related mortality [28% vs 33%; P = 0.418; OR, 0.79; 95% CI, 0.44–1.41) were lower in patients who received CAZ-AVI but the differences were not significant. AKI (15% vs 33%; P = 0.002; OR, 0.37; 95% CI, 0.19–0.69) was significantly less common in patients who received CAZ-AVI. Differences between the 2 groups in microbiologic eradication, 30-day readmission, 30 and 90-day recurrence, length of hospital and ICU stay from the onset of infection, and the duration of mechanical ventilation were not statistically significant (Table 2).

Univariate analysis of 230 patients revealed a significant association between clinical failure and higher APACHE II score, mechanical ventilation, higher CCI, cerebrovascular disease, and endocrine disorder. Factors that may influence clinical outcome are analyzed in Table 3. When the significant factors listed in Table 3 were analyzed by multivariate logistic regression analysis including the results from each participating hospital, only APACHE II score significantly affected the clinical cure (Table 4). After adjusting the difference between the two groups, treatment with CAZ-AVI is independently associated with clinical cure (adjusted OR, 2.75; 95% CI, 1.28–5.91).

Table 1 Demographic and Clinical Characteristics of Study Patients

Characteristics	CAZ-AVI n = 149	IV Colistin n = 81	*P* value
Demographic			
Age in years (mean ± SD)	59 ± 18	57.5 ± 20	0.474
Male, n (%)	93 (62)	50 (61)	0.918
Study site			
KFMC	48 (32)	33 (41)	0.196
KAMC	39 (26)	20 (25)	0.806
KFSHRC	24 (16)	9 (11)	0.302
KSUMC	17 (12)	10 (12)	0.833
SFH	21 (14)	9 (11)	0.521
Comorbidity, n (%)			
AIDS	1 (0.7)	1 (1)	0.660
Cerebrovascular disease	43 (29)	19 (23)	0.378
Chronic heart failure	24 (16)	5 (6)	0.030
Chronic obstructive pulmonary disease	10 (7)	3 (4)	0.345
Connective tissue disease	8 (5)	1 (1)	0.122
Dementia	11 (7)	2 (2)	0.123
Diabetes mellitus	71 (48)	47 (58)	0.133
Endocrine disorder[#]	46 (31)	23 (28)	0.695
Hemiplegia or paraplegia	13 (9)	4 (5)	0.294
History of myocardial infarction	17 (11)	7 (9)	0.512
Hypertension	89 (60)	48 (59)	0.944
Immunosuppressed[†]	33 (22)	16 (20)	0.672
Liver disease	14 (9)	4 (5)	0.229
Moderate to severe chronic renal failure	34 (23)	14 (17)	0.324
Neurological disease	34 (23)	13 (16)	0.224
Peptic ulcer disease	7 (5)	2 (2)	0.405
Peripheral vascular disease	13 (9)	1 (1)	0.023
Charlson comorbidity index, median (IQR)	5 (3–7)	4 (2–6)	0.013
Baseline serum creatinine in μmol/L, median (IQR)	94 (57–160)	73 (44–130)	0.032
Baseline creatinine clearance in mL/min, median (IQR)	60 (33–99)	75 (36–120)	0.112
Indwelling invasive devices, n (%)			
Central venous catheter	77 (52)	33 (41)	0.113
Foley catheter	93 (62)	42 (52)	0.120
Mechanical ventilation	76 (51)	35 (43)	0.258
Severity of illness, n (%)			
Intensive care unit at infection onset	93 (62)	53 (65)	0.650
No sepsis	20 (13)	11 (14)	0.973
Sepsis	90 (61)	51 (63)	0.703
Septic shock	39 (26)	19 (23)	0.650
APACHE II score, median (IQR)	16 (11–20)	15 (11–19)	0.327
Site of infection, n (%)			
HAP	40 (27)	20 (25)	0.722
UTI	30 (20)	14 (17)	0.600
Wound	24 (16)	13 (16)	0.991
Intraabdominal	21 (14)	9 (11)	0.521
VAP	13 (9)	9 (11)	0.557
CLABSI	5 (3)	3 (4)	0.891
Other	16 (11)	13 (16)	–
Presence of bacteremia, n (%)	43 (29)	17 (21)	0.194
Type of CRE, n (%)			
Klebsiella pneumoniae	136 (91)	65 (80)	0.016

(*Continued*)

Table 1 (Continued).

Characteristics	CAZ-AVI n = 149	IV Colistin n = 81	*P* value
E. coli	9 (6)	12 (15)	0.027
Other	4 (3)	4 (5)	–
Polymicrobial infection, n (%)	69 (46)	34 (42)	0.528
Infectious diseases consultation, n (%)	144 (97)	76 (94)	0.317
Time to active therapy in hours, median (IQR)	48 (20–79)	43 (32–67)	0.945
Time to study drug in hours, median (IQR)	60 (48–99)	57 (24–90)	0.142
Combination therapy, n (%)*	34 (23)	57 (70)	< 0.001
Combination with more than one agent, n (%)	0	15 (19)	–
Type of combination therapy			
Aminoglycoside	7 (5)	6 (7)	
Aztreonam	3 (2)	0	
Carbapenem	0	47 (58)	
Cephalosporin	0	2 (3)	
Fluoroquinolone	5 (3)	3 (4)	
Inhaled colistin	3 (2)	0	
Piperacillin/tazobactam	0	6 (7)	
Tigecycline	16 (11)	8 (10)	
Susceptible to at least one combination agent, n (%) ±	13 (38)	16 (28)	0.314
Duration of therapy in days, median (IQR)	12 (8–19)	11 (7–17)	0.213
Overall duration of hospitalization in days, median (IQR)	60 (30–90)	62 (34–124)	0.121
Years of use during the study period	2017–2020	2015–2020	-

Notes: #Any endocrine disorder except diabetes. †Neutropenic, chronic treatment with corticosteroids, active chemotherapeutic management of malignancy, or solid organ/bone marrow transplant patients on immunosuppressant therapy. *Given concurrently with the study drug for at least 48 hours. ±Denominator represents patients who received combination therapy.

Abbreviations: AIDS, acquired immunodeficiency syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation; CAZ/AVI, ceftazidime/avibactam; CLABSI, central line-associated bloodstream infection; CRE, carbapenem-resistant Enterobacterales; IQR, interquartile range; KAMC, King Abdulaziz Medical City; KFMC, King Fahad Medical City; KFSHRC, King Faisal Specialist Hospital and Research Center; KSUMC, King Saud University Medical City; SFH, Security Forces Hospital; HAP, hospital-acquired pneumonia; IV, intravenous; SD, standard deviation; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

Discussion

The current study demonstrated that CAZ-AVI is associated with improved clinical cure and decreased AKI compared to colistin-based regimen in the treatment of infections caused by CRE. The clinical cure was improved by 19% with a number needed to treat of 5 while the AKI was decreased by 18% with a number needed to harm of 6. No statistically significant difference was found in mortality, microbiologic eradication, 30-day readmission, 30 and 90-day recurrence, length of stay, or the duration of mechanical ventilation. The study did not show a significant difference in the in-hospital mortality could be because this outcome is impacted by multiple covariables while the study included several critically ill patients and the fact that the study is underpowered. Given the mortality rates of 35% and 44% with OR of 0.67, assuming Alpha of 0.05 and beta of 0.2, the sample size needed that might detect the difference is about 4 times the current sample size.

This study is in line with recently published comparative studies supporting the preferential use of CAZ-AVI over comparators including colistin-based regimen for the treatment of infections caused by CRE.[24–27] Shields et al, demonstrated improved clinical success and 90-day survival with decreased AKI when CAZ-AVI was compared to other regimens, including colistin-based regimen, for the treatment of bacteremia caused by CRE. However, when CAZ-AVI was only compared to colistin-based regimen, the difference in 90-day survival was not statistically significant. Unlike our study, this study had smaller sample size (n = 109), focused only on bacteremia, included multiple comparators not only colistin-based regimen, while majority of included strains were bla_{KPC}.[24] The preferential use of CAZ-AVI over colistin-based regimen against CRE infections was also demonstrated by van Duin et al. Although it was conducted in prospective manner, unlike our study, the sample size was relatively small (n = 137), colistin dosing was neither available nor standardized, and all tested strains were bla_{KPC}.[25] In another study conducted in Spain, Castón et al demonstrated improved

Table 2 Outcomes in Patients Receiving Ceftazidime-Avibactam versus Intravenous Colistin

Outcome [a]	CAZ-AVI n = 149	IV Colistin n = 81	*P* value	Odds Ratio (95% CI)
Clinical cure	106 (71)	42 (52)	0.004	2.29 (1.31–4.01)
In-hospital mortality	52 (35)	36 (44)	0.156	0.67 (0.39–1.16)
Acute kidney injury	23 (15)	27 (33)	0.002	0.37 (0.19–0.69)
Risk	14	11	–	–
Injury	4	7	–	–
Failure	4	7	–	–
RRT	1	2	–	–
Microbiologic outcome [b]				
Eradication	81 (67)	37 (55)	0.113	1.64 (0.89–3.03)
Persistence	40 (33)	30 (45)		
Infection-related mortality	42 (28)	27 (33)	0.418	0.79 (0.44–1.41)
30-day readmission [c]	15 (16)	5 (11)	0.488	
30-day readmission due to infection [c]	7 (7)	2 (4)	0.528	
30-day recurrence [c]	10 (10)	5 (11)	0.885	
90-day recurrence [c]	11 (11)	6 (13)	0.734	
Length of hospital stay from onset of infection (days)	36 (20–60)	33 (20–72)	0.797	
Length of ICU stay from onset of infection (days)[d]	17 (6–39)	14 (7–26)	0.109	
Duration of mechanical ventilation (days)[e]	11 (5–22)	12 (5–24)	0.483	

Notes: [a]Data represented n (%) or median (IQR). [b]Only included patients who had repeated cultures (n = 121 in ceftazidime-avibactam arm and 67 in colistin arm). [c]Only included patients who survived (n = 97 in ceftazidime-avibactam arm and 45 in colistin arm). [d]Included only patients who were in the ICU at infection onset. [e]Included only patients who were mechanically ventilated during the infection episode.

Abbreviations: CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; ICU, intensive care unit; RRT, renal replacement therapy.

clinical cure with no significant difference in mortality when CAZ-AVI was compared to other regimens. This study was limited to bacteremia in patients with hematological malignancies, included multiple comparators, had small sample size (n = 34), all patients received CAZ-AVI in combination with other antimicrobials as targeted therapy, and did not address the rates of AKI as one of the main outcomes.[26] In more recent study conducted in Italy, Tumbarello et al showed decreased 30-day mortality in patients who received CAZ-AVI as salvage therapy compared to control for the treatment of bacteremia caused by carbapenemase -producing *K. pneumoniae*. In this study, however, 78% of patients with bacteremia received CAZ-AVI in combination, control group included multiple comparators, and AKI was not addressed as one of the outcomes.[27] In the most recent study conducted in Saudi Arabia, Hakeam et al demonstrated that CAZ-AVI is associated with higher clinical success and lower adjusted 14-day mortality compared to colistin. This study was limited by the small sample size, limited to bacteremia cases, and colistin susceptibility was not tested for most isolates.[28] It should be noted that case series also exist including one conducted in Saudi Arabia and showed that CAZ-AVI is associated with high clinical and microbiologic cure rates.[29] The results of our study are also in line with recent data which demonstrated that other novel β-lactam/β-lactamase inhibitors (meropenem/vaborbactam and imipenem/relebactam) are superior to the traditional sub-optimal regimens including colistin-based regimens for the treatment of CRE.[30,31] Our results are comparable to Pogue, et al, which compared novel β-lactam/β-lactamase inhibitor ceftolozane/tazobactam to colistin or aminoglycoside-based regimens for the treatment of infections caused by resistant *Pseudomonas aeruginosa*.[32] Our findings are consistent with the Infectious Diseases Society of America Guidance recommendations which supported the preferential use of novel β-lactam /β-lactamase inhibitors over colistin-based regimen for the treatment of infections caused by CRE and CAZ-AVI in particular for OXA-48-like carbapenemase.[33] Given that NDM-1 is the second most common genes encountered in Saudi Arabia,[16,34,35] CAZ-AVI should only be recommended if either susceptibility, or at least the absence of the most common MBL genes are proven.

Around half of the CRE isolates in this study were carbapenemase producers. The rest were not tested, or were resistant due to other mechanisms like AmpC overexpression with efflux, loss of porins, or outer membrane protein mutations. Consistent with our study, previous studies showed that OXA-48 was the most common gene encoding for carbapenemase-*producing K pneumoniae* in the Kingdom of Saudi Arabia ranging between 68% and 78% of all

Table 3 Univariate Analysis of Factors Associated with Clinical Cure

Variable	Clinical Failure n = (82)	Clinical Cure n = (148)	*P* value
Demographic			
Age in years (mean ± SD)	60 ± 19	57 ± 17	0.232
Male, n (%)	51 (62)	92 (62)	0.996
Comorbidity, n (%)			
Cerebrovascular disease	29 (36)	33 (22)	0.032
Chronic heart failure	12 (15)	17 (12)	0.491
Chronic obstructive pulmonary disease	4 (5)	9 (6)	0.705
Connective tissue disease	3 (4)	6 (4)	0.882
Dementia	7 (9)	6 (4)	0.159
Diabetes mellitus	39 (48)	79 (53)	0.370
Endocrine disorder	34 (41)	35 (24)	0.005
Hemiplegia or paraplegia	4 (5)	13 (9)	0.267
History of myocardial infarction	8 (10)	16 (11)	0.802
Hypertension	53 (65)	84 (57)	0.244
Immunosuppressed	17 (21)	32 (22)	0.875
Liver disease	8 (10)	10 (7)	0.417
Moderate to severe chronic renal failure	19 (23)	29 (20)	0.523
Neurological disease	20 (24)	27 (18)	0.268
Peripheral vascular disease	4 (5)	10 (7)	0.568
Charlson comorbidity index, median (IQR)	5 (4–7)	4 (2–6)	0.029
Indwelling invasive devices, n (%)			
Central venous catheter	46 (56)	64 (43)	0.062
Foley catheter	49 (60)	86 (58)	0.808
Mechanical ventilation	49 (60)	62 (42)	0.009
APACHE II score, median (IQR)	18 (12–25)	15 (9–19)	0.005
Site of infection, n (%)			
HAP	23 (28)	37 (25)	0.614
UTI	15 (18)	29 (20)	0.810
Wound	15 (18)	22 (15)	0.498
Intraabdominal	12 (15)	18 (12)	0.594
VAP	4 (5)	18 (12)	0.072
CLABSI	1 (1)	7 (5)	0.164
Presence of bacteremia, n (%)	26 (32)	34 (23)	0.148
Polymicrobial infection, n (%)	40 (49)	63 (43)	0.364
Time to active therapy in hours, median (IQR)	48 (24–80)	44 (24–75)	0.379
Time to study drug in hours, median (IQR)	55 (24–80)	62 (48–97)	0.074
Duration of therapy in days, median (IQR)	11 (7–18)	12 (9–18)	0.193

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; CLABSI, central line-associated bloodstream infection; IQR, interquartile range; HAP, hospital-acquired pneumonia; SD, standard deviation; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

Table 4 Analysis of Significant Factors Associated with Clinical Cure Using Logistic Regression Model

Variable	Odds Ratio	95% Conf. Interval	*P* value
CAZ-AVI	2.75	1.28–5.91	0.009
Cerebrovascular disease	0.67	0.27–1.62	0.371
Endocrine disorder	0.48	0.20–1.11	0.080
Mechanical ventilation	0.54	0.25–1.17	0.119
Charlson comorbidity index	0.88	0.76–1.03	0.121
APACHE II score	0.93	0.89–0.98	0.011

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; CAZ-AVI, ceftazidime-avibactam.

carbapenemase genes.[16,34,35] Moreover, in one study, all OXA-48 carbapenemase-producing Enterobacterales were susceptible to CAZ-AVI with good profile for safety and effectiveness.[36] This emphasizes the importance of having CAZ-AVI formulary available in all hospitals in the Kingdom and to be used over colistin-based regimen for the treatment of infections caused by CRE.

The retrospective observational nature of the design is the major limitation of our study. Type of carbapenemase was only reported in half of the isolates; however, 98% of the reported carbapenemases were $bla_{\text{OXA-48}}$. Although cases with confirmed non-susceptibility isolates to the study drug being investigated were excluded, around 22% of the included isolates had no susceptibility findings. In addition, CAZ-AVI and colistin were used as sequential therapy in some cases if failure occurred to starting regimens. Overall in-hospital mortality rate could have been underestimated as a quarter to one-third of our cohort had UTI or wound infections which were associated with low risk of mortality. Moreover, as infections due to CRE are not frequently encountered and CAZ-AVI was introduced to the formularies in Saudi Arabian hospitals in 2017, the number of included patients was small. In addition, isolates that carried MBL gene NDM-1, the second most common genes encountered in the Kingdom, were excluded. It is possible that other improvements in care during the study period could have contributed to the improved outcomes with CAZ-AVI as this novel agent was used in 2017 and after. However, it is the largest comparative study to date to address this question and was conducted in 5 tertiary care hospitals. This study included multiple infection sources with similar distribution between the 2 groups. The majority of the strains produced $bla_{\text{OXA-48}}$ which were less addressed by the previous studies. Lastly, the control arm included one comparator with standardized dosing.

In conclusion, this study demonstrated that CAZ-AVI is associated with higher rate of clinical cure and lower rate of AKI when compared with colistin-based regimen for the treatment of infections caused by CRE. Our findings continue to support the preferential use of CAZ-AVI over colistin-based regimen for treatment of these infections.

Abbreviations

AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation; CAZ-AVI, ceftazidime-avibactam; CCI, Charlson comorbidity index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; cIAI, complicated intra-abdominal infections; CLSI, Clinical and Laboratory Standards Institute; CMS, colistimethate sodium; cUTI, complicated urinary tract infections; HABP/VABP, hospital-acquired and ventilator-associated bacterial pneumonia; ICU, intensive-care unit; IQR, interquartile range; IV, intravenous; KAMC, King Abdulaziz Medical City; KFMC, King Fahad Medical City; KFSHRC, King Faisal Specialist Hospital and Research Center; KPC, Klebsiella pneumoniae carbapenemase; KSUMC, King Saud University Medical City; MIU, million international unit; MDR, multidrug-resistant; OR, odds ratio; RIFLE, risk, injury, failure, loss of kidney function, and end-stage kidney disease; SD, standard deviation; SFH, Security Forces Hospital; WHO, World Health Organization.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The study was approved by the IRB of the participating hospitals at KSUMC, KFMC, KFSHRC, KAMC, and SFH. All data were anonymized to maintain participant's privacy. In light of retrospective and anonymous nature of the study, the Ethics committees did not require written informed consent provided by participants. The manuscript complies with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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