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MAJOR ARTICLE

Clinical Characteristics and Outcome of Ceftazidime/Avibactam-Resistant *Klebsiella pneumoniae* Carbapenemase–Producing *Klebsiella pneumoniae* Infections: A Retrospective, Observational, 2-Center Clinical Study

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Background. Recently, *Klebsiella pneumoniae* carbapenemase (KPC)–producing *Klebsiella pneumoniae* (KPC-Kp) with resistance to ceftazidime/avibactam (CZA-R) has been described, including KPC variants that restore carbapenem susceptibility. The aim of the study was to analyze the clinical characteristics and outcomes of infections caused by CZA-R KPC-Kp.

Methods. From 2019 to 2021, a retrospective 2-center study including patients with infections due to CZA-R KPC-Kp hospitalized at 2 academic hospitals in Rome was conducted. Demographic and clinical characteristics were collected. Principal outcome was 30-day all-cause mortality. Statistical analyses were performed with Stata-IC17 software.

Results. Overall, 59 patients were included (mean age, 64.4 ± 14.6 years; mean Charlson comorbidity index score, 4.5 ± 2.7). Thirty-four patients (57.6%) had infections caused by CZA-R and meropenem (MEM)–susceptible strains. A previous CZA therapy was observed in 40 patients (67.8%), mostly in patients with MEM-susceptible KPC variant (79.4% vs 52%, $P = .026$). Primary bacteremia was observed in 28.8%, followed by urinary tract infections and pneumonia. At infection onset, septic shock was present in 15 subjects (25.4%). After adjustment for confounders, only the presence of septic shock was independently associated with mortality ($P = .006$).

Conclusions. Infections due to CZA-R KPC-Kp often occur in patients who had previously received CZA, especially in the presence of strains susceptible to MEM. Nevertheless, one-third of patients had never received CZA before KPC-Kp CZA-R. Since the major driver for mortality was infection severity, understanding the optimal therapy in patients with KPC-Kp CZA-R infections is of crucial importance.

Keywords. carbapenems; ceftazidime/avibactam-resistant KPC-producing *Klebsiella pneumoniae*; ceftazidime/avibactam-resistant meropenem-susceptible KPC-producing *Klebsiella pneumoniae*; KPC variant; meropenem/vaborbactam.

INTRODUCTION

Ceftazidime/avibactam (CZA), a combination of a third-generation cephalosporin and a diazabicyclooctane β-lactamase inhibitor that inactivates Ambler classes A, C, and some class D β-lactamases, has been clinically useful for the challenging treatment of *Klebsiella pneumoniae* carbapenemase (KPC)–producing *K pneumoniae* (KPC-Kp) infections [1], lowering mortality and drug-related adverse events when compared to traditional therapies [2]. Nevertheless, resistance to CZA soon emerged in *K pneumoniae* isolates in the United States, where the first reported clinical case dates to 2015 [3]; in Europe, leading to a European Centre for Disease Prevention and Control rapid risk assessment publication in 2018 [4]; and in China [5], though still with a modest 3%–8% global rate [6, 7]. Increased CZA minimum inhibitory concentrations (MICs) have been related to different mechanisms, often combined within the same strain, including mutations in the β-lactamase Ω-loop [8, 9], but also overexpression of bla_{KPC} genes and mutations in outer membrane porins [10–13]. Among Ω-loop mutations, the D179Y substitution, mainly described in KPC-2– and KPC-3–producing strain variants, stands out not only as a reported threat, but also for the

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concomitant increased susceptibility to carbapenems [14–20], with a subsequent debate on the possibility to use carbapenems as therapeutic options in these cases [6, 21]. However, risk of reversal to the initial profile under selective sublethal carbapenem pressure exists [22], while agents like meropenem-vaborbactam (MVB) and its combination strategies, with retained activity toward this phenotype, have become available [23, 24].

Little is known about the clinical characteristics and therapeutic challenges offered by CZA-R KPC-producing *K pneumoniae* infections, and that is even more true for KPC-Kp variant infections exhibiting susceptibility to meropenem, as most of the evidence still come from small studies or case reports [6, 14, 25]. Therefore, this study aims to investigate the clinical characteristics and treatment strategies of infections caused by CZA-R KPC-Kp strains, with an insight into meropenem-susceptible (MEM-S) KPC-Kp variants and their potential association with 30-day mortality.

METHODS

Study Design and Setting

Adult patients (>18 years old) hospitalized between 2019 and December 2021 at Azienda Ospedaliero Universitaria Policlinico Umberto I and University Hospital Policlinico Tor Vergata, Rome, Italy, with documented CZA-R KPC-Kp infection were included in this retrospective 2-center study. Demographic, clinical, and therapeutic data were retrieved, and the outcome measure was 30-day mortality.

Patients were further divided according to the in vitro susceptibility or resistance to meropenem (MEM-S and MEM-R, respectively), following European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [26]. In detail, MEM resistance was considered if MEM MIC was >8 μg/mL [26].

Inclusion/Exclusion Criteria

Inclusion criteria were (1) adult hospitalized patients with documented infection due to CZA-R KPC-Kp and (2) at least 48 hours of hospitalization. Patients were excluded from the study if (1) aged <18 years, (2) not hospitalized or hospitalized for <48 hours, (3) with infections due to CZA-R bacterial species other than *K pneumoniae*, (4) with infection caused by CZA-R *K pneumoniae* other than KPC producers (metallo-β-lactamases or OXA), (5) colonization due to CZA-R KPC-Kp in the absence of infection, and (6) unavailability of clinical and microbiological data (Supplementary Figure 1).

Data Collection

The following information was reviewed: demographics, burden of comorbidities (expressed by Charlson comorbidity index [CCI]) [27], clinical and laboratory findings, intensive care unit (ICU) admission, previous exposure to CZA before infection, type of CZA-R KPC-Kp infection, presence of KPC variant susceptible to MEM, INCREMENT-CPE Score (ICS) [28], presence of septic shock, microbiological data, antibiotic regimens, therapeutic appropriateness, new onset of CZA-susceptible (CZA-S) strain, clinical cure, 30-day mortality, recurrence of CZA-R KPC-Kp infection, development of secondary infections, and duration of hospital stay after infection onset.

Definitions

Colonization was considered positive culture without concomitant signs and symptoms of infection. Infection onset was defined as the date of development of signs and symptoms of infection.

Infections were defined according to the Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC/NHSN) criteria [29]. Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) were defined in accordance with the CDC/NHSN surveillance definition of healthcare-associated infection for pneumonia with specific criteria [30]. VAP was defined as pneumonia in patients who had a device to assist or control respiration continuously through a tracheostomy or by endotracheal intubation within the 48-hour period before the onset of infection. KPC-Kp bloodstream infection (BSI) was defined when KPC-Kp was isolated from blood cultures (BCs) in the presence of clinical signs of infections, and BSI onset was defined as the date of collection of the index BC. In case of BSI, the likely or ascertained source of infection was indicated by the attending physician or by the infectious disease consultants (A. O. and L. C.) in the medical record according to guidelines [31]. Primary BSI was defined as BSI occurring in patients without a recognized source of infection. Central line–related BSI was defined if the semiquantitative culture of the catheter tip was positive for the same KPC-Kp isolated from the blood [32]. In case of doubt, a panel discussion was performed.

The burden of underlying comorbidities was evaluated by means of CCI [27]. Immunosuppression was defined as either steroid therapy with prednisone (or its equivalent) at a dose >0.5 mg/kg/day for at least 1 month or the receipt of chemotherapy, tumor necrosis factor–α inhibitors, cyclophosphamide, azathioprine, methotrexate, or mycophenolate mofetil in the previous 90 days.

Severity of infection was determined by using ICS calculated at the time of infection onset [28] and septic shock, defined in accordance with the Sepsis-3 criteria [33].

Antimicrobial Treatment Evaluation

Early (within 24 hours) in vitro active therapy was classified as appropriate if at least 1 administered antibiotic exhibited in vitro activity, according to the breakpoints established by EUCAST [26, 34]. If susceptibility test for an antibiotic was not available, it was considered not active.

Definitive antibiotic therapy was defined as the definitive antimicrobial treatment administered after the availability of susceptibility results, even if preliminary.

Early (within 48–72 hours) clinical improvement was defined as at least 1 of the following: weaning from vasopressors if needed at infection onset; fever disappearance >48 hours; procalcitonin reduction by >80% [35]; or C-reactive protein reduction by >75% [36]. Clinical cure was defined as clinical response to treatment with resolution of symptoms/signs of the infection upon discontinuation of antimicrobials [37].

Microbiological response was defined as the negativity of index cultures (when performed) under treatment.

CZA-R KPC-Kp infection relapse was defined as the onset of a second microbiologically documented CZA-R KPC-Kp infection in the 30 days after the end of treatment in a patient who had previously achieved clinical cure and microbiological response.

Secondary infection was defined as an infection (ie, urinary tract infection, pneumonia, bacteremia, candidemia) caused by a microorganism other than KPC-Kp in the 30 days after the start of treatment.

All-cause mortality was collected at 7, 14, and 30 days from infection onset.

Length of stay from infection onset was considered as the number of days from the date of infection to the date of discharge or death.

Microbiology

CARBA SMART selective chromogenic media (bioMérieux, Italy) was used to screen for carbapenemase-producing Enterobacterales. Colonies detected on CARBA SMART were identified with matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics). According to routine hospitals' microbiology laboratory protocol implemented to speed up the diagnostic procedures for positive BCs, bacterial pellet obtained from positive BCs was used for bacterial identification by MALDI-TOF MS (Bruker Daltonics). Antimicrobial susceptibility testing was performed with the Vitek 2 automated system (bioMérieux), the SensiTitre system (Thermo Fisher Scientific), or ITGN Micronaut panels (Diagnostika GmbH, now a company of Bruker Daltonics) run on MICRO MIB (Bruker Daltonics), as appropriate.

Subsequent molecular analysis for the search of *bla*KPC gene was performed for all the strains by the GeneXpert System (Cepheid). When available, details of KPC variants were retrieved according to recently published studies [15, 21, 38–40]. As previously reported, strains positive for a bla_{KPC} gene but negative with lateral flow immunoassays (LFIAs) for carbapenemase detection were presumptively considered KPC-31–producing KPC-Kp and defined as KPC-31-like–producing KPC-Kp [41].

Patient Consent Statement

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. The protocol was reviewed and approved by the local ethical committees (number 0069/2022 for Azienda Ospedaliero Universitaria Policlinico Umberto I and number 177.21 for University Hospital Policlinico Tor Vergata). Informed consent was waived due to the retrospective nature of the research.

Statistical Analysis

Continuous data are expressed as mean ± standard deviation, and categorical variables as numbers and percentage. Dichotomous variables were compared using χ^2 test or Fisher exact test, as appropriate and continuous variables with Student *t* test or Mann-Whitney test, as appropriate. Multivariate Cox regression model was performed to sort out the independent predictors of mortality within 30 days from infection onset, accounting for covariables. *P* value analyses were 2-sided and a *P* value of <.05 was considered statistically significant. All statistical analyses were performed using Stata software, version 17 (StataCorp) and GraphPad Prism, and charts using Microsoft Office and GraphPad Prism.

RESULTS

Study Population According to the Presence of KPC-Variant Strains Susceptible or Resistant to Meropenem

Overall, 59 patients with CZA-R KPC-Kp infection were included in the study, comprising 34 of 59 (57.6%) KPC-Kp variants susceptible to carbapenems (MEM-S); 34 of 59 (57.6%) patients were male, with a mean age of 64.4 ± 14.6 years and a mean CCI of 4.5 ± 2.7 (Table 1). Fourteen deaths were recorded within 30 days from infection onset and 20 during the entire hospitalization, accounting for a 23.7% 30-day mortality rate and 33.9% overall, with no difference observed in KPC-Kp variant detection (20.6% MEM-S vs 28% MEM-R, *P* = .508, and 32.3% MEM-S vs 36% MEM-R, *P* = .770, respectively). Forty-one of 59 patients (69.5%) had a previous isolate of a CZA-susceptible KPC-Kp strain and 40 of 59 (67.8%) received CZA treatment, with a mean time elapsed between CZA-S and CZA-R KPC-Kp strains isolation of 38.2 ± 37.2 days, longer in patients subsequently infected with MEM-S KPC-Kp variant (47.9 ± 43.4 vs 25.8 ± 23.1 days; *P* = .043). Moreover, patients with standing MEM-S KPC-Kp infections tended to be younger (mean, 60.3 ± 14.9 vs 70.1 ± 12.4 years; *P* = .008), hospitalized in ICU wards (25/34 [73.5%] vs 9/25 [36%] patients; *P* = .004), and had been treated more frequently with CZA prior to CZA-R KPC-Kp isolation (27/40 [79.4%] vs 13/25 [52%] patients; *P* = .026) than patients with MEM-R KPC-Kp infections. Though no difference was observed in the mean length of previous treatment with CZA, in MEM-S KPC-Kp infections it was more often administered as monotherapy (11/27 [40.7%] vs 1/13 [7.7%]; *P* = .033), of which 5 of 11 (45.4%) were lower respiratory tract infections.

Table 1. Population Characteristics of Ceftazidime/Avibactam-Resistant (CZA-R) *Klebsiella pneumoniae* Carbapenemase (KPC)–Producing *K pneumoniae* Infections, According to Meropenem-Susceptible and Meropenem-Resistant CZA-R KPC Variants

Characteristic	Overall Population (N = 59 ([100%])	MEM-S KPC Variant (n = 34 ([57.6%])	MEM-R KPC Variant (n = 25 [43.4])	*P* Value
Male sex	34 (57.6)	23 (67.6)	11 (44)	.063
Age, y, mean ± SD	64.4 ± 14.6	60.3 ± 14.9	70.1 ± 12.4	**.008**
CCI score, mean ± SD	4.5 ± 2.7	3.9 ± 2.5	5.2 ± 2.8	.076
ICU admission	34 (57.6)	25 (73.5)	9 (36)	**.004**
SARS-CoV-2 coinfection	10 (16.9)	5 (14.7)	5 (20)	.592
Previous CZA-S KPC-Kp isolation	41 (69.5)	24 (70.6)	17 (68)	.051
Previous CZA treatment	40 (67.8)	27 (79.4)	13 (52)	**.026**
Previous CZA treatment in combination	28/40 (70)	16/27 (59.3)	12/13 (92.3)	**.033**
Cumulative duration of previous CZA treatment, d, mean ± SD	21.8 ± 15.5	22.7 ± 17.1	20 ± 12	.562
Time elapsed between CZA-S and CZA-R KPC-Kp isolation, d, mean ± SD	38.2 ± 37.2	47.9 ± 43.4	25.8 ± 23.1	**.043**
Septic shock at infection onset	15 (25.4)	8 (23.5)	7 (28)	.698
BSI presence	37 (62.7)	25 (73.5)	12 (48)	**.045**
Source of infection				
UTI	16 (27.1)	4 (11.7)	12 (48)	**.002**
HAP/VAP	13 (22.0)	10 (29.4)	3 (12)	.110
cIAI	3 (5.1)	1 (2.9)	2 (8)	.382
CVC-related BSI	7 (11.9)	4 (11.7)	3 (12)	.978
SSTI	3 (5.1)	1 (2.9)	2 (8)	.382
Primary BSI	17 (28.8)	14 (41.2)	3 (12)	**.014**
ICS at infection onset, mean ± SD[a]	6.8 ± 4.0	6.2 ± 3.4	6.8 ± 3.4	.980
ICS ≥8 at infection onset	12/40 (30)	7/29 (24.2)	5/11 (45.5)	.189
CZA MIC, μg/mL, median (range)	16 (12–256)	16 (12–256)	16 (12–256)	.409
MEM MIC, μg/mL, median (range)	2 (0.12–128)	1 (0.12–4)	32 (16–128)	**<.0001**
Time from infection onset to definitive therapy, d, mean ± SD	2.4 ± 2.2	1.7 ± 1.4	3.4 ± 2.7	**.010**
CZA-R KPC-Kp infection definitive treatment				
Carbapenems as monotherapy	8 (13.6)	7 (20.6)	1 (4)	*.065*
Carbapenems in combination	20 (33.9)	12 (35.3)	8 (32)	.791
Colistin-based regimens	10 (16.9)	3 (8.8)	7 (28)	.052
Tigecycline-based regimens	4 (6.8)	1 (2.9)	3 (12)	.171
Meropenem/vaborbactam	11 (18.7)	9 (26.5)	2 (8)	.071
Other treatments[b]	6 (10.2)	2 (5.9)	4 (16)	.204
Early improvement (48–72 h)	37 (62.7)	24 (70.6)	13 (52)	.145
Clinical cure	44 (74.6)	28 (82.3)	16 (64)	.110
Microbiological eradication of CZA-R KPC-Kp[c]	41/53 (77.4)	26/31 (83.9)	15/22 (68.2)	.179
CZA-R KPC-Kp infection relapse within 30 d	9 (15.2)	3 (8.8)	6 (24)	.109
Secondary infections within 30 d	33 (54.0)	20 (58.8)	13 (52)	.602
Mortality within 7 d from infection onset	6 (10.2)	3 (8.8)	3 (12)	.690
Mortality within 14 d from infection onset	10 (17.0)	4 (11.7)	6 (24)	.216
Mortality within 30 d from infection onset	14 (23.7)	7 (20.6)	7 (28)	.508
In-hospital mortality	20 (33.9)	11 (32.3)	9 (36)	.770
New-onset of CZA-S KPC-Kp	12/56 (21.4)	4 (11.8)	8/22 (36.3)	**.044**
Length of stay from CZA-R KPC-Kp infection, d, mean ± SD	55.5 ± 64.1	55.2 ± 61.1	56 ± 69.4	.770

Data are presented as No. (%) unless otherwise indicated. Values in bold refer to statistically significant difference between the two groups ($P < .05$).

Abbreviations: BSI, bloodstream infection; CCI, Charlson comorbidity index; cIAI, complicated intra-abdominal infection; CVC, central venous catheter; CZA, ceftazidime/avibactam; CZA-R, ceftazidime/avibactam resistant; CZA-S, ceftazidime/avibactam susceptible; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; ICS, INCREMENT-CPE Score; ICU, intensive care unit; KPC, *Klebsiella pneumoniae* carbapenemase; KPC-Kp, *Klebsiella pneumoniae* carbapenemase–producing *Klebsiella pneumoniae*; MEM, meropenem; MEM-R, meropenem resistant; MEM-S, meropenem susceptible; MIC, minimum inhibitory concentration; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

[a]Available in 40 of 59 patients only.

[b]Two CZA as monotherapy, 2 fosfomycin + aminoglycoside, 1 trimethoprim-sulfamethoxazole, 1 aminoglycoside as monotherapy.

[c]Available in 53 of 59 patients.

By the time of infection onset, 15 of 59 patients (25.4%) presented with septic shock, evenly distributed among MEM-S and MEM-R KPC-Kp infections (23.5% vs 28%, $P = .698$), and the mean INCREMENT-CPE score at the time of infection, available for only 40 patients, was 6.8 ± 4.0. Presence of BSI was more frequent in KPC-Kp MEM-S variant subgroup (25/34

[73.5%] vs 12/25 [48%]; $P = .045$). Primary BSI resulted as the commonest source of infection in both the overall population (28.8%) and within the MEM-S KPC-Kp subgroup (14/34 [41.2%] vs 3/25 [12%]; $P = .014$), whereas urinary tract infections were more common in MEM-R variants (12/25 [48%] vs 4/34 [11.7%]; $P = .002$) (Figure 1).

Concerning therapy for CZA-resistant KPC-Kp isolates, a notable, though not significant, number of MEM-S KPC-Kp–infected patients received meropenem-vaborbactam (9/34 [26.5%]) or carbapenems, in monotherapy or as part of a combination regimen (7/34 [20.6%] and 12/34 [35.5%] patients, respectively), in average with a shorter time from infection onset to definitive therapy (mean, 1.7 ± 1.4 vs 3.4 ± 2.7 days; $P = .010$).

CZA-R KPC-Kp infection relapse was less common in KPC-Kp MEM-S variants, although not significant (8.8% vs 24%, $P = .109$), while half of the included patients experienced a secondary infection (33/59 [54%]), with no difference according to KPC-Kp variant detection. Data on eradication of CZA-R KPC-Kp strains were available in only 53 of 59 patients. Nevertheless, in 41 of 53 (77.4%) patients, no further CZA-R KPC-Kp isolates were collected, regardless of KPC-Kp phenotype. A new, CZA-S KPC-Kp isolate was further detected in 12 of 56 subjects (21.4%), which was more frequent in MEM-R variants (8/22 [36.3%] vs 4/34 [11.8%]; $P = .044$).

Mean length of hospital stay from infection onset was 55.5 ± 64.1 days, similar in both groups.

Median CZA and MEM MICs were 16 and 2 μg/mL, respectively (range, 12–256 μg/mL for CZA and 0.12–128 μg/mL for MEM). In detail, the $MIC_{50}/_{90}$ was 16/128 μg/mL and 2/32 μg/mL for CZA and MEM, respectively. After stratification for MEM susceptibility or resistance, the CZA MIC values did not differ, while MEM median MICs were 1 μg/mL (range, 0.12–4 μg/mL) and 32 (range, 16–128 μg/mL) for MEM-S and MEM-R strains, respectively (Table 1; Figure 2*A* and 2*C*).

All the strains were KPC producing. For 16 of 59 strains (27.1%), the following KPC variants were available: KPC-67 [15] (n = 3), KPC-68 [15] (n = 1), KPC-70 [38] (n = 2), KPC-39 [15] (n = 1), KPC-31 [21, 38, 39] (n = 6), and KPC-3 [40] (n = 3). Twelve additional strains were KPC-producing *K pneumoniae* but negative with LFIAs and defined as KPC-31-like [41].

After stratification for MEM susceptibility or resistance we found that all KPC-67 variants, 1 KPC-3 variant, and the KPC-39 variant were MEM-R, whereas all the KPC-31, KPC-31-like, KPC-70, KPC-68, and the remaining 2 KPC-3 variants [40] were MEM-S.

Study Population According to 30-Day Mortality

Regarding general characteristics of the included patients, no difference was observed between survivors and nonsurvivors concerning sex, mean age and CCI score, severe acute respiratory syndrome coronavirus 2 coinfection, and ICU stay at the time of CZA-R KPC-Kp infection onset, and, likewise, previous CZA-S KPC-Kp detection, previous CZA treatment, duration, and its administration as part of a combination therapy (Table 2). Septic shock at CZA-R KPC-Kp infection presentation was prevalent in nonsurvivors (7/14 [50%] vs 8/45 [17.7%]; $P = .005$). The mean INCREMENT-CPE score was comparable among subgroups, and no difference was observed using a cutoff of ≥8.

Among therapies administered for the CZA-R KPC-Kp isolates, a prominent, though not significant, number of survivors was treated with meropenem-vaborbactam, with a 9.1% of 30-day mortality, compared with 37.5%, 15%, 30%, and 75% mortality rates for carbapenems in monotherapy, carbapenems in combination, colistin-based combinations, and tigecycline-based combinations, respectively (Figure 3*A*). Among nonsurvivors in tigecycline-based regimens, only 1 patient suffered from pneumonia. Differences in mortality by antibiotic type stratified by MEM susceptibility or resistance are shown in Figure 3*B* and 3*D*.

Early clinical improvement and clinical cure were noted mostly among survivors (35/45 [77.8%] vs 2/14 [14.3%], $P < .001$; 41/45 [91.1%] vs 3/14 [21.4%], $P < .001$, respectively).

No significant difference between MEM-S and MEM-R subgroups was observed in the estimated mortality for any of the analyzed time subsets, namely 7-day ($P = .690$), 14-day ($P = .216$), and 30-day ($P = .508$) (Supplementary Figure 2). Likewise, after stratification according to CZA and MEM MICs, no significant differences were found for 30-day mortality (Figure 2*B* and 2*D*).

In the final multivariate Cox regression model, clinical presentation with septic shock emerged as the only independent factor (odds ratio, 6.02 [95% confidence interval, 1.66–21.89]; $P = .006$) associated with 30-day mortality, after adjustment for CCI score, source of infection, and therapy (Table 3).

DISCUSSION

In this study, we included a total of 59 patients with documented infections due to CZA-R KPC-Kp in 2 academic centers in central Italy. We highlighted the high occurrence of MEM-S KPC-Kp variants as causative agents of CZA-R KPC-Kp infections, while the only factor influencing mortality was septic shock presentation at infection onset.

Patients who had received CZA tended to be more prone to develop an infection sustained by MEM-S variants, especially if CZA was administered as monotherapy for lower respiratory tract infections. On the other hand, patients who developed a subsequent MEM-R KPC-Kp infection were more likely to have received CZA as part of a combination therapy (92.3%), suggesting a relationship between former CZA monotherapy, especially for pneumonia, and CZA-R MEM-S KPC-Kp detection, as already described [42].

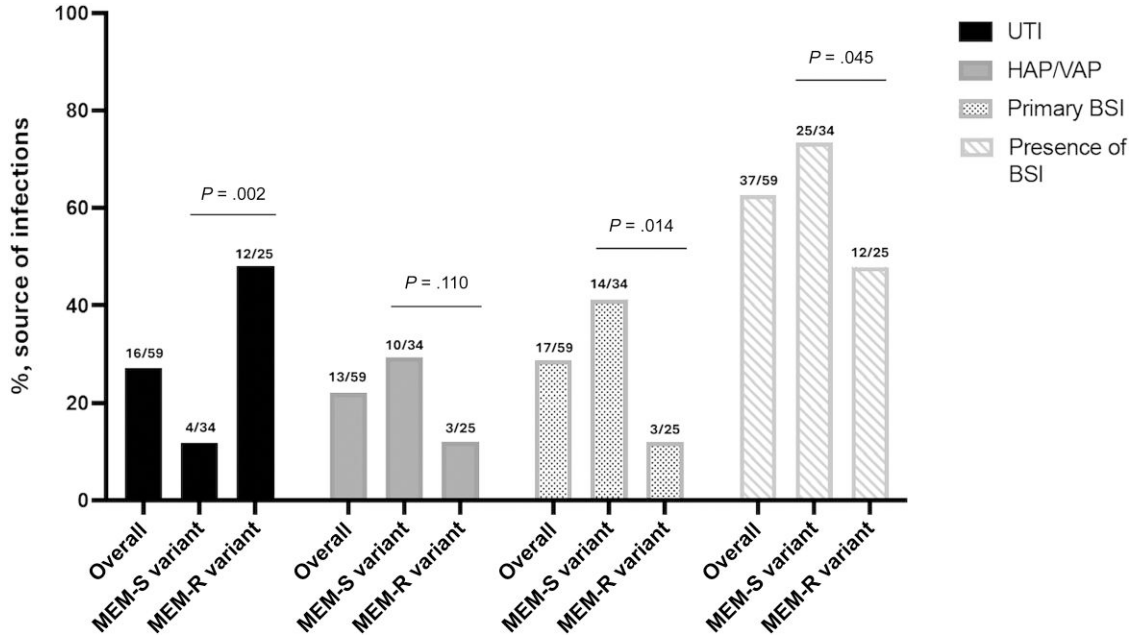

Figure 1. Source of infections in patients infected with ceftazidime/avibactam-resistant *Klebsiella pneumoniae* carbapenemase–producing *K pneumoniae* strains according to meropenem susceptibility or resistance. Abbreviations: BSI, bloodstream infection; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; MEM-R, meropenem resistant; MEM-S, meropenem susceptible; UTI, urinary tract infection.

Interestingly, in our study population of CZA-R KPC-Kp, up to one-third of patients had not been previously treated with CZA, especially in the MEM-R subgroup of infections.

MEM-S KPC-Kp infection was not associated with higher 30-day mortality risk, nor with higher 30-day recurrences or secondary infections. Likewise, after stratification according to CZA and MEM MICs, no significant differences were found for 30-d mortality. Among reinfections, fewer new isolates in the KPC MEM-S variant subgroup restored CZA susceptibility.

Besides, patients with MEM-S variant KPC-Kp infections were more likely younger and more often hospitalized in ICU wards, and time between CZA-S and CZA-R KPC-Kp isolation tended to be much longer than in MEM-R variant KPC-Kp carriers.

Bacteremia was significantly prevalent among patients with MEM-S variant at infection onset and, specifically, primary BSI stands out as the most frequent source of infection in this subgroup, accounting for 41.2% of infections; surprisingly, but nonsignificantly, primary BSI was more common as well among 30-day survivors, even though no difference in survival was observed for any infection site.

The notable 33.9% overall mortality rate reported in our study was comparable to the 37% rate previously described by Di Bella et al in a systematic review analysis of clinical studies on CZA-R KPC–producing Enterobacterales [6], underlining the role of in-hospital complications, mirrored as well in the high proportion of patients (57.6%) hospitalized in ICUs. Regardless of MEM-S variant presence, indeed, the 23% 30-day mortality rate recorded in our study proved to be similar to that described after the introduction of new drugs active against KPC, ranging from 16.4% to 37% [6, 7, 37, 42, 43].

To the best of our knowledge, this is the widest available clinical study on infections caused by CZA-R KPC-Kp and, distinctively, it reports the highest number of MEM-S variant KPC-Kp isolates; this brings concern, especially considering that the data were collected within just 2, though both tertiary, hospital centers, even in the same city. This finding, along with the higher mortality risk associated with septic shock presentation in these infections, which implies, per se, the urgency of an appropriate antibiotic administration, emphasizes the pressing unmet clinical need to identify the optimal strategy for both MEM-R and MEM-S CZA-R KPC-Kp infections.

Overall, the antibiotic regimens administered for both MEM-S and MEM-R variant KPC-Kp infections exhibited considerable variability. Although no difference was observed in the univariate analysis between the 2 susceptibility phenotypes, nor for survival, the crude 30-day mortality rate associated with meropenem-vaborbactam appeared to be lower than the other regimens. This is coherent with recent findings by Tumbarello et al [43], suggesting the role of this agent in the challenging and yet uncertain treatment of CZA-R KPC-Kp infections, with particular regard to BSIs, vastly represented in our study as well.

Nevertheless, no definitive conclusions may be driven given the low number of patients and the difference between the 2 groups in terms of type of infections; indeed, patients infected with MEM-R variants had most commonly urinary tract

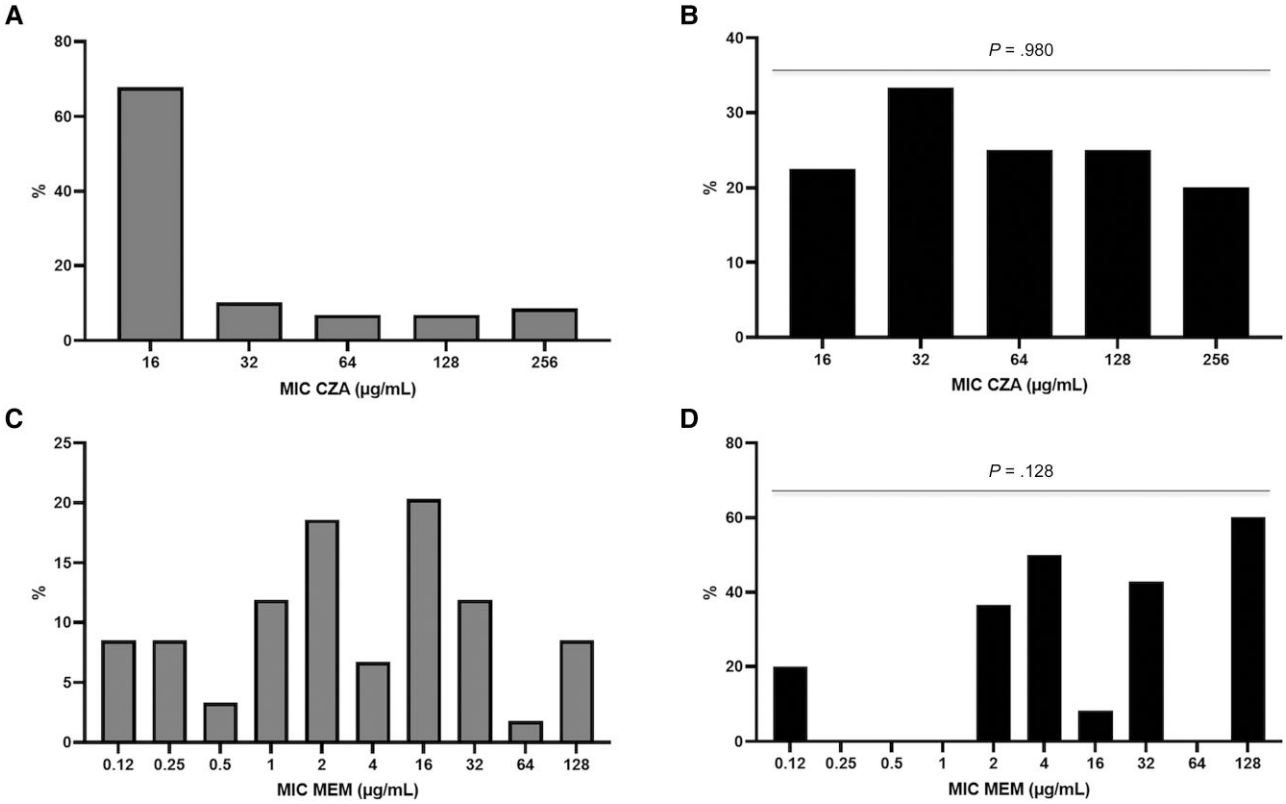

Figure 2. Ceftazidime/avibactam (CZA) and meropenem minimum inhibitory concentration distribution (*A* and *C*) and related 30-day crude mortality rate (*B* and *D*) in patients with CZA-resistant *Klebsiella pneumoniae* carbapenemase–producing *K pneumoniae* infections. Abbreviations: CZA, ceftazidime/avibactam; MEM, meropenem; MIC, minimum inhibitory concentration.

infections, which carry lower mortality than primary bacteremia or pulmonary infections, which were instead frequent in patients with MEM-S variants.

After stratification for MEM susceptibility or resistance, we found that in MEM-S patients, mortality was the lowest in patients receiving carbapenems in combinations followed by MVB, whereas in patients with MEM-R KPC-Kp, no particular differences could be observed. Although we acknowledge that numbers are too small to answer the question of whether CZA-R MEM-S KPC-Kp infections may be still treated with carbapenems, it would be a hypothesis-generating concept to be tested in subsequent prospective and multicenter studies.

Indeed, there is an urgent need for further studies focusing on the treatment of CZA-R KPC-Kp infections, and especially MEM-S variant, as the quarrel between the MVB-based and the carbapenem-based strategy, both as monotherapy or combination, remains wide open. This is particularly true for critically ill patients, since septic shock at infection onset seems to be the only driver of mortality. In these high-risk conditions, also considering the substantial risk of shifting toward a MEM-resistant phenotype, MVB use had been suggested and preferred over carbapenems [25].

On the other hand, meropenem-vaborbactam resistance in CZA-R KPC-Kp infections has already been described, though infrequently, due to mutated porins and overexpression of blaKPC gene [44], in absence of previous drug exposition. This, together with in vitro reports on cefiderocol MIC increase in variant KPC-producing *Escherichia coli* [45] and the detection of colistin-resistance in one-fifth of CZA-R Enterobacterales [6], should warn clinicians on the reliability even of newest and oldest agents. Among newly introduced β-lactams/β-lactamase inhibitors, though, imipenem-relebactam showed stability against those outer membrane porins involved in the highly difficult-to-treat phenotype displaying resistance toward CZA and MVB, offering an appealing alternative [46, 47].

Moreover, the reduced carbapenemase activity of MEM-S KPC-Kp [48] is mirrored in the extended-spectrum β-lactamase–like phenotype that could escape routine rapid detection assays, advocating molecular analysis in patients with risk factors [41, 42] such as, but not limited to, previous CZA exposure, especially in situations such as renal replacement therapy and pneumonia, already known to be associated with treatment failure and CZA resistance emergence [49]. Interestingly, in our study MEM-S KPC-Kp infections were

Table 2. Comparison Between Survivors and Nonsurvivors in Ceftazidime/Avibactam-Resistant *Klebsiella pneumoniae* Carbapenemase–Producing *K pneumoniae*–Infected Patients

Characteristic	30-d Survivors (n = 45 [76.3%])	30-d Nonsurvivors (n = 14 [23.7%])	*P* Value
Male sex	20 (44.4)	5 (35.7)	.564
Age, y, mean ± SD	62.6 ± 14.3	70.1 ± 14.7	.952
CCI score, mean ± SD	4.3 ± 2.4	5.1 ± 3.5	.816
ICU admission	26 (57.8)	8 (57.1)	.573
SARS-CoV-2 coinfection	6 (13.3)	4 (28.6)	.184
Previous CZA-S KPC-Kp isolation	31 (68.9)	10 (71.4)	.857
Previous CZA treatment	32 (71.1)	8 (57.1)	.329
Cumulative duration of previous CZA treatment, y, mean ± SD	23.1 ± 16.5	17 ± 10.2	.164
Previous CZA treatment in combination	22/32 (68.8)	6/8 (75)	.730
Time elapsed between CZA-S and CZA-R KPC-Kp isolation, d, mean ± SD	42.5 ± 39.2	24.8 ± 28.7	.097
Septic shock at infection onset	8 (17.7)	7 (50)	**.005**
BSI presence	34 (75.6)	3 (21.4)	**<.001**
Source of infection			
UTI	13 (28.9)	3 (21.4)	.583
HAP/VAP	8 (17.8)	5 (35.7)	.157
cIAI	2 (4.4)	1 (7.1)	.688
CVC-related BSI	5 (11.1)	2 (14.3)	.748
SSTI	2 (4.4)	1 (7.1)	.688
Primary BSI	15 (33.3)	2 (14.3)	.169
ICS at infection onset, mean ± SD[a]	6.7 ± 4.2	6.8 ± 3.4	.222
ICS ≥8 at infection onset	8/31 (25.8)	4/9 (44.4)	.282
Time from infection onset to definitive therapy, d, mean ± SD	2.6 ± 0.3	2 ± 0.6	.192
Early improvement (48–72 h)	35 (77.8)	2 (14.3)	**<.001**
Clinical cure	41 (91.1)	3 (21.4)	**<.001**
Microbiological eradication of CZA-R KPC-Kp[b]	30/34 (88.2)	11/19 (57.9)	**.011**
CZA-R KPC-Kp infection relapse within 30 d	8 (17.8)	1 (7.1)	.334
Secondary infections within 30 d	26 (57.8)	7 (50.0)	.609
Length of stay from CZA-R KPC-Kp infection, d, mean ± SD	69.3 ± 67.5	11.1 ± 9.9	**<.0001**

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BSI, bloodstream infection; CCI, Charlson comorbidity index; cIAI, complicated intra-abdominal infection; CVC, central venous catheter; CZA, ceftazidime/avibactam; CZA-R, ceftazidime/avibactam resistant; CZA-S, ceftazidime/avibactam susceptible; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; ICS, INCREMENT-CPE Score; ICU, intensive care unit; KPC-Kp, *Klebsiella pneumoniae* carbapenemase–producing *Klebsiella pneumoniae*; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

[a]Available in 40 of 59 patients.

[b]Available in 53 of 59 patients.

more commonly observed in patients receiving CZA monotherapy, of which 45.4% were pneumonias. A definite explanation for this correlation is not yet fully clear, but it underlines a possible risk of enzyme mutation conferring CZA resistance and MEM susceptibility when using CZA in monotherapy, especially for deep-seated infections such as lower respiratory tract infections, and may guide an appropriate empirical therapy covering this particular phenotype. This may further stimulate the discussion on whether to use CZA in monotherapy or in combination: although mortality rates do not differ between CZA monotherapy or combination therapy, favoring its use in monotherapy, the risk of selecting a MEM-S CZA-R KPC-Kp variant has to be considered, since these infections are still characterized by an unknown therapeutic optimal management and outcome, due to the low number of available observations.

A prominent number of patients in our study (32.2%) had not been exposed to CZA, mainly in MEM-R–infected subgroup, where almost half of the population had not received CZA, suggesting the possibility of intrahost rearrangement of KPC-Kp that could lead to the selection of resistant strains [39]. This is consistent with the aforementioned study by Di Bella et al [6], although, alarmingly, the numbers recorded in our study alone (19/59) equal those reported by the systematic review analysis, drawing attention to Italy's evolving ecology, already endemic for KPC-producing Enterobacterales.

This study undoubtedly has several limitations. Primarily, its retrospective design does not allow a confident generalizability, as well as its small sample, which may limit the power to detect differences between MEM-S and MEM-R cohorts, with a possibility of type 2 statistical error. For the same reasons, some imbalance between the groups was present, such as the

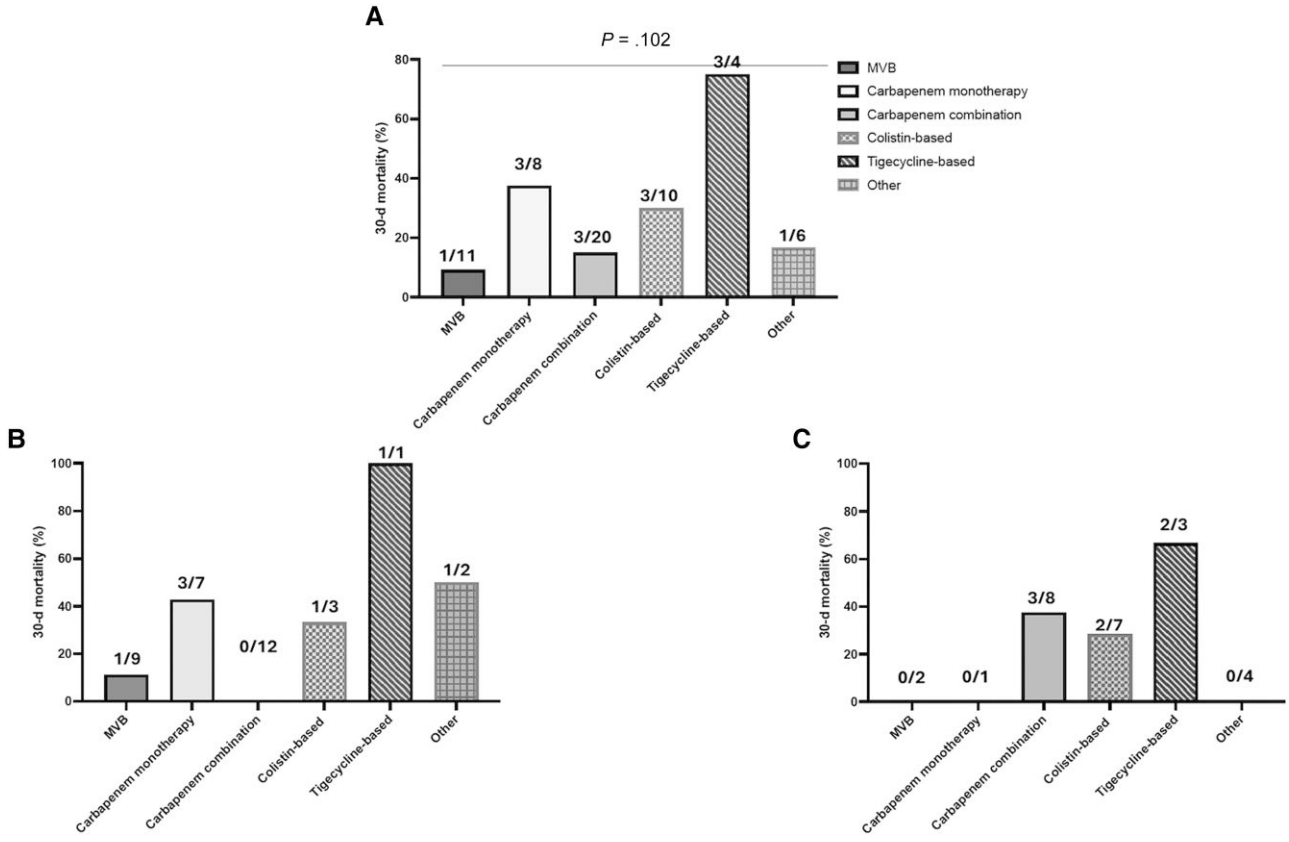

Figure 3. Thirty-day crude mortality according to the therapeutic regimens in patients with ceftazidime/avibactam (CZA)–resistant *Klebsiella pneumoniae* carbapenemase–producing *K pneumoniae* infections (*A*) and according to meropenem susceptibility (*B*) or resistance (*C*). "Other" includes CZA as monotherapy (n = 2), fosfomycin + aminoglycoside (n = 2), trimethoprim-sulfamethoxazole (n = 1), and aminoglycoside as monotherapy (n = 1). Abbreviation: MVB, meropenem/vaborbactam.

Table 3. Multivariate Analysis for 30-Day Mortality

Variables considered in the final Cox regression model	aHR (95% CI)[a]	*P* Value
Septic shock at infection onset	6.02 (1.66–21.89)	**.006**
ICS ≥8 at infection onset	2.03 (.48–8.59)	.332
Infection due to MEM-susceptible KPC variant	1.79 (.49–6.42)	.370

Values in bold refer to statistically significant aHR ($P < .05$).

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; ICS, INCREMENT-CPE Score; MEM, meropenem; KPC, *Klebsiella pneumoniae* carbapenemase.

[a]Adjusted for age, sex, source of infection, and therapy.

different distribution of infections, thus highlighting the need of prospective studies. Nevertheless, although the cohort was fairly small, to the best of our knowledge, this is one of the largest studies focusing on patients with CZA-R KPC-Kp infections. Another major limitation is that no genetic sequencing analysis on mechanism of resistance was performed on all CZA-R strains, possibly lacking the correlation with clinical findings, therapeutic choices, and, therefore, outcome. Furthermore, depending on the inclusion of 2 centers in the study, 2 different automated assays were used to determine drug susceptibility and testing was not repeated to confirm results. Last, data were available from 2 academic centers of the same city in Italy, therefore providing a picture of only a part of our endemic country and therefore not adequate for a wider generalizability of the results.

However, we provided the largest clinical experience available so far on clinical features, therapeutic management, and outcomes of infections caused by CZA-R KPC-Kp including those with restored MEM susceptibility, possibly representing the starting point for additional prospective multicenter studies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conceptualization: A. O., L. C., L. S., and M. V. Data collection: L. C., L. V., P. V., A. L., C. A., A. I., and R. P. Formal analysis: R. P., A. O., and L. C. Writing: G. S. and A. O. Visualization and supervision: L. S. and M. V.

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Data availability. All data relevant to the study are included in the article and are available from the corresponding author upon request.

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Potential conflicts of interest. All authors: No reported conflicts.

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