J Antimicrob Chemother 2021; **76**: 775–783
doi:10.1093/jac/dkaa503 Advance Access publication 29 November 2020

Journal of Antimicrobial Chemotherapy

Ceftazidime/avibactam in the era of carbapenemase-producing *Klebsiella pneumoniae*: experience from a national registry study

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Received 31 August 2020; accepted 6 November 2020

Background: Infections caused by KPC-producing *Klebsiella pneumoniae* (Kp) are associated with high mortality. Therefore, new treatment options are urgently required.

Objectives: To assess the outcomes and predictors of mortality in patients with KPC- or OXA-48-Kp infections treated with ceftazidime/avibactam with an emphasis on KPC-Kp bloodstream infections (BSIs).

Methods: A multicentre prospective observational study was conducted between January 2018 and March 2019. Patients with KPC- or OXA-48-Kp infections treated with ceftazidime/avibactam were included in the analysis. The subgroup of patients with KPC-Kp BSIs treated with ceftazidime/avibactam was matched by propensity score with a cohort of patients whose KPC-Kp BSIs had been treated with agents other than ceftazidime/avibactam with *in vitro* activity.

Results: One hundred and forty-seven patients were identified; 140 were infected with KPC producers and 7 with OXA-48 producers. For targeted therapy, 68 (46.3%) patients received monotherapy with ceftazidime/avibactam and 79 (53.7%) patients received ceftazidime/avibactam in combination with at least another active agent. The 14 and 28 day mortality rates were 9% and 20%, respectively. The 28 day mortality among the 71 patients with KPC-Kp BSIs treated with ceftazidime/avibactam was significantly lower than that observed in the 71 matched patients, whose KPC-Kp BSIs had been treated with agents other than ceftazidime/avibactam (18.3% versus 40.8%; $P = 0.005$). In the Cox proportional hazards model, ultimately fatal disease, rapidly fatal disease and Charlson comorbidity index ≥ 2 were independent predictors of death, whereas treatment with ceftazidime/avibactam-containing regimens was the only independent predictor of survival.

Conclusions: Ceftazidime/avibactam appears to be an effective treatment against serious infections caused by KPC-Kp.

Introduction

Several official organizations, including the WHO[1] and the IDSA,[2] have designated antimicrobial resistance as one of the major problems affecting human health and health economics.[3] Carbapenem-resistant *Klebsiella pneumoniae* producing KPC-type carbapenemases (KPC-Kp) have emerged as important nosocomial pathogens, causing serious infections associated with high mortality.[4–6] Unfortunately, KPC-Kp exhibit extensive drug-resistant phenotypes and there has been an ongoing debate on the best strategies for the management of KPC-Kp infections.[4] The last-resort antibiotics, colistin and fosfomycin, as well as tigecycline, have been used in recent decades in critically ill hosts.[7] However, clinical utility is less than desirable owing to concerns over poor efficacy and their toxicity profiles, as well as matters of rapidly emerging resistance rates.[7,8]

A significant interest has arisen towards novel β-lactam/β-lactamase inhibitor combinations.[9] Ceftazidime/avibactam is a new combination antimicrobial agent consisting of a broad-spectrum cephalosporin, ceftazidime, and a novel non-β-lactam β-lactamase inhibitor, avibactam, demonstrating *in vitro* activity against resistant Gram-negative bacteria, including MDR, XDR and even pan-drug-resistant Gram-negative bacteria producing ESBL, AmpC, KPC and some class D enzymes.[9] Ceftazidime/avibactam has been launched for the treatment of adults suffering from complicated intra-abdominal infection, complicated urinary tract infection and hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), in the USA[10] and Europe,[11] and has also been approved by the EMA for the treatment of patients with bacteraemia associated with complicated urinary tract infection, complicated intra-abdominal infection and HAP/VAP,[12] as well as for infections due to aerobic Gram-negative organisms with limited treatment options.[11] Recently, investigators have highlighted the beneficial effect of ceftazidime/avibactam in the treatment of KPC-Kp, signalling a turning point in the treatment of infections in terms of promising efficacy, favourable outcome and lower mortality.[13–15] However, the real-life experience of ceftazidime/avibactam in the treatment of KPC-Kp is still limited.[13–15]

The aim of the present study was to evaluate the therapeutic efficacy of ceftazidime/avibactam in patients with documented infections caused by *K. pneumoniae* producing KPC or OXA-48, just after the launch of ceftazidime/avibactam in Greece in December 2017. A secondary objective was to assess the efficacy of ceftazidime/avibactam in the subgroup of patients with KPC-Kp bacteraemia compared with a matched cohort of patients with bacteraemic KPC-Kp infections managed with the older antimicrobial agents.

Methods

Description of the study

This was a prospective, multicentre, registry study for ceftazidime/avibactam, organized by the Hellenic Society for Chemotherapy.

Setting

The study was conducted between January 2018 and March 2019 in 14 tertiary care hospitals located throughout Greece [9 in Athens and 5 in other districts (Thessaloniki, Patra, Larisa and Lamia)]. The study protocol was approved by the Ethics Committee of each participating hospital and written informed consent was obtained from all patients or their legal representatives.

Patient population

Patients were eligible for inclusion in the study if they: (i) were ≥18 years old; (ii) had a microbiological documented infection caused by *K. pneumoniae* producing KPC or OXA-48 that exhibited susceptibility to ceftazidime/avibactam; and (iii) had received ceftazidime/avibactam alone or in combination with another antimicrobial agent for at least 72 h. Pertinent information, including demographic characteristics and host-, infection- and treatment-related factors were recorded in a predesigned form. Charlson's comorbidity index, APACHE II score, SOFA score and McCabe classification were evaluated as previously described.[16–20]

Microbiology

Bacterial identification and routine susceptibility testing were performed in the clinical laboratories of each participating hospital in accordance with their standard protocols. Isolates were transferred to the Infectious Diseases Research Laboratory of Hygeia General Hospital for further study. Susceptibilities were retested using the VITEK® 2 system (bioMérieux, Marcy-l'Étoile, France). MICs of ceftazidime/avibactam were determined by Etest (bioMérieux), according to the manufacturer's instructions, as this agent was not included in the VITEK® 2 susceptibility card used. MICs of colistin were further determined by broth microdilution, as the performance of VITEK® 2 for colistin has been reported to be not satisfactory, with an unacceptable rate of very major errors (false-susceptible results) and essential agreement (MICs that differ by less than two dilutions).[21] *Escherichia coli* ATCC 25922, *K. pneumoniae* ATCC 700603 and *E. coli* NCTC 13846 (*mcr-1* positive) were used as quality control strains. The results were interpreted in accordance with the EUCAST clinical breakpoints.[22] Carbapenemase gene content was initially detected using the NG-Test CARBA 5 immunochromatographic assay (NG Biotech, Guipry, France) and confirmed by simplex in-house PCR assays targeting bla_{KPC}, $bla_{OXA\text{-}48\text{-}like}$, bla_{VIM}, bla_{NDM} and bla_{IMP}, with specific primers and conditions described previously.[8]

Antibiotic therapy

Targeted antibiotic therapy was chosen by the attending physician of each patient based on the susceptibility profile of the infecting organism. Ceftazidime/avibactam was administered IV at a dosage of 2.5 g every 8 h in a 2 h infusion.[10,11] The remaining antimicrobial agents were administered as follows: colistin at a loading dose of 9 M IU followed by 4.5 M IU every 12 h in a 1 h infusion; tigecycline at a loading dose of 100–200 mg followed by 50–100 mg every 12 h in a 2 h infusion; fosfomycin at 6 g every 6 h in a 2 h infusion; meropenem at 2 g every 8 h in a 3 h infusion; and gentamicin at 5 mg/kg and amikacin at 15 mg/kg as a single daily dose in a 1 h infusion. Dosages were adjusted to creatinine clearance whenever indicated.[7]

Definitions

The source of infection was determined using the CDC/National Healthcare Safety Network criteria.[23] Bloodstream infections (BSIs) were classified as primary, when no apparent source was identified, as secondary, when a source was identified, or as catheter related. Infection onset was reported as the date of the first specimen collection that yielded the infecting organism. Antimicrobial treatment administered before susceptibility testing was defined as empirical and treatment given after susceptibility testing had become available was defined as targeted. Treatment regimens were classified as monotherapy (treatment with one agent with *in vitro* activity) or combination therapy (treatment with two or more agents with *in vitro* activity). Clinical failure was defined as death or lack of clinical improvement

and microbiological failure as persistence of positive cultures with the index organism (in patients with repeated cultures available). Presumed eradication was defined as suspected microbiological eradication in accordance with clinical improvement without, however, microbiological confirmation due to non-feasibility of appropriate culture specimens.

Statistical analysis

The main focus of interest was targeted antibiotic therapy with ceftazidime/avibactam. The primary outcome variable was the 28 day all-cause mortality, defined as the occurrence of death within 28 days from the date of specimen collection of the index culture. Secondary outcomes were: 14 day all-cause mortality and clinical and microbiological failure at day 14. Continuous variables are reported as mean ± SD or median (IQR) and were assessed using Student's *t*-test (for normally distributed variables) or the Mann–Whitney *U*-test (for non-normally distributed variables), whereas categorical variables are expressed as frequency distributions of the group from which they were derived and were assessed using the χ^2 test. Survivors and non-survivors were assessed to identify factors associated with mortality. Cox proportional hazards regression was performed to identify factors independently associated with mortality. In order to examine the efficacy of ceftazidime/avibactam in the subgroup of patients with bacteraemia, a matched cohort of patients with KPC-Kp BSIs who had been managed in two of the participating hospitals and had received treatment regimens that did not include ceftazidime/avibactam was used as a control group. The two groups were matched with their propensity scores calculated by multivariate logistic analysis using age, Charlson's comorbidity index, McCabe classification, septic shock, ICU stay, source of BSI, colistin MIC and empirical therapy (active/not active) as the predictors. The 28 day all-cause mortality was compared between the matched groups with Cox proportional hazards regression, reporting in each case the *P* value and the HR with its related 95% CI. Data were processed and analysed using SPSS software (version 25) and corroborated with the R statistical package. The level of significance was set at 0.05.

Results

Patients

During the study period, a total of 149 patients were enrolled in the study. Two patients were excluded from the analysis due to bacteria not producing KPC or OXA-48 and the final population consisted of 147 patients. One hundred and nine patients (74.1%) were male and 38 (25.9%) were female; the mean ± SD age of the patients was 60.9±17.10 years. One hundred and twenty-eight (87.1%) infection episodes were hospital acquired and 19 (12.9%) were healthcare associated; an equal number of infections occurred in the wards (73, 49.7%) and in ICUs (74, 50.3%). Bacteraemia was confirmed in 95 (64.6%) patients [31 (21.1%) primary, 44 (29.9%) secondary and 20 (13.6%) catheter related]. Secondary BSI site-specific sources were urinary tract infection (16, 36,4%), VAP/HAP (12, 27.3%), intra-abdominal infection (11, 25%) and skin and skin structure infection (5, 11.3%). VAP and HAP were the most common infections ($n = 37$) followed by complicated urinary tract infection ($n = 33$) and intra-abdominal infection ($n = 15$). The median Charlson comorbidity index was 2; 45 (30.6%) patients had ultimately fatal, 21 (14.3%) patients had rapidly fatal and 81(55.1%) patients had non-fatal underlying disease. The APACHE II and SOFA scores at the onset of infection were 16.5±7.6 and 6.7±4.2, respectively. Fifty patients (34%) manifested septic shock and 97 (66%) sepsis (by Sepsis-3)[24] (Table 1).

Microorganisms

The majority of the isolates (140, 95%) produced KPC, whereas the remaining 7 (5%) produced OXA-48, with a median ceftazidime/avibactam MIC of 1 mg/L (range = 0.25–6 mg/L). As expected, all strains were resistant to penicillin/inhibitor combinations and expanded-spectrum cephalosporins and the vast majority exhibited resistance to meropenem (99%). Rates of resistance to colistin, fosfomycin, tigecycline and aminoglycosides were 34%, 34%, 44% and 69%, respectively.

Treatment

For empirical antimicrobial treatment, 59 patients (40.1%) received no active agent and 88 (59.9%) received at least one active agent. Of note, in 20 patients the active empirical regimen included ceftazidime/avibactam. For targeted therapy, 68 (46.3%) patients received monotherapy with ceftazidime/avibactam and 79 (53.7%) received ceftazidime/avibactam in combination with at least another active agent [colistin ($n = 28$), aminoglycosides ($n = 20$), colistin plus tigecycline ($n = 15$), tigecycline ($n = 9$), trimethoprim/sulfamethoxazole ($n = 3$), fosfomycin ($n = 1$), ciprofloxacin ($n = 1$), colistin plus aminoglycoside ($n = 1$) and tigecycline plus fosfomycin ($n = 1$)]. The median duration of ceftazidime/avibactam treatment was 13 days (range = 5–50 days). Infection source control was performed when indicated in 32 patients [removal of central IV catheter in 20 patients with catheter-related BSIs, nephrostomy or pigtail insertion in 7 patients with urinary tract obstruction, percutaneous or surgical drainage in 3 patients with intra-abdominal or skin and soft tissue infections, and placement of a chest tube in 2 patients with empyema].

Outcome

The all-cause 14 and 28 day mortality was 9% and 20%, respectively. The highest mortality rate (37.8%) was observed in patients with VAP or HAP and the lowest in those with complicated intra-abdominal infection (13.3%) and complicated urinary tract infection (15.2%). At day 14, clinical success was observed in 81.0% (119/147) of patients, clinical failure in 10.2% (15/147) and in 8.8% (13/147) the clinical outcome was undetermined. In terms of microbiological response, at day 14, in 50.4% (74/147) of patients the pathogen was eradicated, in 37.4% (55/147) of patients the pathogen was presumably eradicated and in the remaining 12.2% (18/147) of patients the pathogen persisted. Emergence of resistance to ceftazidime/avibactam during therapy was observed in two patients (1.4%) [one patient with BSI treated with combination therapy and one with complicated urinary tract infection treated with ceftazidime/avibactam monotherapy]. Relapse of infection after discontinuation of ceftazidime/avibactam therapy during hospitalization was observed in six (4.1%) patients [two patients relapsed with KPC-Kp susceptible to ceftazidime/avibactam and four with *K. pneumoniae* producing both KPC and MBL exhibiting resistance to ceftazidime/avibactam].

The effects of host-, infection- and treatment-related factors on 28 day mortality are shown in Table 1. By entering the variables with a potential effect on mortality in the Cox proportional hazards model, rapidly fatal diseases [HR of death compared with non-fatal disease = 4.83 (95% CI = 2.05–11.39); $P = 0.001$], Charlson's comorbidity index ≥2 [HR = 1.16 (95% CI = 1.02–1.33); $P = 0.024$]

Table 1. Univariate analysis of factors associated with all-cause 28 day mortality in 147 patients infected with *K. pneumoniae* producing KPC or OXA-48

Characteristic	All patients (*N* = 147)	Survivors (*N* = 117)	Non-survivors (*N* = 30)	*P*
Age (years), mean (SD)	60.9 (17.1)	59.7 (17.2)	65.5 (16.0)	0.109
Gender, *n* (%)				
male	109 (74.1)	85 (72.6)	24 (80.0)	0.490
female	38 (25.9)	32 (27.4)	6 (20.0)	
Acquisition of infection, *n* (%)				
hospital acquired	128 (87.1)	102 (87.2)	26 (86.7)	1.00
healthcare associated	19 (12.9)	15 (12.8)	4 (13.3)	
Ward at onset of infection, *n* (%)				
ICU	74 (50.3)	59 (50.4)	15 (50.0)	1.00
non-ICU	73 (49.7)	58 (49.6)	15 (50.0)	
Charslon comorbidity index, median (IQR)	2 (1–5)	2 (0–4)	3.5 (1–7)	0.032
Severity of underlying disease, *n* (%)				
non-fatal	81 (55.1)	71 (60.7)	10 (33.3)	0.001
ultimately fatal	45 (30.6)	37 (31.6)	8 (26.7)	
rapidly fatal	21 (14.3)	9 (7.7)	12 (40.0)	
APACHE II score at onset of infection, mean (SD)	16.5 (7.6)	15.4 (7.0)	21.0 (8.4)	0.001
SOFA score at onset of infection, mean (SD)	6.7 (4.2)	6.2 (4.0)	8.3 (4.5)	0.031
Carbapenemase type, *n* (%)				
KPC	140 (95)	113 (96.6)	27 (90)	0.150
OXA-48	7 (5)	4 (3.4)	3 (10)	
Severity of infection, *n* (%)				
sepsis	97 (66.0)	80 (68.4)	17 (56.7)	0.281
septic shock	50 (34.0)	37 (31.6)	13 (43.3)	
Source of infection, *n* (%)				
BSI	95 (64.6)	78 (66.7)	17 (56.7)	0.989
primary	31 (21.1)	25 (21.4)	6 (20.0)	
secondary[a]	44 (29.9)	34 (29.1)	10 (33.3)	
catheter related	20 (13.6)	19 (16.2)	1 (3.3)	
urinary tract infection	33 (22.4)	28 (23.9)	5 (16.7)	
HAP/VAP	37 (25.2)	23 (19.7)	14 (46.7)	
intra-abdominal infection	15 (10.2)	13 (11.1)	2 (6.7)	
other	11 (7.5)	9 (7.7)	2 (6.7)	
Empirical treatment, *n* (%)				
no active drug	59 (40.1)	46 (39.3)	13 (43.3)	0.912
at least one active drug	88 (59.9)	71 (60.7)	17 (56.7)	
Targeted therapy, *n* (%)				
ceftazidime/avibactam monotherapy	68 (46.3)	60 (51.3)	8 (26.7)	0.023
ceftazidime/avibactam combination therapy	79 (53.7)	57 (48.7)	22 (73.3)	

[a]Secondary BSI site-specific sources were urinary tract infection (16, 36,4%), VAP/HAP (12, 27.3%), intra-abdominal infection (11, 25%) and skin and skin structure infection (5, 11.3%).

and combination therapy with ceftazidime/avibactam [HR of death for combination therapy versus monotherapy = 2.49 (95% CI = 1.1–5.63); *P* = 0.029] were identified as independent predictors of death.

Table 2 shows the clinical characteristics of 71 patients with KPC-Kp BSIs who received treatment with a regimen containing ceftazidime/avibactam (cases) and of 71 patients, matched by propensity score, whose KPC-Kp BSIs were treated with regimens not containing ceftazidime/avibactam (controls). The results of univariate analysis of factors associated with 28 day mortality are shown in Table 3. The all-cause 28 day mortality rate of patients treated with ceftazidime/avibactam-based regimens was significantly lower than that of controls (18.3% versus 40.8%; *P* = 0.005). The mortality rates within the various treatment groups among the 142 patients with KPC-Kp BSIs (cases and controls) are shown in Figure 1; the lowest mortality was observed in patients treated with aminoglycoside monotherapy (1/6, 16.7%) or ceftazidime/avibactam-containing regimens (13/71, 18.3%) and the highest in patients treated with colistin monotherapy (4/9, 44%) or tigecycline monotherapy (7/14, 50%).

By entering the variables with a potential effect on mortality in the Cox proportional hazards model, ultimately fatal disease

Table 2. Characteristics of 142 patients with KPC-Kp bacteraemia according to treatment regimen after propensity-score matching

Variable	Therapy		*P*
	other regimens (controls), *N* = 71	ceftazidime/avibactam-based regimens (cases), *N* = 71	
Gender, *n* (%)			
male	47 (66.2)	48 (67.6)	1.000
female	24 (33.8)	23 (32.4)	
Age (years), mean (SD)	64.0 (16.9)	61.4 (17.2)	0.356
Charslon comorbidity index, median (IQR)	2 (1–4)	2 (1–4)	0.471
Severity of underlying disease, *n* (%)			
non-fatal	41 (57.7)	43 (60.6)	0.874
ultimately fatal	20 (28.2)	20 (28.2)	
rapidly fatal	10 (14.1)	8 (11.3)	
Acquisition of infection, *n* (%)			
healthcare associated	10 (14.1)	11 (15.5)	1.000
hospital acquired	61 (85.9)	60 (84.5)	
Ward at onset of infection, *n* (%)			
non-ICU	39 (54.9)	36 (50.7)	0.737
ICU	32 (45.1)	35 (49.3)	
Source of BSI, *n* (%)			
urinary tract infection	9 (12.7)	14 (19.7)	0.363
non-urinary tract infection	62 (87.3)	57 (80.3)	
Severity of sepsis, *n* (%)			
sepsis	42 (59.2)	46 (64.8)	0.604
septic shock	29 (40.8)	25 (35.2)	
Empirical treatment, *n* (%)			
no active drug	32 (45.1)	26 (36.6)	0.393
at least one active drug	39 (54.9)	45 (63.4)	
Colistin MIC, median (IQR)	0.38 (0.25–8)	1.0 (0.5–16)	0.001
Propensity index, mean (SD)	0.45 (0.15)	0.48 (0.16)	0.350

[HR = 2.25 (95% CI = 1.08–4.70); *P* = 0.03], rapidly fatal disease [HR = 6.4 (95% CI = 2.0–20.5); *P* = 0.001] and Charlson comorbidity index ≥2 [HR = 2.44 (95% CI = 1.08–5.52); *P* = 0.032] were identified as independent predictors of death, whereas treatment with ceftazidime/avibactam-containing regimens [HR = 0.37 (95% CI = 0.19–0.71); *P* = 0.003] remained an independent predictor of survival (Table 4 and Figure 2).

Discussion

The findings presented herein provide useful information on the efficacy of ceftazidime/avibactam in the treatment of serious infections caused by *K. pneumoniae* producing KPC or OXA-48. In particular, ceftazidime/avibactam was effective in the treatment of a broad range of serious infections caused by *K. pneumoniae* producing KPC or OXA-48. More importantly, treatment with ceftazidime/avibactam provided survival benefit compared with other antimicrobial agents against KPC-Kp (mostly colistin) and its administration was an independent predictor for favourable outcome in KPC-Kp bacteraemic patients.

A growing body of literature has investigated the treatment outcomes in patients infected with carbapenem-resistant *K. pneumoniae*.[4,25–28] When applying commonly used antibiotics for *K. pneumoniae*, combination treatment with at least two antibiotics with *in vitro* activity has been reported to be beneficial in terms of survival.[25,26] Particularly, the combination of meropenem (if MIC is ≤8 mg/L) with gentamicin or colistin or tigecycline has been associated with a reduction in mortality.[25–28] However, in the absence of a carbapenem in combination treatment, mortality rates ranged around 35%[25] and increased up to 48% in patients with an INCREMENT mortality score ≥8.[27] In our study, meropenem resistance rates rose to 99%, indicating the necessity of a novel treatment for KPC infections. On the other hand, ceftazidime/avibactam, although approved for complicated urinary tract infection and complicated intra-abdominal infection,[10,11] has been mostly utilized in 'difficult-to-treat infections' caused by KPC-Kp.[11,13–15,29–31] In the majority of published studies, mortality rates of patients with KPC infections treated with ceftazidime/avibactam are reported to be below 20%;[13,14,30,31] however, in a few studies the rates exceed 30%.[15,29] Shields *et al.*[13] reported mortality of 15%, whereas van Duin *et al.*[14] reported an even lower mortality rate of 8% (compared with 38% for colistin). In our cohort, the all-cause 28 day mortality rate was rather low (calculated at around 20%). These results are quite impressive taking into

Table 3. Univariate analysis of factors associated with all-cause 28 day mortality in 142 patients with KPC-Kp (cases and controls)

Characteristic	All patients (*N* = 142)	Survivors (*N* = 100)	Non-survivors (*N* = 42)	*P*
Age (years), mean (SD)	62.7 (17.0)	62.2 (17.8)	63.9 (15.3)	0.600
Gender, *n* (%)				
male	95 (66.9)	70 (70.0)	25 (59.5)	0.245
female	47 (33.1)	30 (30.0)	17 (40.5)	
Acquisition of infection, *n* (%)				
hospital acquired	121 (85.2)	86 (86.0)	35 (83.3)	0.796
healthcare associated	21 (14.8)	14 (14.0)	7 (16.7)	
Ward at onset of infection, *n* (%)				
ICU	67 (47.2)	48 (48.0)	19 (45.2)	0.854
non-ICU	75 (52.8)	52 (52.0)	23 (54.8)	
Charslon comorbidity index, median (IQR)	2 (1–4)	2 (0–3)	3 (2–5)	0.007
Severity of underlying disease, *n* (%)				
non-fatal	84 (59.2)	70 (70.0)	14 (33.3)	<0.001
ultimately fatal	40 (28.2)	22 (22.0)	18 (42.9)	
rapidly fatal	18 (12.7)	8 (8.0)	10 (23.8)	
Severity of infection, *n* (%)				
sepsis	88 (62.0)	67 (67.0)	21 (50.0)	0.062
septic shock	54 (38.0)	33 (33.0)	21 (50.0)	
Source of infection, *n* (%)				
urinary tract infection	119 (83.8)	83 (83.0)	36 (85.7)	
non-urinary tract infection	23 (16.2)	17 (17.0)	6 (14.3)	0.806
Empirical treatment, *n* (%)				
no active drug	58 (40.8)	40 (40.0)	18 (42.9)	0.852
at least one active drug	84 (59.2)	60 (60.0)	24 (57.1)	
Targeted therapy, *n* (%)				
ceftazidime/avibactam-based regimen	71 (50.0)	58 (58.0)	13 (31.0)	0.005
other antimicrobial regimen	71 (50.0)	42 (42.0)	29 (69.0)	

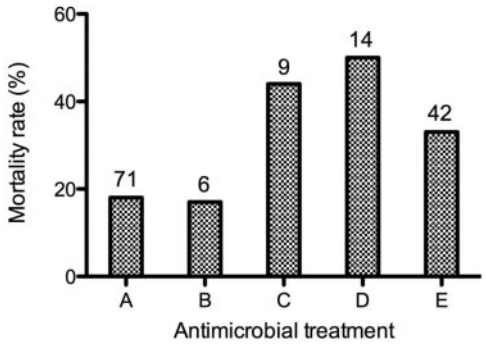

Figure 1. All-cause 28 day mortality in 142 patients with KPC-producing *K. pneumoniae* bloodstream infections according to treatment regimen: A, ceftazidime/avibactam alone or in combination with another agent with *in vitro* activity; B, aminoglycoside monotherapy; C, colistin monotherapy; D, tigecycline monotherapy; E, combination of two or more active antimicrobial agents (not including ceftazidime/avibactam). The bars indicate the mortality rates and the number above each bar indicates the number of patients treated with that regimen.

consideration the critical illness of the patients, 50% being hospitalized in the ICU, with septic shock in 34% and high SOFA and APACHE II scores.

Table 4. Cox proportional hazards model of factors associated with all-cause 28 day mortality in 142 patients with KPC-Kp bloodstream infections

Variable	HR (95% CI)	*P*
Severity of underlying disease		
ultimately fatal/non-fatal	2.25 (1.08–4.70)	0.03
rapidly fatal/non-fatal	6.4 (2.0–20.5)	0.001
Charlson comorbidity index ≥2	2.44 (1.08–5.52)	0.032
Septic shock/sepsis	1.67 (0.90–3.12)	0.100
Ceftazidime/avibactam-based therapy/other antimicrobials	0.37 (0.19–0.71)	0.003

Empirical therapy for the treatment of KPC-Kp BSI is an essential matter. Adequate and timely administration of empirical therapy has been linked with improved survival. In an observational study with 102 patients with KPC-Kp BSI, the median time to an appropriate antibiotic was shorter in patients who survived, and receipt of therapy with *in vitro* activity within 24 h was associated with reduced 30 day mortality.[32] Moreover, receipt of ceftazidime/avibactam within 48 h of infection onset was associated with reduced

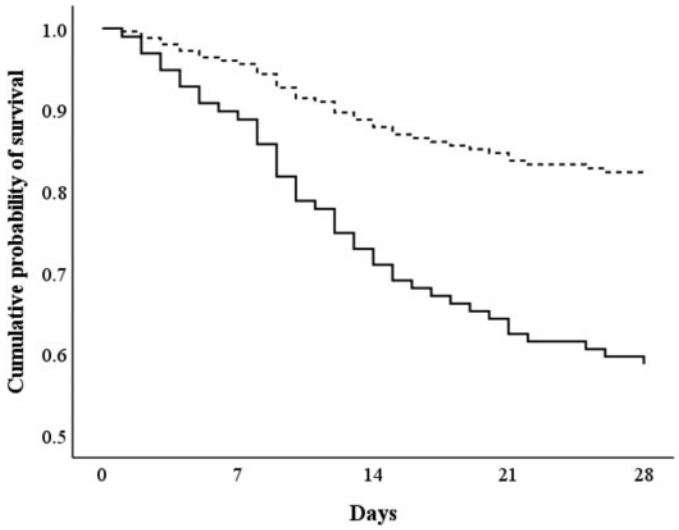

Figure 2. Cumulative probability of survival of 142 patients with KPC-producing *K. pneumoniae* bloodstream infections according to treatment regimen adjusted for severity of underlying diseases (McCabe classification), Charlson's comorbidity index and septic shock. Broken line, regimens containing ceftazidime/avibactam; continuous line, other treatment regimens (not containing ceftazidime/avibactam). HR = 0.37 (95% CI = 0.19–0.71); $P = 0.003$ (Cox proportional hazards regression model).

clinical failure [OR = 0.409 (95% CI = 0.180–0.930)].[31] Notably, ceftazidime/avibactam regimens were also associated with reduced risk of a composite endpoint (30 day mortality or nephrotoxicity).[32] In our study, empirical therapy with at least one drug with *in vitro* activity amongst survivors was correlated with higher percentages of survival (71/117, 60.7%), when compared with patients treated empirically with no active regimen (46/117, 39. 3%) (Table 1).

In the present study, ceftazidime/avibactam treatment in the subgroup of patients with KPC-Kp bacteraemia resulted in a significantly lower mortality rate (18%) compared with that achieved by other antimicrobial agents, which rose to 41%. Also, it is important to note, that in our cohort, treatment with ceftazidime/avibactam-containing regimens was the only independent predictor of survival. Our findings are in line with those of an Italian study that showed 30 day mortality among 104 patients with bacteraemic KPC-Kp infections treated with ceftazidime/avibactam to be lower than that of a matched cohort whose KPC-Kp bacteraemia was treated with drugs other than ceftazidime/avibactam.[15] Similarly, in another cohort study, ceftazidime/avibactam was superior to other antimicrobial agents in the treatment of carbapenem-resistant Enterobacteriaceae (CRE) infections in terms of survival, clinical outcome and microbiological eradication.[30]

In the pre-ceftazidime/avibactam era, combination treatment with two or more agents with *in vitro* activity was considered to be superior to monotherapy in the treatment of CRE infections, particularly in patients with septic shock, high mortality score or rapidly fatal underlying diseases.[25–28] In the present study, however, combination therapy with ceftazidime/avibactam did not provide any survival benefit as compared with ceftazidime/avibactam monotherapy. Instead, the patients treated with ceftazidime/avibactam alone had better outcomes compared with those treated with ceftazidime/avibactam in combination with another active agent. The observed difference, in favour of the monotherapy group, could be explained by the inclusion of more serious infections in the combination group as physicians have the temptation to treat critically ill patients with more than one antibiotic. Indeed, in the present study, combination therapy was prescribed more often in more severe and septic shock patients (monotherapy versus combination treatment, 36% versus 64%; $P = 0.165$). It is worth mentioning, however, that this difference was lost in the propensity-matched patients with BSIs. It is important to notice that ceftazidime/avibactam monotherapy has been applied in other studies and has also shown remarkable clinical success rates.[13,15,31,33] Furthermore, in a meta-analysis, including 11 studies with 396 subjects (202 in the ceftazidime/avibactam combination group and 194 in the ceftazidime/avibactam monotherapy group), ceftazidime/avibactam monotherapy and ceftazidime/avibactam combination therapy against CRE infections resulted in similar outcomes with regard to microbiological eradication and mortality rates.[34] Likewise, in a more recent network meta-analysis, consisting of 13 studies with 503 patients, no difference was observed in terms of mortality regarding ceftazidime/avibactam monotherapy and combination treatment [OR = 0.96 (95% CI = 0.65–1.41)].[35] The consistent lack of benefit of combination therapy across studies[13,15,31,33] and the potential toxicity of combination therapy[13,31] raises a major question about any additional benefit provided by ceftazidime/avibactam combination as compared with monotherapy and merits further investigation. However, more evidence is required in order to make robust conclusions regarding ceftazidime/avibactam monotherapy or combination therapy for the treatment of KPC-Kp infections.

It is of great significance to mention that treatment of different types of infection among patients with CRE pathogens differs dramatically.[15] The lowest mortality rates were observed in complicated intra-abdominal infection and complicated urinary tract infection, in accordance with other studies dealing with KPC-Kp infections.[15,26] On the other hand, it has been clearly illustrated that pneumonia is a risk factor for ceftazidime/avibactam treatment failure.[36] In our study, the highest mortality rate was noticed in the subgroup of patients with pneumonia (reaching 38%). Furthermore, in a retrospective study, clinical success rates in patients with pneumonia were the lowest (36%) in comparison with patients with bacteraemia (75%).[36] The adverse outcome among patients with CRE pneumonia cannot be clearly attributed to pharmacokinetic parameters, as ceftazidime/avibactam achieves adequate concentrations in the epithelial lining fluid.[37] However, ceftazidime/avibactam pharmacokinetics in critically ill patients have not yet been studied. On the other hand, in a Phase 3 randomized trial (REPROVE study), ceftazidime/avibactam was found to be non-inferior to meropenem in patients with nosocomial pneumonia caused by Gram-negative organisms.[38] Despite the non-inferiority of ceftazidime/avibactam to meropenem for nosocomial pneumonia, it should be underlined that only six patients were infected with CRE in the aforementioned study, limiting our ability to draw conclusions on the efficacy of ceftazidime/avibactam in nosocomial pneumonia caused by KPC-producing pathogens.[38] Therefore, further studies focusing on VAP/HAP caused by MDR and XDR CRE treated with ceftazidime/avibactam are required.

Although ceftazidime/avibactam is mostly prescribed for KPC-Kp infections,[13–15] ceftazidime/avibactam has been reported as having *in vitro* activity against 92.5% of OXA-48-producing isolates;[39] however, clinical experience is limited and the data are conflicting.[29,40,41] In our series, only seven infections were caused by OXA-48 producers and the observed mortality rate was 43%. However, the small sample hindered the ability to make firm conclusions. Sousa *et al.*[40] reported 54 patients treated with ceftazidime/avibactam as salvage treatment for infections caused by OXA-48-producing *K. pneumoniae* with a 30 day mortality rate of 22%. Likewise, in a smaller retrospective study with 24 infections caused by OXA-48 producers, the 30 day mortality was 8.3%.[41] On the other hand, Temkin *et al.*,[29] in a retrospective study, noticed a higher mortality in patients with OXA-48-producing Enterobacterales (8/13, 61.5%) compared with patients with infections caused by KPC producers (6/23, 26.1%). Therefore, more data are required to elucidate the role of ceftazidime/avibactam in the treatment of infections caused by OXA-48-producing *K. pneumoniae*.

Development of resistance is a major issue of concern during treatment with ceftazidime/avibactam. Soon after ceftazidime/avibactam entered the market, both *in vitro* and *in vivo* emergence of resistance to ceftazidime/avibactam was observed.[13,15,42–44] In our cohort, resistance during therapy was observed in two patients (1.4%) and relapse with a ceftazidime/avibactam-resistant strain (producing both KPC and MBL) occurred in 2.7%. Similar rates of resistance to ceftazidime/avibactam have been reported in other studies,[15,31] with the exception of the study by Shields *et al.*,[13] reporting a higher resistance rate (8.1%) during treatment. Nevertheless, the emergence of resistance to ceftazidime/avibactam is independent from previous antimicrobial exposure and, therefore, is more worrisome and prompts early awareness.[45,46]

Our findings should not be interpreted without considering several limitations. We acknowledge the observational character of the study and the inherent shortcomings that exist in this type of study. Thus, unrecognized variables with potential effects on outcome might have influenced the results. However, a propensity-matched group of patients with KPC bacteraemic infections was used and multivariate Cox regression analysis was performed to control for such confounders and potential bias.

Notwithstanding these limitations, the data presented herein highlight ceftazidime/avibactam as an independent predictor in terms of survival, in particular in bacteraemic patients, for the treatment of infections caused by carbapenemase-producing *K. pneumoniae* and provide practical and useful information that may assist clinicians to adopt more effective strategies for the treatment of KPC infections.

Acknowledgements

Part of the work was presented in the European Congress of Clinical Microbiology and Infectious Diseases Abstract Book 2020 (Abstract 5234).

We thank Rania Karantani for technical work and Miltiades Kyprianou for outstanding statistical analysis.

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Funding

This study was supported by the Hellenic Society for Chemotherapy.

Transparency declarations

I.K. has received speaker's honoraria from Pfizer and bioMérieux, G.L.D. has received grants and honoraria from Pfizer and honoraria from Menarini and MSD outside of the submitted work, A.G. has received speaker's honoraria from Pfizer, S.S. has received speaker's honoraria from Pfizer, K.A. has received speaker's honoraria from Pfizer, G.P. has received speaker's honoraria from Pfizer, Angelini, Bio-Rad, MSD and Pfizer, and H.G. has received speaker's honoraria from Pfizer and MSD. All other authors: none to declare.

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