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Risk factors and outcomes of infections by ceftazidime/avibactam resistant, KPC-producing *Klebsiella pneumoniae*: results from a retrospective study.

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Summary

Abstract

Introduction. The KPC carbapenemase is the most widespread mechanism of resistance to carbapenems and has the greatest clinical impact. The availability of ceftazidime/avibactam (CZA) has represented a real breakthrough in treating infections caused by KPC-producing pathogens, primarily *Klebsiella pneumoniae* (Kp). However, KPC variants with acquired resistance to CZA (CZA-R) emerged soon and spread with increasing frequency, often displaying a paradoxical recovery of susceptibility to meropenem (MEM). In very recent years, new therapeutic options with activity against CZA-R KPC variants have become available, including cefiderocol (CFDC), imipenem/relebactam (IMR) and meropenem/vaborbactam (MVB), the latter being the regimen with the widest clinical use. Nevertheless, practical experience and official guideline recommendations are still limited about the treatment of CZA-R KPC-Kp.

Objective. The aim of this study is to analyse from a clinical point of view a population of patients infected with CZA-R KPC-Kp and to compare the different treatment regimens in real life scenarios. The study also aims to investigate the impact of meropenem resistance reversal and to examine the characteristics and outcomes of patients treated with MVB compared to those receiving treatment based on older-generation drugs.

Results. We studied 137 patients with a microbiologically confirmed and treated CZA-R KPC-Kp infection. These patients have multiple comorbidities, with long hospital stays, and have often already been heavily exposed to CZA. The CZA-R KPC-Kp infections were categorised as BSI (44.5%), LRTI (34.3%), UTI (12.4%), IAI (2.9%), and other (5.8%). Over 51% of the pathogens showed an MEM-S phenotype and this population exhibited different clinical characteristics compared those with MEM resistant infections. The regimens used were MVB (44.5%), MEM-containing (32.8%), older-generation antibiotics (excluding MEM) in 20 patients (14.6%), CFDC-containing (4.4%), and IMR-containing (3.6%). The overall 30-day mortality rate was 18.2% and was associated with therapeutic appropriateness, source control, and increment-CPE score. Patients treated with MVB display a survival advantage in the VAP subgroups and in those starting therapy early. Besides, MVB was associated with fewer secondary candidemias.

Conclusions. This study attempts to shed light on the characteristics of CZA-R KPC-Kp infections. Treatment with MVB appears to offer some advantages in terms of outcome.

Introduction

The β-lactam antibiotics and the antibiotic resistance

The morbidity and mortality of infectious diseases dropped in the last century thanks to development of antimicrobials, greater access to healthcare, and public health initiatives. However, global connectivity, climate change and demographic shifts lead to constant evolution, and we are now entering a new era characterised by outbreaks of emerging, re-emerging, and endemic pathogens that often display reduced susceptibility to antimicrobials [1].

In fact, the antimicrobial resistance (AMR) undermines our ability to treat infections and is one of the greatest threats to development and global health. It is linked to antibiotic misuse in animals, plants, and humans, and affects all world regions, regardless of income level [2]. In 2021 almost 5 million deaths were associated with AMR [3] as well as increased hospitalisations, longer hospital stays, greater demand for intensive care, and reduced productivity [2].

AMR descend from natural genetic evolution of organisms under selective pressure of antimicrobials, so it is ineluctable and intrinsic to the existence of microorganisms and antimicrobials. Practically consists of a series of chemical and molecular strategies implemented by microorganisms to fend our attack with antimicrobials. The genes that codify for resistance derive from de novo mutations or transfer of genetic material [4].

Since Italian scientist Bartolomeo Gosio discovered an antibiotic in 1893, approximately fifteen different classes of antimicrobials have been identified [5-6]. The β-lactam class was the first group implemented on a large scale and remains the cornerstone of our chemical arsenal [7]. The mechanisms of resistance against β-lactams belong to 4 classes: drug uptake limitation, drug efflux, drug target modification, and drug inactivation [4, 7]. Although resistance is often multifactorial, the drug inactivation through β-lactamases, enzymes with specific ability to hydrolyse β-lactams, is by far the most prevalent cause of β-lactam

resistance. Their first identification dates to 1940, but further sequencing clarified that β-lactamases constitute a family of up to 4,300 molecules [7].

The most widely used classification of β-lactamases is Ambler's, which is based on amino acid sequences and reflects evolutionary history and phylogenetic relationships, dividing enzymes into 4 classes. Classes A, C and D are serine β-lactamases as use a serine molecule in their active site. Class B are metal β-lactamases (MBL), which use a zinc atom [7]:

- Class A β-lactamases includes the first discovered β-lactamase, penicillinase PC1, and have the notable capacity to broaden the spectrum of action through new point mutations. Examples are TEM and SHV, which hydrolyse aminopenicillins and first generation cephalosporins, and CTX-M, which hydrolyses penicillins and up to third generation cephalosporins. Also includes KPC, the most widely distributed carbapenemase.
- Class B β-lactamases are MBLs, ancient, widespread, with a spectrum that includes penicillins, cephalosporins, and carbapenems, being monobactams the only exception.
- Class C β-lactamases (Amp-C) are encoded in the chromosomal genome and not normally expressed. Exposure to β-lactams leads to derepression and MIC increase after the start of treatment.
- Class D β-lactamases, nicknamed OXA because the first identified had a narrow spectrum for oxacillin; actually, have a broad spectrum. The most clinically relevant include OXA-48 and OXA-23/24 [7].

The impact of antimicrobial resistance

The annual cost of AMR in the US has been estimated to $20 billion, with a further $35 billion to account for the reduced productivity [8]. Italy is one of the countries worst affected by multidrug-resistant organisms (MDROs), with an estimated one-third of all attributable deaths in the European Economic Area and a burden comparable to the cumulative effect of HIV, tuberculosis and influenza [9].

MDRO infections have a worse prognosis compared to those by sensitive pathogens. A US study found that the mortality in patients with a bloodstream infection (BSI) increased progressively as the number of available antimicrobial agents decreased [10]. A twenty-year analysis of haematological patients with BSI revealed that MDRO infections were independently associated with a 3-fold increase in the odds of 30-day mortality (5.6-fold in carbapenem-resistant pathogens) [11]. Similarly, a case-control analysis reported that MDROs were associated with an increased risk of hospital mortality and readmission [12].

In areas with a high endemic AMR such as Italy, the transmission dynamics of MDROs often involve hospital outbreaks. These events are dramatic, affect critically ill patients spreading horizontally through healthcare personnel and environmental colonisation. Hospital outbreaks often result in many casualties and require implementation of infection control measures [13-16]. In addition, the antibiotic resistance mechanisms have ability to move from endemic to free areas. As an example, in 2019 two outbreaks of *Klebsiella pneumoniae* producing New Delhi Metallo-β-lactamase (NDM) occurred almost simultaneously in the German region of West Pomerania and the Italian region of Tuscany [17-18].

Most antibiotic classes were discovered until mid-1900s, but the availability of new molecules slowed dramatically since then, as the complexity and rapid evolution of AMR discouraged pharmaceutical companies from research. This stagnation in pipeline exacerbated the misuse of existing molecules in a vicious cycle that promotes AMR escalation [4]. The National Action Plan to Combat Antimicrobial Resistance (PNCAR), launched in Italy in 2017, and renewed in 2022, is showing encouraging results, although still insufficient and with regional differences [19]. Following the model adopted for pollution, experts are calling for an even stronger intervention by the European Union, involving legal mechanisms, warning zones, minimum gold standards, annual targets and school education [20].

The problem of carbapenems use

First discovered in 1976, carbapenems are versatile drugs, with high tissue penetration, low rate of allergic reactions or cross reactions, moderate adverse effects and resistant to hydrolysis by many β-lactamases of Gram-negative bacilli (GNB) pathogens, owning a broad spectrum of action. For these reasons, these β-lactams are "last resort" agents for serious GNB infections [21] and standard treatment for various clinical conditions by international guidelines [22].

At the same time, the overuse of carbapenems had the greatest impact compared to any other antibiotic class to the current pandemic of AMR [23]. The intensity of carbapenem prescriptions correlates with resistance [24] and their use directly increases the number of carbapenem-resistant infections [25]. Conversely, reducing carbapenem prescriptions had a positive clinical impact [26].

To understand the scale of the problem, we should consider that WHO since 2017 publishes a list of priority pathogens to guide research and investment on AMR. In the 2024 list, the carbapenem-resistant *Enterobacterales* (CRE) were ranked as "critical" and therefore given the top high priority for epidemiological control, investments, and management [27].

Unfortunately, the reduction of carbapenem prescriptions turned out more complicated than expected as the problem have deep roots, including the proliferation of medical-legal disputes and the practice of defensive medicine [28]. In a 2017 retrospective analysis, carbapenem prescriptions were inappropriate in 46%; while no difference emerged in outcome between physicians who accepted carbapenem discontinuation and those who continued it, the latter developed more carbapenem-resistant infections [29].

The rise of carbapenem resistance

The first identification of a carbapenemase happened in the mid-to-late 1980s with a chromosomally encoded MBL in Gram-positive bacilli. Then, the landscape suddenly changed in the early 1990s, when different carbapenemases (IMP, OXA and KPC) encoded

on plasmids, rather than on chromosomes, were rapidly described. From that point on, a concern of species-specific clonal diffusion, turned into interspecific dissemination becoming a problem of global significance [30]. In the following decades, the world witnesses a true pandemic of carbapenem resistant GNB, particularly affecting the *Enterobacterales* [31]. The Chinese surveillance system reported an increase of CRE infections from 2015 to 2020 by more than 60% [32]. *K. pneumoniae* in particular become increasingly significant, accumulating numerous resistance mechanisms and accounting for up to 32% of nosocomial infections [33].

The classes of carbapenemases have a different geographical distribution [34]. Class D (OXA-48-like) is rare in the US, but common in the Mediterranean region, Middle East, Europe, Asia, and South America. Class B (MBL) are particularly prevalent in Asia; the most notable members are NDM and VIM. Finally, class A mainly correspond to the KPC group and is the worldwide most common mechanism of carbapenem resistance [35].

The KPC carbapenemase: international diffusion and clinical relevance

The 2024 guidelines of the Infectious Disease Society of America (IDSA) on antimicrobial-resistant GNB infections define CRE as resistant to at least one carbapenem or that produce carbapenemase. In the US 83% of CRE use a carbapenemase and 86% of carbapenemases are KPC [22]. The term "KPC" arose from "*K. pneumoniae* carbapenemases" as they were first identified in 1996 in a patient in North Carolina, US, infected by *Klebsiella* [36].

KPC carbapenemases are codified by the gene *bla*$_{KPC}$ and its global spread is one of the most successful MDRO pandemics in the history [31]. The enzyme is made up of an average of 293 amino acids, organised into two subdomains consisting of α-helices and β-sheets. The active site, which contains the catalytic serine residue S70, is in a pocket at the interface between the two subdomains [37]. Its diffusion is mainly due to the clonal expansion of some major clones of *K. pneumoniae* strains like the sequence type 258 (ST258) (USA and Israel), and more recently ST512 (Italy), ST11 (China) and ST437 (Brazil) [37-38]. These

strains possess either the *bla*$_{KPC-2}$ or the *bla*$_{KPC-3}$ gene, which are usually located on the Tn4401 transposon [31]. The gene subtype KPC-2 is the most frequent, followed by KPC-3, KPC-9, KPC-12, KPC-18, although Italy, Israel and USA show a predominance of KPC-3 [37].

The countries with the highest prevalence of KPC-producing *Klebsiella pneumoniae* (KPC-Kp) are the United States, Italy, Greece, China, Israel, Brazil, and Colombia [39]. A multicentre study collected 24,924 hospital samples during 2019-2021 from medical centres in Europe, Asia and Latin America and found a 4.4% overall rate of carbapenem resistance. KPC was the most common mechanism (43.1%), followed by NDM (26.6%) and OXA-48 (18.7%). KPC-3 prevailed in Western Europe (86.8% of KPC), while KPC-2 in Latin America (94.0% of KPC) [40]. In the US, KPC showed an epidemic character with peaks of up to 36% of *K. pneumoniae* in 2006 in New York, then falling to 13% in 2013 [35]. In Greece almost 40% of *K. pneumoniae* carry the *bla*$_{KPC}$ gene [41]. Israel launched a strict epidemiological control plan, which led to a reduction in CRE isolates from 16% to 10%, but 80% of CRE isolates remain KPC producing [42].

In Italy the first KPC-Kp was reported in Florence in 2008, and in Rome in 2009. Initially, two STs were present, but ST258 eventually prevailed. The cases were concentrated particularly in intensive care units (ICUs), before spreading horizontally to medical and surgical wards. The rate of CRE bacteraemia increased from 2% in 2009 to 19% in 2012 [43].

The current epidemiological situation in Italy is far from encouraging. According to the Istituto Superiore di Sanità, Italy suffered 3,867 cases of CRE bacteraemia in 2023, an increase compared to both 2022 and the period from 2016 to 2021. The highest number of reported cases was in Central Italy, followed by the South and the Islands, and then Northern Italy. Patients were predominantly male, with a median age of 72 years; 74% of cases occurred in hospital, but the number of cases with symptoms appearing at home is increasing. *K. pneumoniae* was responsible for almost all cases (96.7%). The enzyme was KPC in 74.9%, MBL in 13.9%, OXA-48-like in 4.8%, and a combination in 3.4% [44].

The clinical relevance of the KPC pandemic stems from the ability to hydrolyse all β-lactams, including penicillins, cephalosporins, monobactams and carbapenems. KPC is not inhibited

by classic β-lactamase inhibitors like clavulanate, sulbactam and tazobactam. Furthermore, the *bla*KPC gene is often harboured on large plasmids with accompanying resistance determinants including those responsible for resistance to fluoroquinolones, aminoglycosides, tetracyclines and cotrimoxazole, resulting in MDROs [31, 36]. Since 2015, the polymyxin resistance gene *mcr-1* has also begun to spread among *Enterobacterales*, particularly CREs. This worrying development has been linked to the widespread use of polymyxins in veterinary medicine and agriculture [45].

The high mortality rate of CRE infections is a great concern. In a Greek study on KPC-Kp BSI among patients in ICU observed a mortality of 43.4% [46]. A study of 991 patients from seventy-one hospitals worldwide in 2017–2018 found an unadjusted 30-day mortality for BSI by CRE *K. pneumoniae* of 34% [47]. A retrospective cohort of CRE BSIs from European hospitals reported a mortality of 43% between 2004 and 2013 [48]. In South Africa, CRE BSI mortality between 2015 and 2018 was 38% [49].

The poor prognosis of KPC infections is multifactorial. Firstly, these pathogens spread in nosocomial settings, particularly in ICUs [50], therefore, the underlying conditions of patients are often already compromised. In addition, being resistant to first-line antibiotics, the empirical therapy frequently turns out inadequate, causing a treatment delay. Finally, at the onset of the KPC pandemic, the available therapies were often second-line options with unsatisfactory efficacy, lacking strong clinical evidence and associated with high rates of adverse reactions [36]. Main treatments included: colistin-based combinations, whose use is limited by nephrotoxicity and suboptimal PK; carbapenem-based combinations; combination of two carbapenems, such as meropenem (MEM) and ertapenem; old-generation antibiotic combinations including fosfomycin, tigecycline or aminoglycosides [36].

Of importance, the KPC carbapenemase has had the greatest impact on Western and high-income countries, which represent the main markets for innovative drugs. This has likely boosted research into new treatment options earlier than for other dangerous enzymes, such as NMD, which historically affected areas with less influence on the pharmaceutical

research agenda [51]. The development of new weapons against KPC infections started after 2010 and in 2015 ceftazidime/avibactam became available in the market.

The advent of ceftazidime/avibactam

Ceftazidime/avibactam (CZA) is an intravenous combination of avibactam, a diazabicyclooctane β-lactam inhibitor with reversible activity on class A, C and some class D β-lactamases, and ceftazidime, a third-generation cephalosporin with anti-*Pseudomonas* activity, mixed in a fixed 1:4 ratio [52-53]. Avibactam exerts covalent acylation of its targets, restoring the activity of ceftazidime against *Enterobacterales* producing ESBL, AmpC, KPC, OXA-48, and difficult-to-treat *P. aeruginosa* [54].

In 2016 the European Medicines Agency (EMA) approved CZA for complicated intra-abdominal infections (cIAIs), complicated urinary tract infections (cUTIs), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and GNB infections with limited treatment options [55].

A systematic review and meta-analysis of fifty-four observational studies conducted up to 2018 involved 3,352 patients with carbapenem-resistant *K. pneumoniae* before availability of CZA. KPC was the most frequent resistance mechanism, BSI, and HAP the most common infections. The pooled clinical response was 69.0% and mortality 37.2%. No significant difference was found between carbapenems, polymyxins, aminoglycosides, tigecycline, and other regimens [56]. A large, multicentre, retrospective study was conducted in five Italian hospitals on 661 adults with KPC-Kp infection. The empirical treatments were microbiologically inadequate in 55.2%. The most prescribed single-drug regimens were colistin, tigecycline and gentamicin (46.4%), while combinations (53.6%) always included MEM. The 14-day mortality was 34.1% [57].

CZA overturned these unsatisfactory outcomes and after its introduction quickly established itself as the treatment of choice. A retrospective observational study of 138 adults with KPC-Kp infection who received CZA rescue found a mortality significantly

lower than in control group (36.5% vs 55.8%) [58]. In mechanically ventilated patients, most of whom experiencing septic shock and multi-organ failure, a CZA-containing regimen was an independent predictor of survival [59]. Karaiskos et al. analysed data from the Hellenic CZA Study Group and found that mortality was significantly lower in subjects with KPC-Kp BSI treated with CZA-containing regimens than in those treated with older agents, mainly colistin and tigecycline (18.3% vs. 40.8%) [60]. A large retrospective analysis of the post-marketing CZA real-life use in 22 Italian hospitals confirmed CZA as a valid therapeutic option: 30-day mortality of 25.3%, lower than with non-CZA based regimen [61]. Although more than 70% of cases were treated with combination therapies (CZA plus fosfomycin, tigecycline, gentamicin, or meropenem), no significant difference was found between monotherapy and combination [61].

The emergence of KPC variants and the resistance to ceftazidime/avibactam

If CZA represented a turning point in the treatment of infections by KPC producers, pitfalls emerged soon after its market release. Early real-life studies revealed a 10–30% failure rate when used on *in vitro* susceptible pathogens [62, 63]. These unsatisfactory results were particularly evident in specific clinical conditions that are thought to alter the pharmacokinetic/pharmacodynamic (PK/PD) profile of CZA causing under-exposure [64]. In 2015, Nicolau et al. demonstrated that epithelial lining fluid (ELF) penetration of CZA in healthy subjects was only 30% of plasma values [65], with similar results in neutropenic mice [66]. In a retrospective study, pneumonia was an independent risk factor for clinical failure of CZA, while continuous haemodialysis treatment (CRRT) predicted microbiological failure and resistance emergence [62]. Clinical and microbiological failure associated with *in vivo* development of resistance were also observed in cases of septic thrombosis and delayed source control [67-68]. The selection of CZA-R KPC variants was associated with suboptimal drug exposure during the first days of treatment with current dosage standard [69]. Further studies strengthened the doubts on dosage and dosage

adjustments, finding increased mortality among subjects receiving renal adjusted dose [70, 64].

After sporadic isolations occurring between 2006 and 2018, starting from 2019 the reports of CZA-resistant (CZA-R) KPC variants increased dramatically [38]. A systematic review has shown that 80% of CZA-R KPC-Kp isolates originate from the USA, Greece, and Italy. These strains mainly belong to the ST258 strain, and approximately one third of patients have no previous exposure to CZA. Furthermore, over 50% of CZA-R isolates exhibited a paradoxically restored sensitivity to MEM [71-74] with an ESBL-like phenotype. Nevertheless, the treatment of these isolates with carbapenems was deemed risky and deceptive [75].

The main mechanism of CZA resistance is point mutations in the *bla*$_{KPC}$ gene affecting the Ω-loop of the lactamase, which increase flexibility, enhancing its ability to trap ceftazidime while reducing avibactam's binding affinity [53]. A wide variety of KPC variants were identified, with over two hundred *bla*$_{KPC-2}$ and *bla*$_{KPC-3}$ variants to date. The most common *bla*$_{KPC-3}$ variant, *bla*$_{KPC-31}$, was described in Italy in 2019. Similarly, the most frequent *bla*$_{KPC-2}$ variant, *bla*$_{KPC-33}$, was first reported in Italy in 2020 [38]. The amino acid located in position 179 is a mutation hotspot, with various substitutions described like D179Y, D179N and D179A. The latter three mutations correspond to the enzyme subtypes KPC-31, KPC-32 and KPC-33, respectively. Notably, D179N increases MIC for CZA while reducing MIC for MEM and justifying the ESBL-like phenotype [37]. Compared to other lactamases, the KPC enjoys greater thermodynamic stability, withstand changes in the active site and adapt to the environment. The phenomenon of CZA-resistance was interpreted as an evolutionary trade-off, whereby the selective pressure exerted by CZA administration results in the emergence of resistant variants, even at the expense of restoring sensitivity to other β-lactams. This adaptation may represent the KPCs' weakness because balancing resistance to CZA and other β-lactams probably imply a significant fitness cost [37]. Other Authors glimpse a seesaw effect and highlight the risk that this phenomenon may confound the routine *in vitro* phenotypic testing based on carbapenemase detection, causing false negatives and

misidentification [38]. However, most CZA resistance is caused by accumulation of multiple mechanisms, including porin channels Omp35 and Omp36 mutations, KPC gene duplication and efflux pumps overexpression [76], and the fitness cost could be different depending on the type [77].

The spread of KPC variants is divergent and epidemiologically adapted. Following one year of surveillance at Policlinico Umberto I Hospital, Carattoli et al. characterised nine distinct CZA-R KPC-3 variants, five of which not previously reported. Some isolates had regained MEM sensitivity (MIC <8 μg/mL). Of concern, the study highlighted that concurrently to vertical evolutionary trajectory there was a horizontal transmission of strains to patients not previously exposed to CZA [78]. At the present time, the estimate of 10% CZA-R prevalence among KPC producers in Italy [71, 79], jeopardise the appropriateness of CZA prescription.

New β-lactams for ceftazidime/avibactam resistant KPC producers

In recent years, several new antibiotic options were released for KPC-producing infections.

Meropenem/vaborbactam (MVB) was approved in 2018 for cUTI, cIAI, HAP (including VAP) and infections by GNBs when other treatments are not effective [80]. It had been available in Italy since 2021 and is the most used drug in CZA-R KPC-producing infections. This coformulation is composed of vaborbactam — a new, competitive, high-affinity β-lactamase inhibitor with a boron ring structure — and MEM [81]. An *in vitro* study assessed MVB and its comparators on a global collection of 991 KPC-producing *Enterobacterales*, achieving 99% of susceptibility. Furthermore, the MIC_{90} values of MVB were 4–32 times lower than CZA for *K. pneumoniae* and *E. coli*. Of importance, no differences emerged when the data were stratified by KPC variant [82]. MVB benefit excellent PK properties, as the curves of the two components are superimposable, so vaborbactam protects effectively MEM reducing the development of resistance. Additionally, both components demonstrated excellent penetration into the ELF [81].

If CZA resistance is primarily mediated by *bla*$_{KPC}$ mutations, the resistance to MVB depends mainly on increases copy number and/or porin mutations. The latter mechanism can be overcome by high tissue concentration, possible thanks to MVB's PK properties [83]. Also, the advantages of MVB extend to the PD level. Crystallographic studies suggest that Ω-loop point mutations, such as D179N, do not affect the binding capacity of vaborbactam [38]. In an in vitro study, MVB was active in all CZA-R KPC samples, although increasing concentrations was necessary [84]. Therefore, MVB is considered to have a greater genetic barrier to resistance development than CZA [83].

CZA is not the first β-lactam/inhibitor combination to experience PK problems. In theory, the inhibitor protects the β-lactam partner from β-lactamases restoring its activity, but in practice this restorative effect results highly dependent on the ratio between the inhibitor and the β-lactam partner [85]. The two components may not follow the same excretion pathway, so a change in renal function may affect them differently. In the case of piperacillin/tazobactam, the 8:1 ratio is likely detrimental to the functioning, whereas this effect is mitigated by the 3:1 ratio of ceftolozane/tazobactam [85]. The piperacillin/tazobactam ratio has been shown to vary significantly with changes in renal function, reaching up to 10:1 in patients with increased renal clearance [86]. In critically ill patients receiving continuous infusion of CZA, the free-avibactam concentration was more affected by clearance variations than the free-ceftazidime concentration, resulting in a disparity [87]. Similarly, the study by Gatti et al showed that the ratio of ceftazidime to avibactam varied considerably (from 1.29:1 to 13.46:1) according to creatinine clearance [88]. At present, it is unclear whether a combination of β-lactam and inhibitor formulated at a 1:1 ratio, like MVB, may have a natural PK advantage under special conditions, such as in critically ill patients, over imbalanced formulations and whether this may have a clinical impact. Anyway, in a small study on biliary infections in liver transplants the 1:1 proportion between MEM and vaborbactam concentrations was unchanged in the bile, allowing to assume that the joint PK/PD behaviour of MVB may result appropriate in deep seated infections [89].

MVB worked as rescue therapy for CZA-R KPC-producing infections [67-68, 90]. Still, there is no direct head-to-head clinical comparison between MVB and CZA but only retrospective studies. Ackley showed higher recurrence and resistance development in the CZA group. Interestingly, CZA resistance developed among patients with pulmonary infection or CRRT (two conditions involving probable altered PK of CZA) [91]. In a retrospective multicentre study, conducted among patients from five different Italian ICUs, no difference in mortality between MVB or CZA in KPC-Kp BSI or pneumonia emerged in the overall analysis. However, MVB significantly improved the early clinical response compared to CZA and unmatched patients with septic shock had a reduction in mortality with MVB [92]. In a large US retrospective study a slight, non-significant advantage of MVB was highlighted [93].

Imipenem/relebactam/cilastatin (IMI/REL) is a new pairing of an old carbapenem with relebactam, a new bicyclic diazabicyclooctane β-lactamase inhibitor with activity against class A and C β-lactamases. The chemical composition provides higher resistance to porin mutation and efflux pumps. [94]. IMI/REL was approved for HAP, VAP, BSI and other GNB infections with limited treatment options [95] and is available in Italy since 2022. The PK profile is favourable, with overlap of components and high pulmonary penetration [94]. An in vitro study showed that IMI/REL overcomes KPC mutations at position 179 and thus is likely effective on mutated KPC-2 [96]. The use of IMI/REL in the treatment of CZA-R KPC variants is still limited but real-life experience on patients with elevated clinical complexity was encouraging [97].

Cefiderocol (CFDC) is a new-generation cephalosporin conjugated to a siderophore that enables bacteria penetration via the iron uptake system and overcomes porin mutations and efflux pumps. Once inside, exhibits exceptional resistance to β-lactamases [98]. EMA granted approval in 2020 for adults with GNB infections and limited treatment options [99] and was available in Italy since 2021. In an in vitro study, CFDC was effective on all KPC strains, including CZA-R variants [100]. However, in subsequent studies a frequent cross-resistance between CFDC and CZA emerged, and Authors even recommend CFDC combination with new β-lactamase inhibitors [101]. In fact, a very high rate of CFDC

resistance was reported among CZA-R *Enterobacterales* compared with CZA-S (80% vs 7%) [102-103].

The treatment of KPC variants

The phenomenon of KPC variants again posed a challenge to the treatment of KPC producers. As with the emergence of the first KPCs, initially this resurged menace prompted clinicians to arrange treatment regimens using various combinations of older-generation antibiotics like MEM, tigecycline, colistin and fosfomycin, depending on residual sensitivities [92]. The arrival of MVB, IMI/REL and CFDC offered new, potentially more effective weapons. MVB, CZA, and IMR are all considered options for wild type KPC-producing pathogens by IDSA guidelines. A slight preference is expressed for MVB as probably has a greater resistance barrier, while IMR is in third place as the evidence is scarce. CFDC is reserved for patients with few options [22]. Regarding mutated KPC, the IDSA guidelines recognise that most mutations affect the susceptibility to CZA and that clinical significance of carbapenem resistance reversal is unknown. Poor practical indication is provided: repeat sensitivity testing in patients with previous CRE infection; and in such cases, avoid empirical retreatment with the same drug, as there is a risk of resistance emerging of 10-20% for CZA and 5% for MVB [22].

So, it is currently unclear the most appropriate treatment for CZA-R KPC-producers. This uncertainty depends also on the large epidemiological variability of these enzymes, which constitutes a different scenario in each centre, leaving a significant need for patient customisation [38]. A molecular study of 31 KPC isolates collected over a year from six hospitals in Rome illustrates the variety of these variants. Three different clones were present, with ST512 being the most common. Authors identified eleven different variants, four previously unknown. Five CZA-R isolates had wild-type KPC and their porin mutations did not differ, so resistance was attributed to higher blaKPC expression [104]. A recent Italian multicentre in vitro study provided data on 264 KPC strains from BSI: 93.9% were sensitive to CZA, 95.1% to MVB, and 97% to IMI/REL, 90.5% to colistin, 65.5% to

fosfomycin and 7.2% to MEM. Mutations of the *bla*KPC gene caused CZA resistance only in 76.9% and of these 31.2% had co-resistance to MVB and IMI/REL [79].

The variants with recovered sensitivity to MEM (MEM-S) are more common in some epidemiological contexts [105], but this ESBL-like appearance may not be good news and even result in a trap. *In vitro* exposure to sublethal concentrations of KPC-3 variants that were initially MEM-S has selected for strains with high MICs to both CZA and MEM [106]. Similarly serial passages in sublethal concentrations of MEM selected resistance to both CZA and MEM [107]. However, the clinical significance is unclear, and a high dose meropenem may overcome this drawback [72].

Real-life clinical data on KPC variants are limited, small sized and heterogenous. The first assessment is a review of nine cases occurred between 2016 and 2019. A history of cancer or transplantation was prevalent, and all subjects had previously been treated with CZA. The most common infection was pneumonia (67%). Treatment was mainly based on combination, and mortality high (50%). As for MEM-S variants, the Authors proposed using the Increment CPE score (ICS): low risk patients (ICS<8) can be treated with combinations of older-generation drugs, while high risk ones (≥8) require MVB [75].

An Italian multicentre study analysed thirty-seven adults treated with compassionate MVB for KPC-Kp infection, 60% CZA-R and all MEM-R. Within CZA-R subgroup, 68% were admitted to the ICU, 68% had BSI and 23% LRTI. MVB was part of combination therapy in 54.5%. Clinical cure in the CZA-R was 81.8% and in-hospital mortality 18.2%. Overall, the activity of MVB on KPC variants was judged satisfactory [108].

A report analysed 17 ICU patients with colonisation or infection by CZA-R KPC-Kp and regained MEM sensitivity, 29.4% already treated with CZA for wild type KPC. All phenotypic tests for carbapenemase turned out negative while genetic test revealed KPC-33 derived from D179Y substitution in 16/17 individuals, so that a single outbreak origin was hypothesized. MVB was administered to 41.2% and mortality was 58.8%. Many patients developed superinfections during treatment [105].

In collaboration with the Policlinico of Tor Vergata, our study group has conducted a retrospective bicentric study on patients with CZA-R KPC-Kp infection, deepening the clinical differences associated to the MEM susceptibility pattern. Of 59 CZA-R KPC-Kp patients, 67.8% had previously received CZA, and 57.6% of the isolates were MEM-S. MEM-S group was composed by younger individuals, more exposed to CZA and more commonly hospitalized in the ICU. Most patients were treated with MEM monotherapy or in combination with old-generation antibiotics, while 26.5% received MVB. The overall 30-day mortality was 23.7%, but MEM-S subgroup had less relapses [73]. Of further relevance, this study identified a lower, although not significant, crude mortality rate in patients treated with MVB compared to other regimens [73].

A retrospective analysis was conducted on mixed infections by KPC CZA-R (N=34) and CZA-S (N=118) *K. pneumoniae*. CZA-R were more frequently of nosocomial origin and more exposed to carbapenems, had often already experienced a KPC infection, and frequently had tracheostomy tubes. CZA-R KPC-Kp was treated with older-generation antibiotics, often combined with CZA, due to the unavailability of newer drugs. There was no statistically significant difference in mortality between CZA-S and CZA-R patients (48.3% vs 41.2%), but colistin was protective against mortality in CZA-R [109].

An observational retrospective study analysed thirty-seven events of BSI by CZA-R KPC producers with respiratory tract as the predominant source. Susceptibility to at least one carbapenem was frequently restored (over 60%). Patients were primarily treated with a combination of at least two antibiotics (51%). The regimens included: aminoglycoside (43%), MVB (35%), carbapenem (27%), fosfomycin (22%), tigecycline (19%), CZA (16%), colistin (14%). The 30-day mortality was 16.2%, relapse occurred in 18.9% and secondary candidemia in 8.1% [110].

A large retrospective cohort enrolled 342 KPC-producing infections who received MVB. The infections were BSIs in 50.3% and LRTIs in 31.3%. The isolates were CZA-R in 24.8%, and although this subgroup was not described in detail, it is reported a mortality of 24.2% when

MVB was initiated as first-line therapy and 36.5% when second line. The outcome of first-line MVB for CZA-R infections did not differ from CZA-S [111].

A recent Taiwanese study conducted between 2019 and 2024, analysed sixty cases of CZA-R KPC-Kp infections, mainly isolated from sputum and blood. Seventy per cent were previously exposed to CZA for a median of 13.5 days. Of the CZA-R isolates, thirty-six were variants (most KPC-33) and often showed MEM sensitivity (72.2%). Access to new drugs was not available, so patients were treated with older-generation antibiotics (mainly MEM combined with colistin or tigecycline), with a poor treatment adequacy rate (47.8%). The 14-day mortality was 19.6% [112].

Aim of the work

The principal objective of this study was to analyse from a clinical point of view the characteristics, the evolution and the outcome of the population infected with *Klebsiella pneumoniae* producing KPC and resistant to CZA. Furthermore, we wanted to investigate the use and effectiveness of new drugs available for this type of infection in the real world.

Among these new drugs, meropenem/vaborbactam is currently the most used, but only few studies analysed its effectivity against CZA-resistant KPC variants.

The secondary objectives of this study were therefore to explore in depth the population infected by CZA-resistant KPC treated with MVB and to further elucidate whether the meropenem susceptibility phenotype of these CZA-resistant isolates has any clinical impact.

Materials and methods

Study population

We conducted a retrospective analysis of a monocentric cohort of 137 adults hospitalised at Policlinico Umberto I (a tertiary university hospital in Rome) between 2019 and 2025. All the patients had documented, monomicrobial, culture confirmed infection caused by *Klebsiella pneumoniae* producing KPC (KPC-Kp) and resistant to ceftazidime/avibactam (CZA-R) and received specific treatment.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

(i) patients aged 18 years or over.

(ii) patients with CZA-R KPC-Kp infection requiring specific treatment prescribed by an infectious disease specialist for this pathogen; and

(iii) patients who had received at least 48 hours of the aforementioned treatment.

The exclusion criteria were:

(i) definitive treatment for CZA-R KPC-Kp lasting less than 48 hours.

(ii) infection due to carbapenem-resistant *K. pneumoniae* harbouring resistance mechanisms other than KPC production (e.g. OXA-48-like or MBLs).

(iii) infections by carbapenem-resistant bacterial species other than *K. pneumoniae*.

(iv) polymicrobial infection, except for CoNS isolation which was considered contamination.

(v) unavailability of clinical and microbiological data.

Patient identification

The microbiology laboratory firstly flagged the patients after detection of CZA-R KPC-Kp. Two clinicians independently evaluated each signalled case, who jointly decided whether to include it based on the inclusion and exclusion criteria.

Data collection strategy

Once patients were deemed eligible, the following data were extracted from their electronic medical records: demographic data; comorbidity burden; ward of CZA-R KPC-Kp isolation; clinical and microbiological reports; history of exposure to CZA; microbiological characteristics; severity of CZA-R KPC-Kp infection; outcome; recurrence of infection; development of secondary infections; and length of hospital stay.

Outcomes

The primary outcome was 30-day mortality from the CZA-R KPC-Kp index sample collection.

Secondary outcomes were:

(i) clinical cure.
(ii) relapse of infection by CZA-R KPC-Kp.
(iii) onset of secondary infection between 3 and 30 days from the start of treatment.

Definitions

Antimicrobial susceptibility was interpreted according to the current EUCAST clinical breakpoints, with the ceftazidime/avibactam resistance breakpoint set at >8 mg/L [113].

The onset of infection was defined as the date on which signs and symptoms of infection first appeared.

Bloodstream infections (BSIs) by CZA-R KPC-Kp were diagnosed when CZA-R KPC-Kp was isolated from blood cultures (BCs) in the presence of clinical signs of infection, and BSI onset was defined as the date of collection of the index BC [114].

Lower respiratory tract infections (LRTIs) by CZA-R KPC-Kp were defined as new onset of clinical and radiographic signs of pneumonia and isolation of CZA-R KPC-Kp from a respiratory sample (bronchoalveolar fluid lavage or tracheal aspirate) [114].

Urinary tract infections (UTIs) by CZA-R KPC-Kp were defined as new onset of fever (> 38 °C), urgency, frequency, dysuria, or suprapubic tenderness with no other recognized cause and with positive urine culture (over 10^5 microorganisms for ml of urine) for CZA-R KPC-Kp [114].

Intraabdominal infections (IAIs) by CZA-R KPC-Kp were defined as culture positive for CZA-R KPC-Kp from purulent material from intraabdominal space obtained during a surgical operation, drains or needle aspiration [114].

All other infections were defined according to standard ECDC definitions [114].

The probable or established source of infection was reported in the medical record by the attending physician or the infectious disease consultant and defined according to guidelines [114]. Primary BSIs were defined as BSIs occurring in patients without a recognized source of infection. Central line-related BSIs (CLRBSIs) were considered if semiquantitative culture of the catheter tip was positive for the same KPC-Kp isolated from the BC [115]

The burden of underlying comorbidities was assessed using the Charlson comorbidity index (CCI) [116]. Immunosuppression was defined as either steroid therapy with prednisone (or equivalent) at a dose of >0.5 mg/kg/day for at least four weeks, or as receipt of chemotherapy, TNF-α inhibitors, cyclophosphamide, azathioprine, methotrexate or mycophenolate mofetil in the previous 90 days, in accordance with published data on infection risk and immunosuppressive thresholds [117-118].

Infection severity was determined using the increment-CPE score (ICS) calculated at the time of infection onset [119] and the Pitt bacteraemia score (PBS) [120]. Septic shock was defined according to the SEPSIS-3 criteria [121].

Source control of infection was intended as physical measures performed to remove the origin or reduce the burden of infection and are paramount in infection treatment. Examples of source control include replacing an infected central venous catheter or draining an abdominal abscess. In the analysis of the clinical records, it was noted whether the type of infection involving the patient required the execution of source control, and if it was performed or has not been done due to patient instability or technical difficulties.

Evaluation of antibiotic regimen and of response to treatment

Empirical therapy was considered adequate if prescribed within 24 hours of the onset of symptoms and if at least one of the drugs prescribed subsequently demonstrated *in vitro* activity in susceptibility testing according to the current breakpoints established by EUCAST [113].

The definitive therapy was considered adequate if prescribed within 72 hours of the onset of symptoms and if at least one of the drugs prescribed exhibited *in vitro* activity in susceptibility testing according to the current breakpoints established by EUCAST [113].

The available scientific literature suggests that meropenem plays an ambivalent role in the treatment of CZA-R KPC-Kp. For this reason, we decided to evaluate the effect of treatment regimens containing meropenem also independently of other treatment regimens containing older generation antibiotics, especially in the subgroup affected by meropenem susceptible pathogens. In regimens containing meropenem, this was always prescribed at a high dosage (6 grams per day).

Prolonged antibiotic infusion was defined as an antibiotic dose administered over a period of at least three hours.

Clinical cure was defined as clinical response to treatment with resolution of symptoms/signs of the infection upon discontinuation of antimicrobials [61].

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

A secondary infection was defined as an infection (i.e. UTI, pneumonia, BSI or candidemia) caused by a microorganism other than KPC-Kp between 3 and 30 days from the start of treatment. The threshold of at least 3 days of therapy to hypothesise an association between secondary infection and antibiotic treatment was chosen arbitrarily, although animal studies show a temporarily detectable alteration after only 3 days of antibiotics [122].

Adverse reactions to the definitive therapy were considered as such when indicated in the medical record by the treating physician.

Microbiology

CARBA SMART selective chromogenic media (BioMérieux, Italy) were used to screen for carbapenemase-producing *Enterobacterales*. Colonies detected on CARBA SMART were identified using matrix-assisted laser desorption/ionisation–time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics). According to the routine protocol implemented in hospital microbiology laboratories to speed up diagnostic procedures for positive blood cultures (BCs), the bacterial pellet obtained from positive BCs was used for bacterial identification by MALDI-TOF MS (Bruker Daltonics). Antimicrobial susceptibility testing was performed using the Vitek 2 automated system (bioMérieux), the SensiTitre system (Thermo Fisher Scientific) or ITGN Micronaut panels (Diagnostika GmbH, now part of Bruker Daltonics), depending on the circumstances. Subsequent molecular analysis to search for the blaKPC gene was performed by the GeneXpert® System (Cepheid, CA, USA).

Ethics

The study was approved by the local Ethical Committees (no. 0069/2022 and subsequent amendments) and conducted according to the guidelines of the Declaration of Helsinki. Informed consent was waived due to the retrospective design of the research.

Statistical analysis

Data are presented as medians with interquartile ranges (IQRs) for continuous variables and as simple frequencies, proportions, and percentages for categorical variables. The Mann–Whitney test and the ANOVA test were used for unpaired samples, as appropriate. Dichotomous variables were compared using Fisher's exact test or chi-squared test, as appropriate. Survival was analysed using Kaplan–Meier curves and the statistical significance of the differences between the two groups was assessed using the log-rank test. Factors with a univariable value of $p<0.05$ and those deemed clinically significant were included in the final multivariable Cox regression model to identify the independent predictors of 30-day mortality. *P* value analyses were two-sided and a *p* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Program for the Social Sciences software package (IBM SPSS Statistics for Windows, version 27.0. Armonk, NY, USA).

Results

Selection of patients

A total of 276 patients with CZA-R KPC-Kp microbiological isolates were identified between June 2019 and January 2025 and were evaluated for eligibility. The flowchart of selection process is depicted in Figure 1. Of the 276 patients, 45 were initially excluded: 24 due to polymicrobial infection, 17 due to co-production of metal-β-lactamase and/or OXA-48-like β-lactamase, and 4 because they had less than 18 years of age. Of the remaining 231, 61 were excluded because they did not receive a treatment specifically aimed at CZA-R KPC-Kp infection for at least 48 hours. Of the remaining 170, 33 were excluded due to inaccessibility to their records. Finally, data were collected and analysed from 137 patients who had been treated for a culture confirmed CZA-R KPC-Kp infection.

Analysis of the whole population

Of the 137 patients with CZA-R KPC-Kp infection (Table 1), 65.7% were male, with a median age of 66.4 years. There was a high prevalence of comorbidities (median CCI of 5) and 61.3% of patients were in an ICU at the time of infection onset. The most common comorbidities were diabetes mellitus (27.0%), cardiovascular diseases (58.4%), neurovascular diseases (40.9%), chronic renal failure (27.0%), COPD (24.1%), and neoplasms (17.5%). Most of the population was already carrying a rectal colonization with KPC-Kp at the time of infection onset (79.6%).

A sizeable proportion of the cohort (54.7%) had previously undergone CZA treatment during the hospitalization. This previous administration of CZA was mainly received following a diagnosis of KPC-Kp LRTI (33.3%), KPC-Kp BSI (28.0%) or was prescribed empirically because of a septic syndrome in a patient with KPC-Kp colonisation (30.7%). As might be expected, these previous KPC-Kp isolates for which patients had been treated with CZA displayed a wild-type KPC phenotype: CZA sensitivity (median CZA MIC 2 μg/mL) and predominantly showed resistance to MEM (median MEM MIC 32 μg/mL). The median

duration of previous exposure to CZA was 21 days. This exposure time was often cumulative, resulting from more than one treatment cycle of CZA prescribed during that hospitalisation (42.7% had received more than one treatment cycle, 14.7% more than two). Standard doses (2.5g every 8 hours) were administered to 88.0% of the group with previous CZA exposure, while 12% had renal adjusted dose.

The index infection by CZA-R KPC-Kp occurred after a median time of hospitalization of 44 days and in most cases presented as BSI (44.5%), followed by LRTI (34.3%), UTI (12.4%), IAI (2.9%), and other (5.8%) (Figure 2). These index infections were often severe, with 24.8% displaying septic shock, a median PITT score of 3.0 (IQR 1.0-4.0), and a median ICS of 6.0 (IQR 5.0-10.5).

The responsible CZA-R KPC-Kp isolate was susceptible to MEM in 51.8% of cases, suggesting the presence of a KPC-31 like variant.

Empirical treatment was generally started immediately after sample collection (median of 0 days), while definitive treatment was initiated after a median of 3 days (IQR 1-4).

The definitive treatment contained MVB in 61 patients (44.5%), contained MEM in 45 patients (32.8%), was composed by older-generation antibiotics (excluded MEM) in 20 patients (14.6%), while contained CFDC in 6 patients (4.4%), and IMR in 5 patients (3.6%) (Figure 3). The older-generation antibiotic category included various combinations of colistin, aminoglycosides, tigecycline, fluoroquinolones, fosfomycin, and cotrimoxazole. Colistin was the most prescribed drug in this group (7 patients), followed by fosfomycin (5 patients) and tigecycline (3 patients). The MEM-containing category included patients treated with MEM monotherapy (9 patients), combined with an older-generation antibiotic (35 patients) or with another carbapenem (1 patient). MEM was always prescribed as a high dosage scheme (6g daily).

Combination therapy, i.e. treatment with more than one antibiotic, was prescribed to 50.4% of the whole population. Antibiotic treatment was administered as extended infusion in 65.0%. Source control of the infectious focus (e.g. removal of an infected central venous

catheter or abscess drainage) was performed in 71.6% of cases for whom it was considered necessary.

In light of the antibiogram results, the empirical treatment (prescribed within 24 hours from index sample collection) was considered adequate for 34.3%. In light of the antibiogram results and of the time (days) from index sample collection the definitive treatment (prescribed within 72 hours from index sample collection) was considered adequate for 65.7%. The antibiotic treatment course for CZA-R KPC-Kp infection lasted a median of 15 days (IQR 10-20).

Clinical cure was achieved in 73.0% of patients and a relapse of CZA-R KPC-Kp infection was detected in 27.3% of evaluable cases.

A secondary infection between 3 and 30 days from the start of definitive treatment developed in 47.0%. The most frequent secondary infections were bacterial BSI and candidemia (40.0% and 32.3%, respectively) (Figure 4).

The 30-day mortality rate (calculated from the day the CZA-R KPC-Kp positive sample was collected) was 18.2%, while the overall in hospital mortality was 38.7%.

Comparison between patients with infection by a CZA-R KPC-Kp displaying resistance and those displaying susceptibility to meropenem

The 137 patients in the population were compared according to the susceptibility profile to MEM showed by their CZA-R KPC-Kp isolate (Table 2): 71 (51.8%) were susceptible (MEM-S), suggesting a KPC-31 like variant, and 66 (48.2%) were resistant (MEM-R). These two groups showed demographical differences: MEM-R patients were significantly older (median age 70.3 vs 63.0, p=0.020) and had a higher burden of comorbidities (median CCI 6.0 vs 5.0, p=0.020), particularly of chronic renal failure (37.9% vs 16.9% vs p=0.007).

Although not statistically significant, patients in the MEM-R group also demonstrated a higher prevalence of additional comorbidities, including diabetes (33.3% vs 21.1%),

cardiovascular disease (63.6% vs 53.5%), obesity (19.7% vs 14.1%), and immunodeficiency (15.2% vs 11.3%). The index infection occurred earlier in the MEM-R group (35 vs 51 days, p=0.033).

Instead, MEM-S patients were younger, less comorbid, but more commonly admitted to the ICU at the time of infection (70.4% vs 51.5%, p=0.035). In addition, a significantly higher proportion of MEM-S individuals had previously been exposed to CZA compared to MEM-R patients (66.2% vs 42.4%, p=0.006). Besides, the MEM-S group although received a similar number of previous cycles of CZA (median 1 cycle, IQR 1-2) was exposed to a longer previous therapy with CZA (22 days vs 14 days, p=0.034).

In terms of phenotypic characteristics, the MEM-S isolates had significantly higher median MICs for CZA (32 μg/mL vs 16 μg/mL; p=0.005), as well as lower median MICs for MVB (0.5 μg/mL vs 2.0 μg/mL; p=0.008).

Patients in the MEM-R group were more likely to receive treatment containing MVB than those in the MEM-S group (56.1% vs. 33.8%, p=0.028). Conversely, MEM-S were more likely to receive treatment containing MEM (42.3% vs. 22.7%, p=0.028) or other older generation antibiotics (16.9% vs 12.1%, p=0.028).

No significant difference was found in clinical cure, mortality, or secondary infections between the groups. However, the MEM-R group experienced a significantly higher number of relapses from CZA-R KPC-Kp infection (38.2% vs. 16.4%, p=0.018) and an unsignificant trend toward higher number of adverse events that the treating physicians associated with definitive antibiotic treatment (7.6% vs. 1.4%, p=0.078) and of *Clostridioides difficilis* enteritis occurring during definitive treatment (6.1% vs. 1.4%, p=0.146).

Taking the MEM-S subgroup alone, it was performed an analysis comparing those treated with a regimen that included MEM (N=30) and those treated with a regimen that included MVB (N=24) (Table 3), founding no significant difference in outcomes. Although MVB appears to have a lower mortality, no significant difference emerged when further

subgroups of septic shock, ICS≥8, VAP, LRTIs, BSIs, definitive therapy received within 24 or 48 hours were analysed (Table 3).

Analysis of thirty-day survival

The patients that were alive 30 days after the collection of the CZA-R KPC-Kp positive sample had a significantly lower burden of comorbidities (median CCI of 5.0 vs 6.0, p=0.014) and were less frequently already admitted in the ICU at the infection onset (57.1% vs 80.0%, p=0.041) (Table 4).

A greater severity of infection characterized the deceased group: higher need for CRRT (32.0% vs 8.9%, p=0.005) and vasoactive drugs (52.0% vs 22.3%, p=0.005), higher frequency of septic shock (44.0% vs 20.5%, p=0.021), higher Pitt score (median 4.0 vs 2.0, p<0.001) and ICS (median 11.0 vs 6.0, p<0.001). VAP was more prevalent (81.8% vs 38.9%, p=0.017).

Furthermore, patients with unfavourable outcome were less likely to receive definitive antibiotic treatment deemed appropriate in terms of sensitivity and/or timing (40.0% vs 71.4%, p=0.005) and to receive infection source control when clinically required (45.5% vs 76.2%, p=0.038). The MEM-S phenotype was fairly distributed between survived and deceased (50.9% vs. 56.0%, p=0.665).

To investigate the independent role of certain factors on 30-day mortality, a multivariable analysis was performed using Cox regression and the days from sample collection as time variable (Table 5). The following categorical covariates were entered: ICS ≥ 8 (considering that this score includes in its own also the CCI and Pitt score), being affected by VAP, index infection occurring in the ICU, having received appropriate definitive therapy as according to the methods criteria, and having received source control of the infection when clinically necessary. In addition, the model was also adjusted for MEM susceptibility phenotype and for the prescription of MVB. Multivariable analysis showed that receiving appropriate definitive therapy and receiving source control, when necessary, had an independent

protective role on 30-day mortality (p=0.009 and p=0.017, respectively), while an ICS value ≥ 8 was independently associated with 30-day mortality (p=0.013).

The effect on mortality of the time required to initiate definitive treatment was deepened. When considering all together the five treatment regimens, no significant difference was found according to time to initiation of definitive treatment. Instead, taking in consideration only the group treated with an MVB-containing regimen (N=61), the 30-day mortality differed significantly when MVB prescription was made within 72 hours after the index sample collection (Kaplan-Meier curve, log rang test p=0.047) (Fig. 5).

Analysis of patients treated with meropenem/vaborbactam compared to patients treated with old-generation regimens (meropenem included)

Cases treated with MVB-containing regimen (N=61) were compared with those who received treatment based on older generation drugs or a MEM-containing regimens (N=65) (Table 6). Patients treated with CFDC and IMR were excluded from this analysis due to an insufficient sample size and logical inconsistencies in the direct comparison between new first-line drugs.

Patients receiving MVB had a heavier burden of comorbidities (median CCI 6.0 vs 5.0, p=0.041) and a higher prevalence of chronic renal failure in particular (34.4% vs 18.5%, p=0.046). Even without statistical significance, the MVB group was less frequently exposed to CZA (45.9% vs 60.0%, p=0.153) and for a shorter period (median 19.5 vs 24.0 days, p=0.098).

The type of index infection differed: the MVB group had fewer urinary tract infections (3.3% vs 20.0%, p=0.018) and a higher number of respiratory infections (39.3% vs 26.2%, p=0.018). Among the respiratory infections, VAPs were particularly common in MVB-containing group (58.3% vs 23.5%, p=0.027).

In the treatment of the index infection by CZA-R KPC-Kp, MVB was part of antibiotic combination less frequently than the drugs in the older regimen group (24.6% vs 70.8%, p<0.001) and was generally administered as an extended or continuous infusion (91.8% vs 43.1%, p<0.001).

CZA-R KPC-Kp isolates in the MVB-containing group were less commonly susceptible to MEM (39.3% vs 64.6%, p=0.007).

The mortality, relapses and adverse event rates did not differ between the two treatment groups, but patients treated with MVB experienced fewer secondary infections (36.7% vs 59.4%, p=0.013). In particular, candidemia during definitive treatment occurred less frequently in the MVB group, i.e. in 5/61 cases (8.2%), while in the old regimens group it occurred in 14/65 cases (21.5%), resulting in a statistically significant difference (p=0.023). Differently, the number of bacteraemias did not differ between the two groups (old regimen 20% vs MVB 18%, p not significant).

Within this population treated with a regimen containing MVB or with a treatment regimen based on older generation drugs (including MEM), we performed mortality analyses on specific subgroups (Table 7). The subgroups with septic shock, LRTIs, and BSIs showed no significant differences. In the subgroup with VAP (N=18), MVB was associated with significantly lower 30-day mortality (21.4% vs. 75.0%, p=0.045). In the subgroup that received definitive therapy within 24 hours (N=42), the subgroup that received it within 48 hours (N=63), and the subgroup that received it within 72 hours (N=85) MVB showed a significant advantage in 30-day mortality (Table 7).

Kaplan-Meier curves for 30-day mortality were also performed for the VAP and definitive therapy within 72 hours subgroups. Patients with VAP treated with MVB showed significantly better 30-day survival (p=0.034) than those treated with old-treatment regimens (Fig. 6). Patients who started definitive treatment within 72 hours had significantly better 30-day survival (p=0.033) if their therapy was MVB-containing rather than an old-treatment regimen (Fig. 7).

Discussion

The introduction of CZA represented a new hope for KPC-producing infections but a number of unresolved issues soon dampened the enthusiasm. Pneumonia and renal replacement therapy were identified as risk factors for failure and resistance emergence [Shields2018]. A renal adjusted dose of CZA was an independent risk factor for mortality in respiratory or intra-abdominal infections [61]. These data, combined with suboptimal lung penetration [65], casted doubts on CZA PK and dose adjustment, which were corroborated by subsequent studies [70].

Furthermore, recent years witnessed a KPC strike back with the spread of CZA-R variants [38], whose mortality range between 20% to 40% [109, 112] and eerily reminisce the 37% of KPC infections before CZA introduction [56].

To further complicate the situation, many variants recover carbapenem-sensitivity (ESBL-like phenotype). This may mislead laboratory identification [37] making these variants a real phantom menace and despite apparent susceptibility, treatment with carbapenems was discouraged [106]. Initially, clinicians resorted to customized drug combinations based on residual sensitivities, but in the very last years the availability of new options such as MVB, IMR and CFDC shifted the balance once again.

We analysed a cohort of 137 hospitalised adults with CZA-R, KPC-Kp infections who received different treatment regimens. The whole population showed that this type of infection affects young elderly people (median 66.4 years), burdened by multiple comorbidities (median CCI 5) and predominantly male (65.7%). The demographic characteristics are consistent with other studies on KPC variants (median 58-73 years) [108, 110, 112] and with the report of the Istituto Superiore di Sanità on CRE bacteraemia which affect prevalently male of 60-79 years [44]. The high prevalence of comorbidities is common among carbapenem-resistant GNB infections [123], although it was lower in other experiences (median CCI 3-4) [75, 109-110]. Male gender is a risk factor for MDRO

pathogens due to a hormonally dampened immune response, a high prevalence of obstructive urological conditions, and to chronic metabolic and cardiovascular diseases [124].

Before the index infection, the majority (79.6%) had already acquired KPC-Kp rectal colonisation, similarly to prior reports [110]. In addition, more than half (54.7%) had already required CZA treatment, which is a proportion slightly higher than previously reported (23.5-49.0%) [105, 110, 112] but nearly identical to a study on MVB compassionate use (54.5%) [108] and lower than 67.8% of previous experiences [73]. The duration of previous CZA exposure reported by Liu et al was shorter (13 vs 21 days) [112]. However, in this study the exposure referred to multiple cycles of CZA treatment (median 1, IQR 1–2) received by the patient before the index infection.

Logically, previous treatment with CZA had been generally prescribed for KPC-Kp isolates with a classic phenotype (CZA-S, MEM-R). The most common indication was a respiratory infection (33.3%), followed by an empirical indication (30.7%). In the literature a prior confirmed infection from KPC-Kp is described in 7.9-17.6% [105, 109] and up to 72% [74], while in other works a prior CZA-S isolate was present in 69.5% [73].

A high prior exposure to CZA in patients with CZA-R KPC-Kp infection is expected [112]. *In vivo* resistance development was reported after prolonged prescriptions (weeks) and often generating different clones within the same individual [125-126]. A retrospective study on 90 CZA exposed patients, found that 6.6% developed a CZA-R KPC-Kp infection, and notably, all had presented with a respiratory infection and many had undergone CRRT [69]. If one of the mechanisms determining the emergence of CZA resistance is CZA exposure, probably other ones are conditions and diseases that cause altered drug PK [62]. This assumption fits well with the fact that, in our population, a pulmonary infection was the most common indication of previous CZA exposure. Insufficient pulmonary penetration of CZA [66] is the reason of attempts to combine CZA with other molecules in pulmonary infections [127]. In 104 lung transplant recipients with KPC-Kp pneumonia receiving CZA, 9.6% developed a KPC variant [128]. In *Pseudomonas* pneumonia, those receiving CZA

developed resistance significantly more than those treated with ceftolozane/tazobactam (40% vs 10%) [129]. However, over 45% of our population contracted an infection by a CZA-R KPC variant without CZA exposure. This sadly suggests that many cases originated by horizontal transmission [78, 130].

The index infection occurred after a median of 44 days, longer than previously described (13-35 days) [75, 105, 110], except for Liu et al. (49 days) [112].

The distribution of CZA-R KPC-Kp index infections mirrors other studies, with a predominance of BSIs and LRTIs, followed by UTIs [108-109, 112]. Instead, our population suffered a more severe infection than most of other cohorts (septic shock 24.8% vs 4.5-11.1%) [108, 112], while a similar severity (median ICS of 6) is encompassed only by Boattini et al which included BSIs only [110].

Covering a broad time frame (2019–2025), this retrospective study allows for comparison of different treatment regimens used for CZA-R KPC-Kp infections: MVB-containing was the most used (44.5%), followed by MEM-containing (32.8%) and older-generation drugs (14.6%). Previous studies used MVB in 18.6–41.2% of cases [73, 105, 110], but some recently published studies still did not have access to new drugs and employed variable combinations of CZA, MEM and colistin [109, 112].

We observed a 30-day mortality rate of 18.2%, which is optimistic compared to studies that prevalently used MEM and older-generation antibiotics (41-50%) [75, 109], but the analyses where greater use was made of new drugs showed a limited fatality (16.2-24.5%) [110-111].

Overall demographic and clinical characteristics of our population corroborate the little we know on CZA-R KPC-Kp infections. The higher exposure to CZA could be linked to the higher comorbidity burden, and the higher severity of symptoms may originate from the fact that our population experienced the index infection after a longer hospitalization.

In the present study mortality was associated to ICU admission, CCI, VAP, CRRT, vasoactive drugs, ICS and Pitt scores, while appropriateness of therapy and performance of source control were protective. The multivariable analysis confirmed an independent

association with 30-day mortality of ICS, appropriate definitive therapy, and source control. ICS, which includes in its own septic shock, CCI, and Pitt score, weights the patient baseline conditions and the infection severity, and confirmed to be a powerful predictor of mortality [131], as it was even in non-bacteraemic infections [132]. The results are consistent with previous experiences in CZA-R KPC-Kp, where mortality was predicted by septic shock [73] and by CCI, chronic renal failure, CRRT, ICS, AKI, and cardiac surgery indication [110]. Although in a mixed population (CZA-S/R), Tumbarello found septic shock, CCI, dialysis, COVID-19 and ICS associated to death, while MVB prescription within 48 hours was protective [111]. It is reassuring that therapy appropriateness and source control remain mortality predictors as this place physician's actions back centre stage. Researching and remediating the infection focus is one of the most impactful measures [133] even more in MDROs with limited pharmacological options.

As for appropriateness of therapy, in the present study it was defined as simultaneous presence of two fundamental components: microbiological adequacy and early administration. In fact, mortality is strongly influenced by treatment delay [48]. It is interesting that, when analysing the impact of initiation time on mortality, this was not significant in the overall population, but it was significant in the subgroup treated with MVB within 72 hours from sample collection. This could indicate that MVB, being generally highly active on KPC variants, is the regimen that best benefits from an early prescription.

Patients with infection by carbapenem-sensitive (MEM-S) and carbapenem-resistant (MEM-R) pathogens were compared. This was done in continuity with another retrospective study conducted between 2019 and 2021 by our study group on 59 patients [73]. MEM-S patients were younger, more exposed to CZA, and more frequently admitted to the ICU. In addition, there was a significant difference in the type of index infection between the two groups, and although not significantly the MEM-R group had a higher number of CZA-R KPC-Kp relapse infections [73].

Accordingly, in the present study the MEM-R group was older, with more comorbidities, and less exposed to CZA. MEM-R infection occurred earlier during hospitalization and less

frequently during their ICU stay. The MEM-R pathogens had lower MICs for CZA compared to the MEM-S. No differences emerged in severity nor in mortality, but MEM-R patients experienced more CZA-R KPC-Kp infection relapses (38.2 vs 16.4, p=0.018) and tendency toward more adverse events (7.6 vs 1.4, p=0.078).

Similarly to our finding, in another retrospective study it was noted a non-significant survival advantage for MEM-R [110], but the fact that MEM-S patients are more often admitted to the ICU weighs heavily. In the study by Liu et al, 72% of KPC variants were MEM-S, and as KPC variants had lower 14-day mortality than CZA-S, it can be speculated that MEM-S had lower mortality [112], but no comparison was made with MEM-R group. Corcione included only MEM-S, reporting a median age of 57 years and a low comorbidity burden (2 out of 17 had oncological disease). Their mortality was high (58%) but biased by the 100% ICU admission [105].

Noteworthy the two populations are treated differently, with frequent use of MEM containing regimens among MEM-S (42.3%) and of MVB containing regimens among MEM-R (56.1%). Moreover, MEM-R isolates have a significantly higher MIC for MVB than MEM-S (median of 0.5 vs 2.0 μg/ml, p=0.008). This observation finds support in the literature. An in vitro study examined 18 strains of KPC-Kp with MICs for MVB ranging from 0.06 to 32 μg/mL to determine the concentrations of MEM and VAB required to prevent resistance. Strains with an already high MEM MICs required a higher concentration of MEM and VAB to suppress resistance [83]. The correlation between MEM MIC and MVB MIC suggests that a high MEM MIC hinders the ability of vaborbactam to restore susceptibility. This can be explained by additional resistance mechanisms, as porin mutations most commonly correlate with an increase in MIC for MVB and the action of vaborbactam through carbapenemase inhibition supply only partial compensation in the overall sensitivity balance provided by the antibiogram. In Wilson et al.'s study, the addition of vaborbactam reduced the MIC of MEM in KPC variants, but significantly less so in strains with mutated *ompK36* genes [84]. It is not known whether this higher MIC for MVB in KPC mutant strains with MEM-R phenotype has any clinical significance. In any case, in this study, a high MIC

for MVB was not associated with higher mortality (median 0.8 in survivors vs 1.0 in deceased, p=0.705). We can only speculate that, since MVB susceptibility testing is not routinely performed in all centres, it may be recommended to perform it at least in the presence of high MICs to MEM or (a less recommended alternative) to use MVB in combination therapy for MEM-R cases to reduce the risk of resistance.

Overall, the idea that arises regarding the MEM resistance phenotype of CZA-R KPC-Kp is that MEM-S and MEM-R may represent two clinically distinct populations. MEM-S involves young-adult with few comorbidities, ICU admitted, that after KPC colonization often receive empirical CZA. The ESBL-like phenotype could be the result of an evolutionary trade-off mechanism whereby the pathogen acquires a high-level resistance to CZA but partially loses immunity to other β-lactams, particularly carbapenems [37]. Conversely, MEM-R are older and comorbid, commonly admitted to medical wards and less exposed to CZA. Rather than resulting from a de novo evolutionary process, their CZA-R infection may come from horizontal transmission through breaches in containment measures [78]. This could also explain why MEM-R patients become infected with CZA-R earlier than MEM-S patients. Other hospitals have also reported cases of colonisation and infection with CZA-R KPC-Kp, which occurred just few months after CZA market release and independently of CZA administration [130].

Current guidelines slightly favour MVB over CZA for KPC-producing infections, basing on resistance emergence of 10–20% after CZA treatment and 5% after MVB, on frequent (>80%) cross-resistance between CZA and CFDC [22] and on limited data about IMR [97]. Nevertheless, recommendations on KPC variants remain elusive, including only preventive strategies such as repeating sensitivity tests after new KPC isolation and avoiding empirical re-exposure to a previously prescribed drug [22]. It was therefore worthwhile to examine in greater depth the subgroup of individuals that were treated with MVB (N=61) and confronting them with a regimen based on older generation antibiotics, including MEM (N=65). We excluded IMR and CFDC from this analysis, because of the small sample size and because it would not be reasonable to compare first-line options.

Those receiving MVB had significantly more comorbidities, and particularly a higher frequency of chronic renal failure. MVB was almost always administered by extended infusion to optimise its PK as indicated by EMA instructions, which set a 3-hour infusion [80].

The index infections in the MVB group were more often LRTIs (39.3%), and in particular VAP, while UTIs prevailed in the group treated with older-generation drugs. The 30-day mortality observed in the present study among individuals treated respectively with MVB and older treatment regimens was 14.8% and 20.0% (p=0.488). LRTI and specifically VAP commonly have a mortality higher than UTIs for a variety of reasons [134], so MVB outcomes not significantly different from the other group is an encouraging result. Furthermore, the fact that clinicians tend to reserve MVB for infections with higher mortality rates, such as LRTIs and specifically VAPs, suggests that they have an important level of confidence in this drug. Moreover, MVB was often administered as monotherapy, suggesting that clinicians felt greater confidence in this drug while tended to reinforce other therapeutic options through combination.

When mortality was analysed within specific subgroups revealed a possible advantage of MVB compared to older generation drug regimens, the latter having higher mortality in patients with VAP and in the subgroups that received soon definitive therapy (within 24, 48 or 72 hours) (Tabel 7). The better result of MVB on VAPs can be explained by the good penetration of both components in the ELF [81]. The better result of MVB among those with early initiation of definitive therapy may be attributed to the fact that MVB, having broad activity against KPC variants, was often ex post the correct empirical choice, and was therefore maintained, fully exploiting the clinical benefit of early initiation of therapy. This perspective could indicate that MVB should be preferred as empirical therapy in patients colonised with KPC, since if the antibiogram then shows the presence of a variant, the treatment was active from the outset.

Literature information on CZA-R KPC-Kp infection treated with MVB is still limited and this represent the widest cohort. A 2023 report states that 42.9% of the 7 patients treated

with MVB had suspected VAP but does not distinguish mortality [105]. In another study 35% of CZA-R received MVB and mortality did not differ from other regimens (around 16%) [110]. Tumbarello et al involved 37 adults (70% in ICU) with KPC infection (90% BSI or LRTI) treated with compassionate use of MVB. The isolates were all MEM-R phenotype and 22 were CZA-R. This subgroup achieved clinical cure in 81.1% and had an in-hospital mortality rate of 18.2%, compared to 77.0% and 36.1% respectively in our case series. The disparity may be justified by a lower median age, comorbidity burden, index infection severity, and respiratory infections than those of our group [108]. In the large Italian multicentre study on MVB in KPC-Kp infections it was not provided a detailed description of CZA-R subgroup (24.8%), but the 30-day mortality was 24.2% and 36.5%, when MVB was prescribed as a first- or second-line therapy, respectively. Significantly higher of what observed here, also considering that UTIs were the most common infections in the CZA-R subgroup [111].

The group treated with MVB experienced significantly fewer secondary infections than the group treated with older-generation drugs (36.7% versus 59.4%, p = 0.013). In the study by Oliva et al., secondary infections were quite common, affecting 54% of patients [73], while Boattini et al. reported candidemia events only in 8%. Similarly, in the current study, candidemia occurred in five out of 61 patients treated with MVB (8.2%), and was significantly lower compared to those treated with an old-drug regimen (p=0.023). Secondary infections, especially fungal infections, in patients being treated with broad-spectrum systemic antibiotics for bacterial infections, are an important yet poorly understood issue [135], probably associated with clinical deterioration caused by the index infection, invasive procedures often required for treatment, and dysbiosis caused by antibiotic therapy. In a retrospective clinical study on the use of the CZA+FOF combination in patients with KPC-Kp BSI, 34.4% had secondary infection, 23.8% candidemia [136]. It could be argued that receiving a single antibiotic molecule rather than a combination causes a minor compromission of microbial flora [137], but this remains speculative and needs further specific investigation.

Notably, this study found that patients treated with MEM-containing regimens (N=45) did not experience worse outcomes or higher relapse compared to other regimens. While the use of MVB against MEM-R isolates can currently be considered common, the issue remains more open for MEM-S. In our subgroup analysis of mortality among MEM-S (Table 3), MVB displayed lower mortality rates than MEM, also in high-risk groups like high ICS, sepsis and VAP, but differences were not statistically significant. Therefore, the hypotheses of rapid recovery of MEM resistance in CZA-R MEM-S variants [106-107] were not confirmed. This discrepancy can be explained by the fact that those studies were conducted *in vitro* only, and that in our study MEM was mostly used at a high dosage [72] and in combination with another older-generation drug (71.1%), conditions that may have prevented the emergence of resistance.

This study has several limitations. Firstly, the retrospective and monocentric nature of the study introduces bias, reducing the generalisability of the results. Furthermore, the study design did not allow us to identify the type of KPC variant or other potentially associated resistance mechanisms, such as porin mutations, at a genetic level. Additionally, some of the screened patients who were potentially eligible for the study were excluded due to the unavailability of clinical data, potentially causing a selection bias. The small sample size of the imipenem/relebactam and cefiderocol groups prevented us from conducting an in-depth analysis, whereas this was possible for the meropenem/vaborbactam group. Considering only patients with CZA-R KPC-Kp infection who received targeted antibiotic treatment for at least 48 hours may have led to an underestimation of mortality, as most patients excluded due to treatment lasting less than 48 hours died prematurely. Finally, the significance of some interesting results is diminished by the fact that they emerged from subgroup analyses, which in themselves represent a source of bias.

Conclusions

This study contains the largest cohort of CZA-R KPC-Kp infection treated with MVB and support the use of MVB as an excellent option for CZA-R KPC-Kp infections. In fact, MVB achieved similar outcomes to other regimens despite often being used in patients with more complex clinical and infection characteristics. Furthermore, potential advantages of MVB over older-generation treatments have emerged in subgroups of patients with VAP and in those who start definitive treatment early. Lower rate of secondary candidemia was also demonstrated. In addition, it has been confirmed that early initiation of MVB can significantly improve outcomes also in the overall population. Analysing the population with CZA-R MEM-S infection, MVB had a mortality advantage on MEM, but this was not statistically significant, possibly because of the low subgroup numerosity or even because MEM has always been done at high doses and often in combination. A comparison with existing literature suggests that mortality is lower in studies in which new drugs are available, although this cannot be taken as a rule. However, treatments consisting of older generation drugs should not be completely ruled out, as new drugs may be in short supply due to their cost, as demonstrated by recent studies conducted in the Middle East and East Asia [Ahmed2024; Liu2025]. Furthermore, high dose carbapenems are prescribed in cases of MVB and IMR, the use of which should be limited as much as possible for antibiotic stewardship matters and reduction of future resistance emergence. CZA-R isolates appear to show different origins and demographics depending on their susceptibility to meropenem. The predictivity of meropenem resistance for a higher meropenem/vaborbactam MIC is an interesting cue but need further in-depth analysis.

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Figures

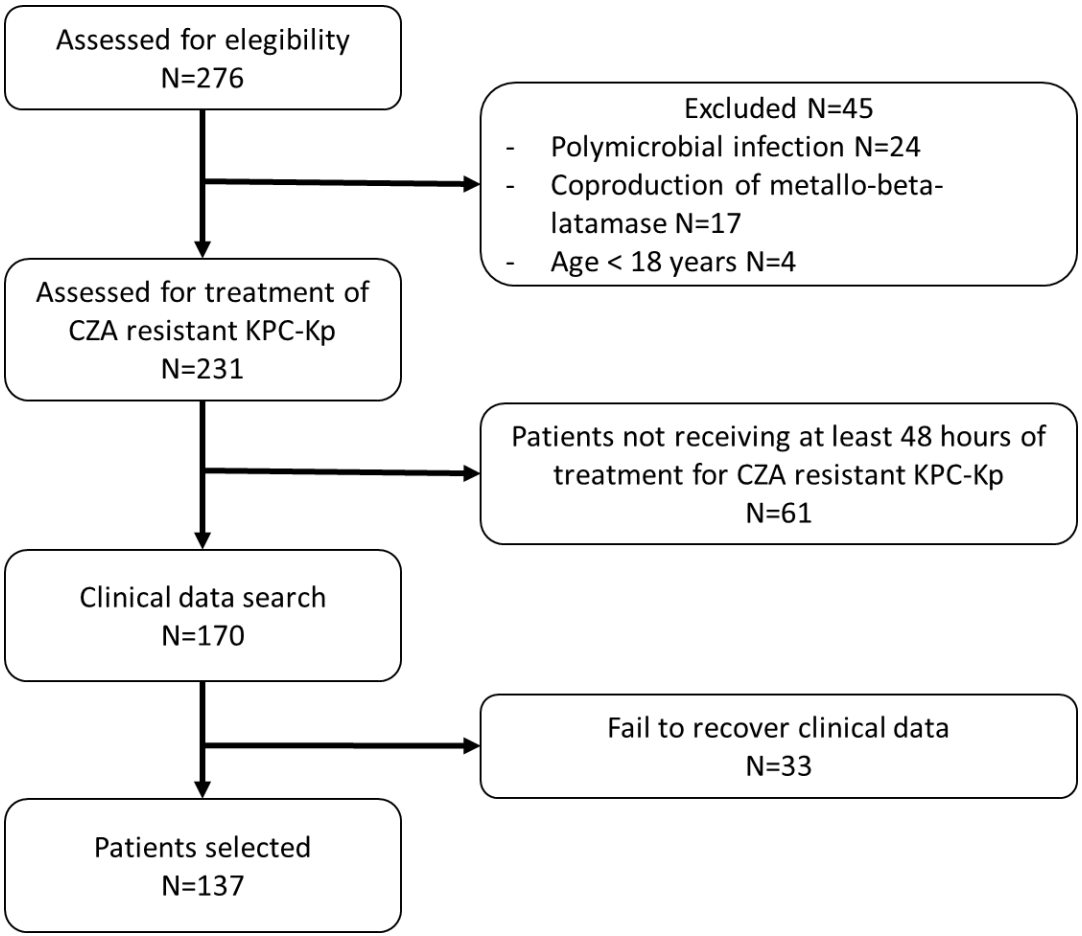


Figure 1. Flowchart of patient selection progress.

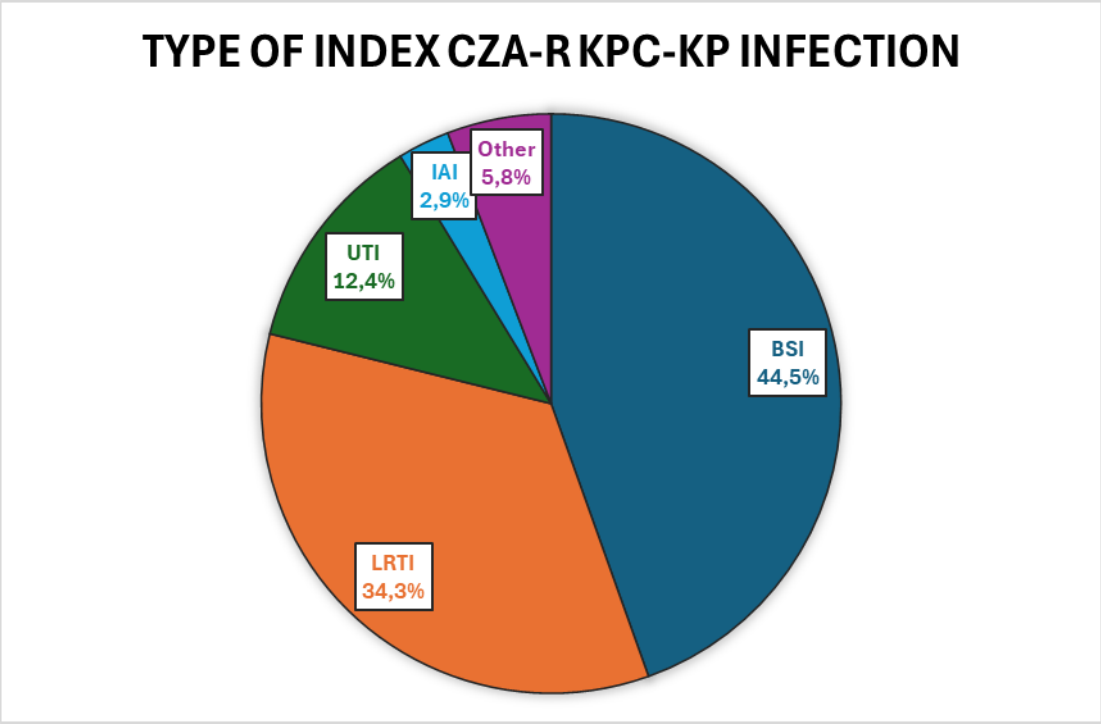


Figure 2. Distribution of diverse types of infections by ceftazidime/avibactam resistant KPC-Kp.

BSI, bloodstream infection; LRTI, lower respiratory tract infection; IAI, intrabdominal infection; UTI, urinary tract infection.

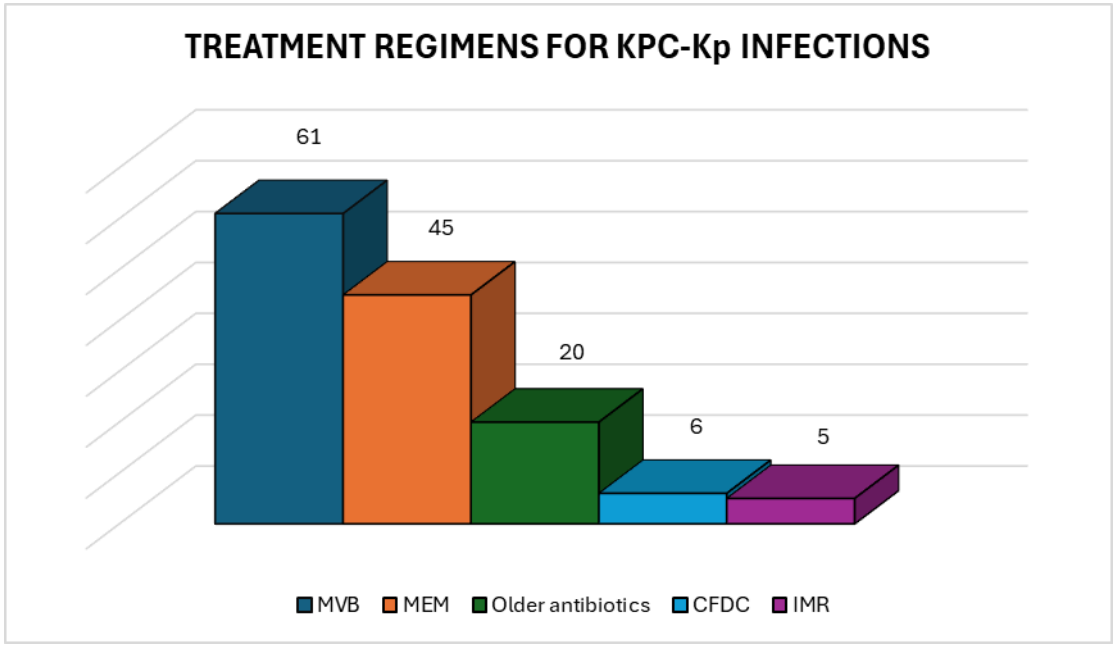
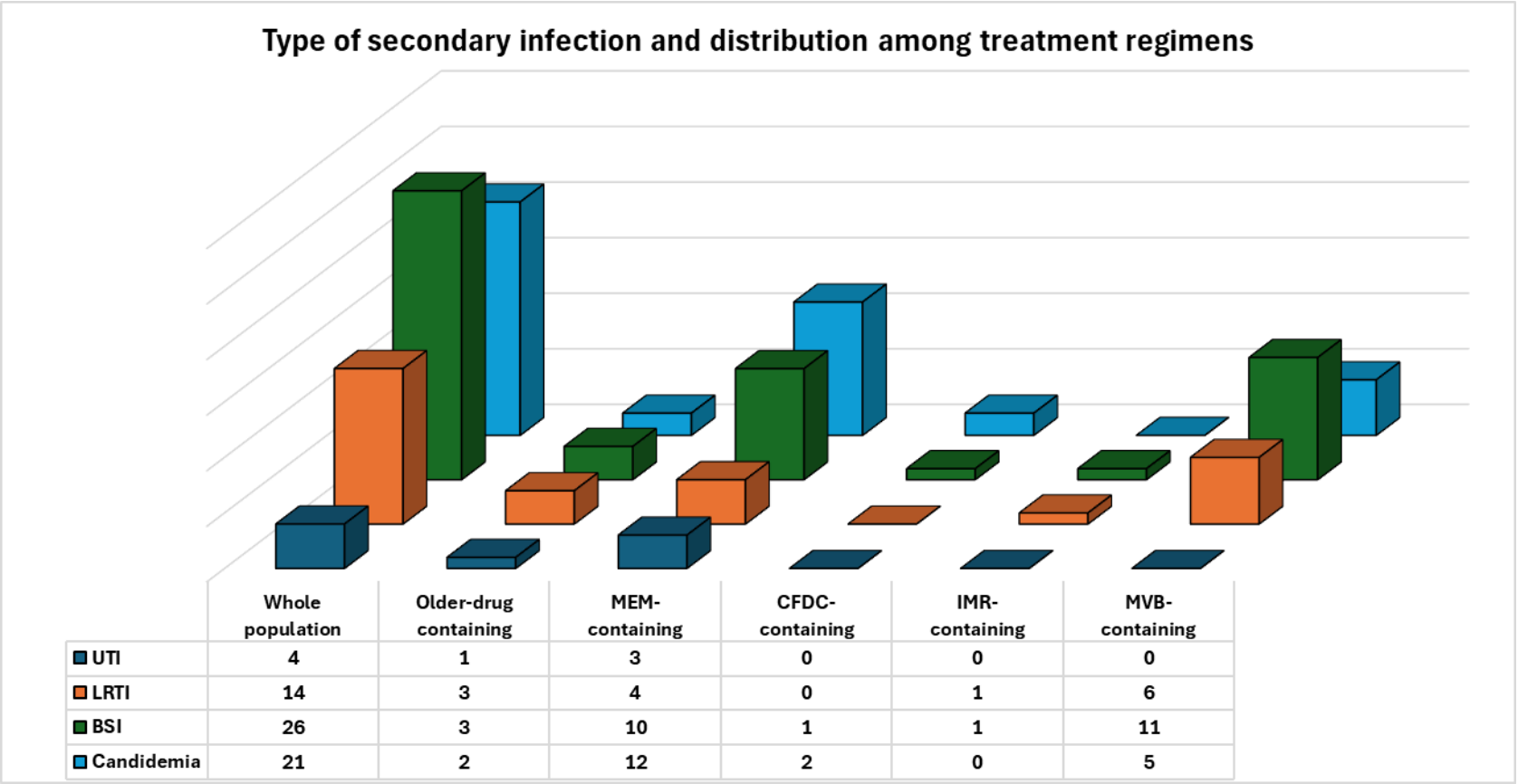


Figure 3. Distribution of treatment regimens prescribed for ceftazidime/avibactam resistant KPC-Kp infections.

CFDC, cefiderocol; IMR, imipenem/relebactam; MEM, meropenem; MVB, meropenem/vaborbactam.



	Whole population	Older-drug containing	MEM-containing	CFDC-containing	IMR-containing	MVB-containing
UTI	4	1	3	0	0	0
LRTI	14	3	4	0	1	6
BSI	26	3	10	1	1	11
Candidemia	21	2	12	2	0	5

Figure 4. Distribution of secondary infections.

CFDC, cefiderocol; MEM, meropenem; IMR, imipenem/relebactam; MVB, meropenem/vaborbactam.

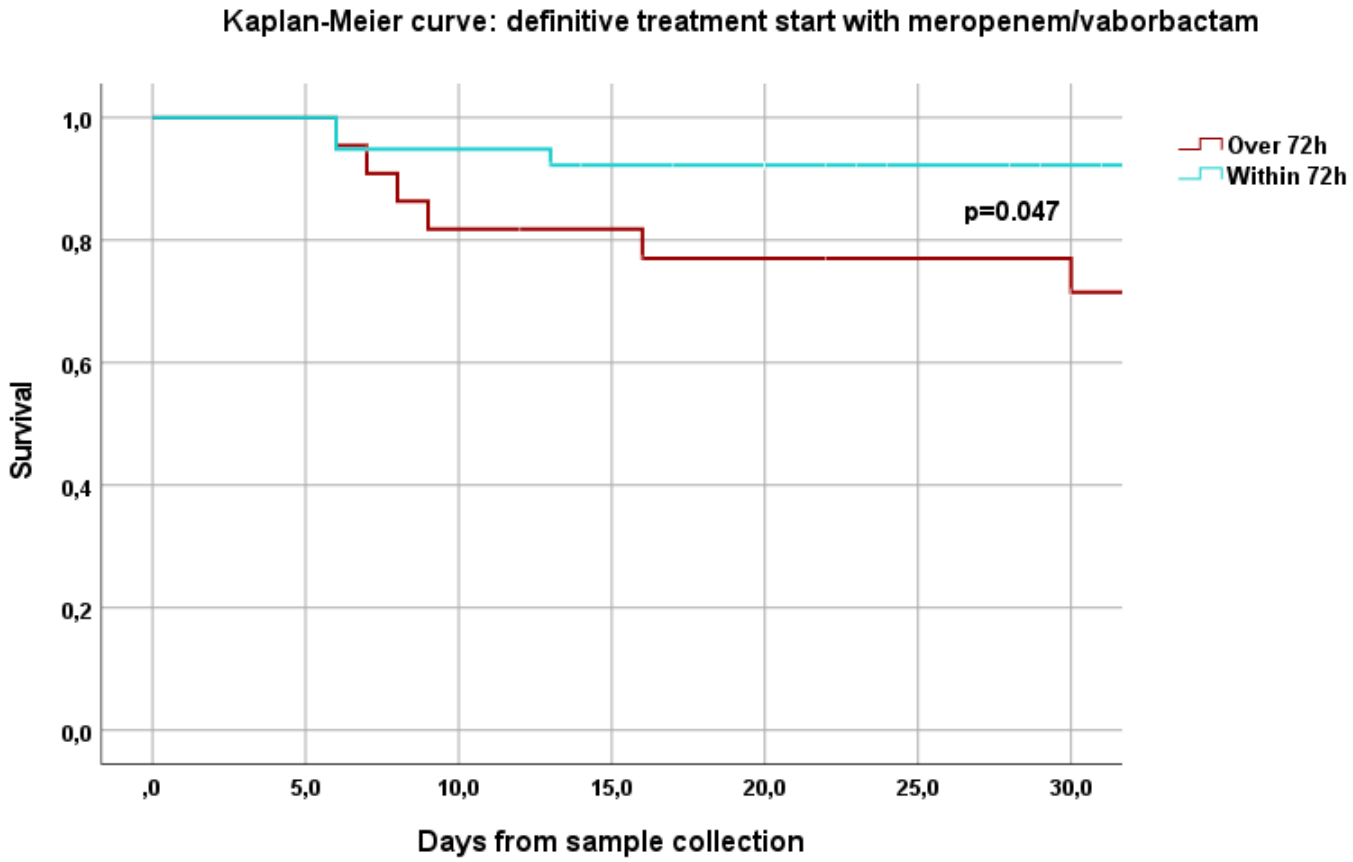


Figure 5. Kaplan-Meier curve for 30-day survival in patients receiving meropenem/vaborbactam (MVB) according to definitive therapy prescription within 72 hours (blue line) or over 72 hours (red line).

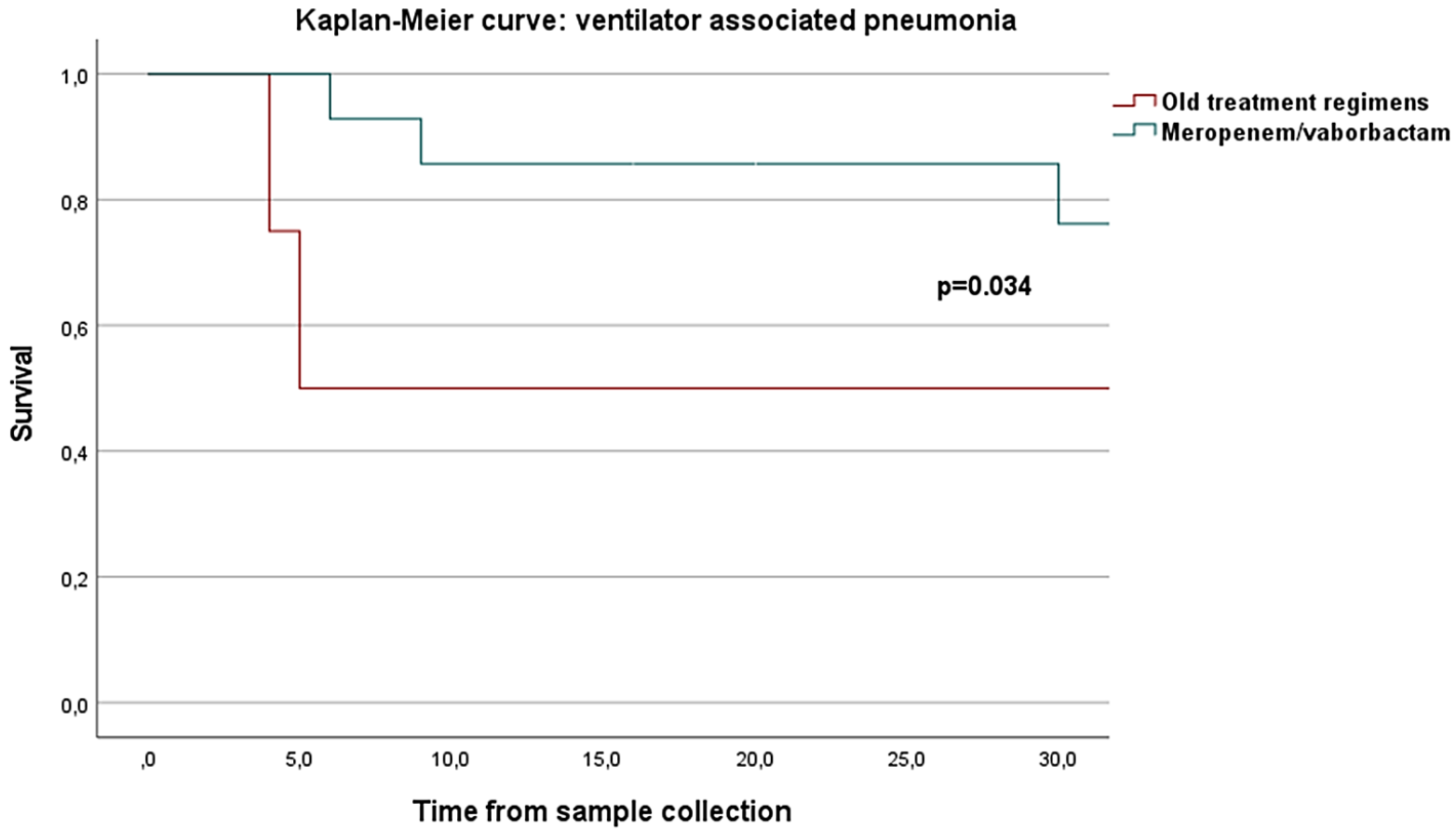


Figure 6. Kaplan-Meier curve for 30-day survival in patients with ventilator associated pneumonia and treated with meropenem/vaborbactam (blue line) or with a regimen based on older generation antibiotics (red line).

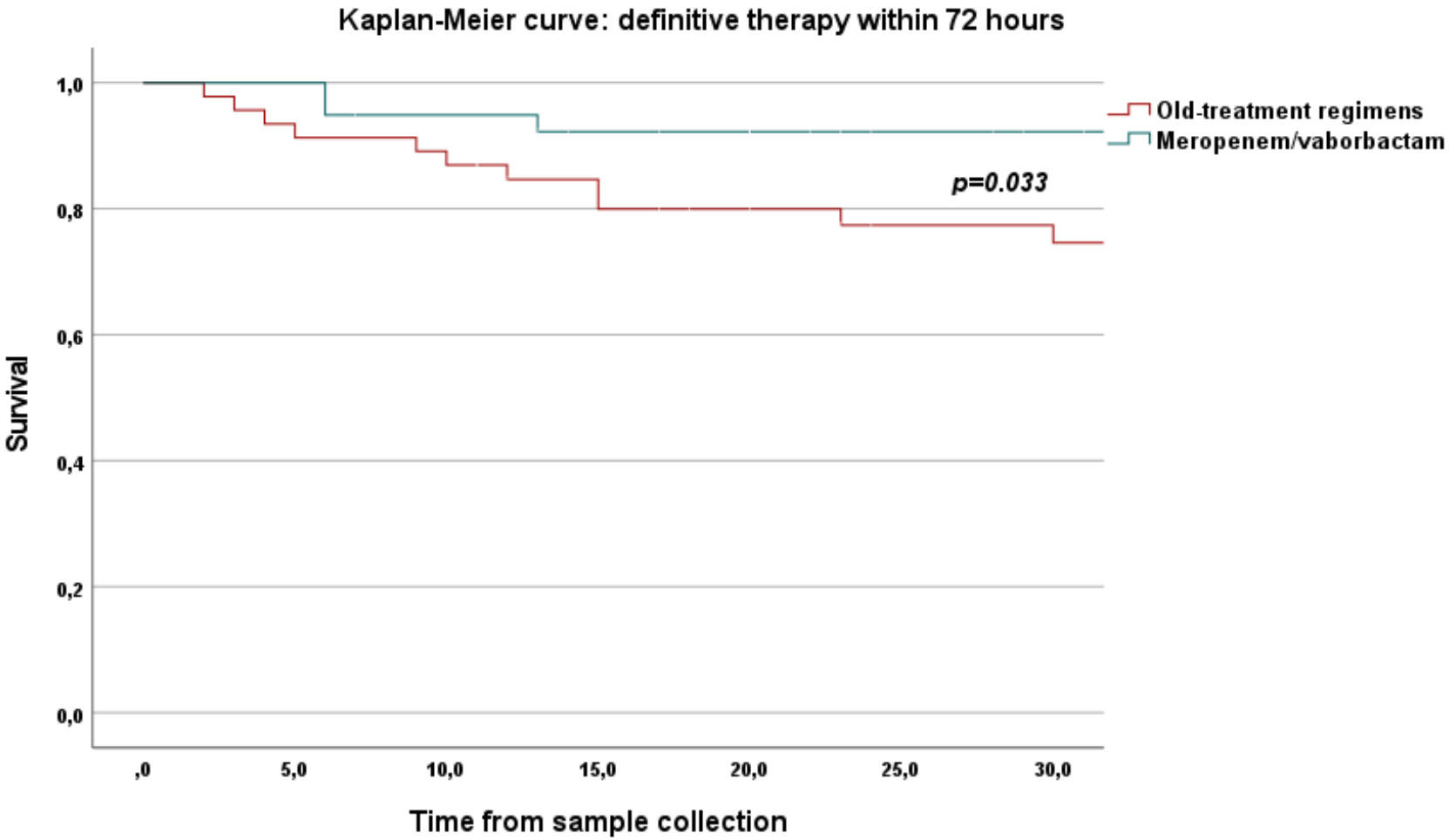


Figure 7: Kaplan-Meier curve for 30-day survival among patients receiving definitive therapy within 72 hours. Prescription of meropenem/vaborbactam (blue line) or of a regimen based on older generation antibiotics (red line).

Tables

Table 1. Whole population and comparison of the five treatment regimens

Variable	Whole population (N=137)	Older generation antibiotics (MEM excluded) (N=20)	MEM-based (N=45)	CFDC-based (N=6)	IMR-based (N=5)	MVB-based (N=61)	*p*
Gender male: n (%)	90 (65.7)	13 (65.0)	27 (60.0)	5 (83.3)	4 (80.0)	41 (67.2)	0.736
Age: median (IQR)	66.4 (54.9-75.9)	60.6 (48.0-79.8)	62.3 (52.1-72.4)	56.8 (46.8-69.4)	68.1 (60.9-77.5)	69.0 (57.7-76.5)	0.409
Isolation occurred in ICU: n (%)	84 (61.3)	13 (65.0)	28 (62.2)	5 (83.3)	4 (80.0)	34 (55.7)	0.576
CCI: median (IQR)	5.0 (3.0-7.0)	5.0 (2.3-7.0)	4.0 (3.0-6.0)	6.0 (3.5-6.3)	6.0 (2.5-8.5)	6.0 (4.0-7.0)	0.339
CCI ≥3: n (%)	113 (82.5)	15 (75.0)	36 (80.0)	5 (83.3)	4 (80.0)	53 (86.9)	0.771
Diabetes: n (%)	37 (27.0)	2 (10.0)	12 (26.7)	2 (33.3)	1 (20.0)	20 (32.8)	0.377
Cardiovascular disease: n (%)	80 (58.4)	11 (55.0)	23 (51.1)	4 (66.7)	2 (40.0)	40 (65.6)	0.519
Neurovascular disease: n (%)	56 (40.9)	6 (30.0)	23 (51.1)	2 (33.3)	2 (40.0)	23 (37.7)	0.505
COPD: n (%)	33 (24.1)	5 (25.0)	11 (24.4)	1 (16.7)	1 (20.0)	15 (24.6)	0.993
CKD: n (%)	37 (27.0)	6 (30.0)	6 (13.3)	2 (33.3)	2 (40.0)	21 (34.4)	0.158
Chronic liver disease: n (%)	6 (4.4)	1 (5.0)	0	0	1 (20.0)	4 (6.6)	0.202
Neoplasia (solid and/or haematologic): n (%)	24 (17.5)	3 (15.0)	9 (20.0)	2 (33.3)	1 (20.0)	9 (14.8)	0.798
Solid neoplasia: n (%)	18 (13.1)	3 (15.0)	7 (15.6)	1 (16.7)	0	7 (11.5)	0.868
Haematologic neoplasia: n (%)	8 (5.8)	1 (5.0)	2 (4.4)	1 (16.7)	1 (20.0)	3 (4.9)	0.496
Obesity: n (%)	23 (16.8)	1 (5.0)	9 (20.0)	1 (16.7)	0	12 (19.7)	0.449
Immunodeficiency: n (%)	18 (13.1)	5 (25.0)	3 (6.7)	0	1 (20.0)	9 (14.8)	0.251
Solid transplant: n (%)	7 (5.1)	2 (10.0)	0	0	1 (20.0)	4 (6.6)	0.179
CVC or PICC carrier at the time of infection onset: n (%)	83 (60.6)	10 (50.0)	27 (60.0)	4 (66.7)	3 (60.0)	39 (63.9)	0.857
Rectal colonization by KPC-Kp at the time of infection onset: n (%)	109 (79.6)	15 (75.0)	37 (82.2)	5 (83.3)	4 (80.0)	48 (78.7)	0.970
Time (days) from hospitalization to start of a large spectrum antibiotic therapy: median (IQR)	1.0 (0-3.0)	1.0 (0-8.0)	1.0 (0-2.5)	0 (0-0.5)	1.0 (0-1.5)	1.0 (0-3.5)	0.303
Previous CZA treatment: n (%)	75 (54.7)	8 (40.0)	31 (68.9)	5 (83.3)	3 (60.0)	28 (45.9)	0.053
Previous CZA MIC (µg/mL): median (IQR)	2.0 (1.0-4.0)	2.0 (2.0-4.0)	2 (0.8-4.0)	1.0 (0.8-4.0)	4.0 (1.8-7.0)	3.0 (1.0-4.5)	0.469
Previous MEM MIC (µg/mL): median (IQR)	32 (32-32)	32 (32-32)	32 (32-32)	32 (32-64)	32 (32-32)	32 (32-32)	0.154
Indication for previous CZA treatment: n (%)							
- **BSI**	21 (28.0)	1 (12.5)	8 (25.8)	2 (40.0)	1 (33.3)	9 (32.1)	0.403
- **LRTI**	25 (33.3)	3 (37.5)	14 (45.2)	1 (20.0)	0	7 (25.0)	
- **UTI**	5 (6.7)	0	2 (6.5)	0	0	3 (10.7)	

- **IAI** - **Empirical for sepsis in KPC-Kp colonization**	1 (1.3) 23 (30.7)	1 (12.5) 3 (37.5)	0 7 (22.6)	0 2 (40.0)	0 2 (66.7)	0 9 (32.1)	
Previous daily dose (g) of CZA received: median (IQR)	7.5 (7.5-7.5)	7.5 (7.5-7.5)	7.5 (7.5-7.5)	7.5 (3.7-7.5)	7.5 (1.9-7.5)	7.5 (7.5-7.5)	0.380
Number of days of CZA treatment previously received: median (IQR)	21.0 (12.5-32.0)	24.0 (15.0-52.3)	24.0 (15.0-35.0)	16.0 (10.5-32.0)	15.0 (14.0-15.0)	18.0 (9.5-28.0)	0.422
Cycles of CZA therapy received: median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.8)	2.0 (1.0-2.0)	1.0 (1.0-1.5)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	0.734
Previous CZA received as monotherapy: n (%)	25 (33.3)	4 (50.0)	10 (32.3)	0	2 (66.7)	9 (31.0)	0.276
Index infection by CZA-R KPC-Kp: n (%) - **BSI** - **LRTI** - **UTI** - **IAI** - **Other**	 61 (44.5) 47 (34.3) 17 (12.4) 4 (2.9) 8 (5.8)	 6 (30.0) 7 (35.0) 6 (30.0) 0 1 (5.0)	 26 (57.8) 10 (22.2) 7 (15.6) 1 (2.2) 1 (2.2)	 1 (16.7) 5 (83.3) 0 0 0	 1 (20.0) 1 (20.0) 2 (40.0) 1 (20.0) 0	 27 (44.3) 24 (39.3) 2 (3.3) 2 (3.3) 6 (9.8)	 **0.006**
VAP (confirmed or probable) out of 47 respiratory tract infection	23 (48.9)	2 (28.6)	2 (20.0)	5 (100)	0	14 (58.3)	**0.021**
Time (days) from hospitalization to infection by CZA-R KPC-Kp: median (IQR)	44 (21-78)	40 (13-76)	55 (35-90)	35 (27-65)	47 (31-77)	36 (15-70)	0.211
CRP (mg/dL): median (IQR)	12.3 (7.2-20.4)	16.5 (7.0-24.5)	11.5 (7.0-17.3)	17.4 (14.3-25.9)	11.4 (3.3-33.9)	11.5 (7.1-21.8)	0.382
PCT (ng/mL): median (IQR)	1.3 (0.4-7.5)	1.0 (0.3-4.4)	1.5 (0.3-10.3)	0.9 (0.4-1.2)	2.3 (0.5-30.1)	2.0 (0.5-8.4)	0.464
CRRT required during infection: n (%)	18 (13.1)	5 (25.0)	3 (6.7)	1 (16.7)	1 (20.0)	8 (13.1)	0.356
Vasoactive drugs required during infection: n (%)	38 (27.7)	6 (30.0)	12 (26.7)	3 (50.0)	0	17 (27.9)	0.481
Septic shock: n (%)	34 (24.8)	5 (25.0)	10 (22.2)	3 (50.0)	0	16 (26.2)	0.417
Pitt score at infection onset: median (IQR)	3.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-4.5)	4 (3.8-6.3)	2.0 (0-3.0)	3.0 (2.0-4.0)	**0.049**
ICS at infection onset: median (IQR)	6.0 (5.0-10.5)	5.0 (5.0-8.0)	6.0 (5.0-10.0)	11.5 (8.0-13.5)	5.0 (3.0-9.5)	8.0 (5.0-11.0)	**0.028**
ICS ≥ 8 at infection onset: n (%)	64 (46.7)	6 (30.0)	18 (40.0)	6 (100)	2 (40.0)	32 (52.5)	**0.029**
CZA MIC (µg/mL): median (IQR)	16 (16-56)	16 (16-32)	32 (16-64)	32 (16-152)	16 (14-144)	16 (16-176)	0.628
MEM MIC (µg/mL): median (IQR)	8 (1-32)	3 (1-32)	2 (0.3-16)	3 (1-32)	32 (18-48)	32 (2-32)	**<0.001**
MEM susceptible: n (%)	71 (51.8)	12 (60.0)	30 (66.7)	4 (66.7)	1 (20.0)	24 (39.3)	**0.028**
MVB MIC (µg/mL): median (IQR) [available in 54]	0.75 (0.31-2.00)	0.9 (0.2-1.0)	0.2 (0.1-0.9)	128.0 (1.0-128.0)	4.0 (2.5-6.0)	0.8 (0.5-2.0)	**0.011**
Time (days) from isolation of CZA-S to isolation of CZA-R KPC-Kp: median (IQR)	36.0 (19.5-78.5)	22.5 (8.3-64.3)	46.5 (27.8-86.3)	25.0 (11.0-52.5)	61.0 (22.5-263.0)	34.5 (15.5-76.8)	0.161
Time (days) from sample collection to start of empiric therapy: median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-1.8)	1.0 (0.0-2.0)	0.0 (0.0-0.8)	0.0 (0.0-2.5)	0.0 (0.0-1.0)	0.253
Time from sample collection to start of definitive therapy (days): median (IQR)	3.0 (1.0-4.0)	3.0 (2.0-4.0)	3.0 (1.0-4.5)	4.5 (1.5-7.5)	3.0 (2.5-4.0)	2.0 (1.0-4.0)	0.524

Definitive therapy: n (%) - **Older generation antibiotics (MEM excluded)** - **MEM-based** - **CFDC-based** - **IMR-based** - **MVB-based**	 20 (14.6) 45 (32.8) 6 (4.4) 5 (3.6) 61 (44.5)	/	/	/	/	/	/
Combination therapy: n (%)	69 (50.4)	10 (50.0)	36 (80.0)	6 (100)	2 (40.0)	15 (24.6)	**<0.001**
Appropriate empiric therapy: n (%)	47 (34.3)	3 (15.0)	16 (35.6)	2 (33.3)	2 (40.0)	24 (39.3)	0.393
Appropriate definitive therapy: n (%)	90 (65.7)	10 (50.0)	30 (66.7)	3 (50.0)	4 (80.0)	43 (70.5)	0.415
Extended or continuous infusion: n (%)	89 (65.0)	3 (15.0)	25 (55.6)	4 (66.7)	1 (20.0)	56 (91.8)	**<0.001**
Source control performed: n (%) [required in 74]	53 (71.6)	6 (60.0)	15 (62.5)	0	2 (66.7)	30 (85.7)	**0.038**
Duration of definitive therapy (days): median (IQR) [excluded patients dead within 30 days from start]	15 (10-20)	16 (10-21)	14 (11-20)	11 (5-18)	14 (4-25)	15 (11-21)	0.528
Clinical cure: n (%)	100 (73.0)	15 (75.0)	33 (73.3)	1 (16.7)	4 (80.0)	47 (77.0)	**0.035**
Colonisation by CZA-R KPC-Kp after treatment of infection: n (%) [evaluable in 115 cases]	28 (24.3)	7 (38.9)	9 (24.3)	1 (33.3)	1 (20.0)	10 (19.2)	0.560
Relapse of infection: n (%) [evaluable in 110 cases]	30 (27.3)	6 (35.3)	11 (30.6)	1 (100)	0	12 (23.5)	0.227
Secondary infection between 3 and 30 days from start of definitive therapy: n (%) [evaluable in 135 patients]	65 (47.4)	9 (45.0)	29 (65.9)	3 (50.0)	2 (40.0)	22 (36.7)	0.062
Type of secondary infection: n (%) [% of group] [evaluable in 65 cases] - **UTI** - **LRTI** - **BSI** - **Candidemia**	 4 (6.2) [2.9] 14 (21.5) [10.2] 26 (40.0) [19.0] 21 (32.3) [15.3]	 1 (11.1) [5.0] 3 (33.3) [15.0] 3 (33.3) [15.0] 2 (22.2) [10.0]	 3 (10.3) [6.7] 4 (13.8) [8.9] 10 (34.5) [22.2] 12 (41.4) [26.7]	 0 0 1 (33.3) [16.7] 2 (66.7) [33.3]	 0 1 (50.0) [20.0] 1 (50.0) [20.0] 0	 0 6 (27.3) [9.8] 11 (50.0) [18.0] 5 (22.7) [8.2]	0.588
Positive BCs 72 hours after start of definitive therapy: n (%) [performed in 75.4% of BSIs]	18 (39.1)	0	9 (47.4)	0	0	9 (42.9)	0.340
Positive BSc 7 days after start of definitive therapy: n (%) [performed in 49.2% of BSIs]	8 (26.7)	0	4 (30.8)	0	0	4 (26.7)	0.657
Positive BCs 14 days after start of definitive therapy: n (%) [performed in 36.1% of BSIs]	4 (18.2)	0	1 (11.1)	0	0	3 (30.0)	0.385
AR to definitive therapy: n (%)	6 (4.4)	0	3 (6.7)	0	0	3 (4.9)	0.731
Type of AR: n (%) [evaluable in 11 cases] - **Allergic**	 1 (16.7)	 /	 1 (33.3)	 /	 /	 0	 0.513

- **Kidney toxicity** - **Haematological toxicity**	2 (33.3) 3 (50.0)		1 (33.3) 1 (33.3)			1 (33.3) 2 (66.7)	
Development of CDI during definitive treatment: n (%)	5 (3.6)	0	3 (6.7)	0	0	2 (3.3)	0.333
Cumulative mortality at 7 days from index sample collection: n (%)	13 (9.5)	0	5 (11.1)	2 (33.3)	0	6 (9.8)	0.150
Cumulative mortality at 14 days from index sample collection: n (%)	18 (13.1)	2 (10.0)	7 (15.6)	2 (33.3)	0	7 (11.5)	0.485
Cumulative mortality at 30 days from index sample collection: n (%)	25 (18.2)	4 (20.0)	9 (20.0)	3 (50.0)	0	9 (14.8)	0.214
Overall in-hospital mortality: n (%)	53 (38.7)	7 (35.0)	20 (44.4)	4 (66.7)	0	22 (36.1)	0.195
LOS from sample collection (days): median (IQR)	40 (19-73)	34 (21-58)	45 (17-74)	18 (11-41)	38 (21-138)	44 (20-81)	0.519
LOS from start of definitive therapy (days): median (IQR)	38 (15-67)	29 (17-55)	42 (12-68)	12 (4-40)	34 (17-136)	39 (17-79)	0.390
Overall LOS (days): median (IQR)	101 (55-143)	79 (46-129)	109 (58-186)	75 (43-83)	107 (69-187)	101 (50-136)	0.290

Abbreviations: AR, adverse reaction; BC, blood cultures; BSI, bloodstream infection; CCI, Charlson comorbidity index; CDI, Clostridioides difficilis infection; CFDC, cefiderocol; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CVC, central venous catheter; CZA, ceftazidime/avibactam; CZA-R, ceftazidime/avibactam resistant; IAI, intrabdominal infection; ICS, Increment CPE score; ICU, intensive care unit; IMR, imipenem/relebactam; IQR, interquartile range; KPC-Kp, KPC producing K. pneumoniae; LOS, length of stay; LRTI, lower respiratory tract infection; MEM, meropenem; MVB, meropenem/vaborbactam; PCT, procalcitonin; PICC, peripherally inserted central catheter; UTI, urinary tract infection; VAP, ventilator associated pneumonia.

Table 2. Analysis according to the meropenem susceptibility			
Variable	**MEM-S (N=71)**	**MEM-R (N=66)**	***p***
Gender male: n (%)	48 (67.6)	42 (63.6)	0.719
Age: median (IQR)	63.0 (51.1-72.6)	70.3 (56.7-77.9)	**0.020**
Isolation occurred in ICU: n (%)	50 (70.4)	34 (51.5)	**0.035**
CCI: median (IQR)	5.0 (2.0-6.0)	6.0 (4.0-8.0)	**0.020**
CCI ≥3: n (%)	53 (74.6)	60 (90.9)	**0.014**
Diabetes: n (%)	15 (21.1)	22 (33.3)	0.126
Cardiovascular disease: n (%)	38 (53.5)	42 (63.6)	0.298
Neurovascular disease: n (%)	30 (42.3)	26 (39.4)	0.862
COPD: n (%)	17 (23.9)	16 (24.2)	0.967
CKD: n (%)	12 (16.9)	25 (37.9)	**0.007**
Chronic liver disease: n (%)	3 (4.2)	3 (4.5)	0.927
Neoplasia (solid and/or haematologic): n (%)	13 (18.3)	11 (16.7)	0.826
Solid neoplasia: n (%)	11 (15.5)	7 (10.6)	0.455
Haematologic neoplasia: n (%)	4 (5.6)	4 (6.1)	0.915
Obesity: n (%)	10 (14.1)	13 (19.7)	0.493
Immunodeficiency: n (%)	8 (11.3)	10 (15.2)	0.615
Solid transplant: n (%)	2 (2.8)	5 (7.6)	0.262
CVC or PICC carrier at the time of infection onset: n (%)	46 (64.8)	37 (56.1)	0.382
Rectal colonization by KPC-Kp at the time of infection onset: n (%)	54 (76.1)	55 (83.3)	0.397
Time (days) from hospitalization to start of a large spectrum antibiotic therapy: median (IQR)	1.0 (1.0-3.0)	1.0 (1.0-2.0)	0.549
Previous CZA MIC (μg/mL): median (IQR)	2.0 (0.9-4.0)	3.0 (1.0-4.0)	0.217
Previous MEM MIC (μg/mL): median (IQR)	32 (32-32)	32 (32-32)	0.788
Previous CZA treatment: n (%)	47 (66.2)	28 (42.4)	**0.006**
Indication for previous CZA treatment: n (%)			
- **BSI**	14 (29.8)	7 (25.0)	0.291
- **LRTI**	17 (36.2)	8 (28.6)	
- **UTI**	1 (2.1)	4 (14.3)	
- **IAI**	1 (2.1)	0	
- **Empirical for sepsis in KPC-Kp colonization**	14 (29.8)	9 (32.1)	
Previous daily dose (g) of CZA received: median (IQR)	7.5 (7.5-7.5)	7.5 (7.5-7.5)	0.616
Number of days of CZA treatment previously received: median (IQR)	22.0 (15.0-35.0)	14.0 (9.2-28.0)	**0.034**
Cycles of CZA therapy received: median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.711
Previous CZA received as monotherapy: n (%)	16 (33.1)	9 (32.1)	0.915
Index infection by CZA-R KPC-Kp: n (%)			
- **BSI**	37 (52.1)	24 (36.4)	0.432
- **LRTI**	22 (31.0)	25 (37.9)	
- **UTI**	7 (9.9)	10 (15.2)	
- **IAI**	2 (2.8)	2 (3.0)	
- **Other**	3 (4.2)	5 (7.6)	
VAP (confirmed or probable) out of 47 respiratory tract infection	12 (54.5)	11 (44.0)	0.471

Time (days) from hospitalization to infection by CZA-R KPC-Kp: median (IQR)	51 (28-83)	35 (14-66)	**0.033**
CRP (mg/dL): median (IQR)	12.4 (7.4-20.4)	12.1 (7.1-19.5)	0.878
PCT (ng/mL): median (IQR)	1.5 (0.4-8.2)	1.3 (0.4-6.0)	0.789
CRRT required during infection: n (%)	8 (11.3)	10 (15.2)	0.615
Vasoactive drugs required during infection: n (%)	19 (26.8)	19 (28.8)	0.850
Septic shock: n (%)	18 (25.4)	16 (24.2)	0.881
Pitt score at infection onset: median (IQR)	3.0 (1.0-4.0)	3.0 (1.0-4.0)	0.676
ICS at infection onset: median (IQR)	6.0 (5.0-10.0)	8.0 (5.0-11.0)	0.740
ICS ≥ 8 at infection onset: n (%)	29 (40.8)	35 (53.0)	0.173
CZA MIC (μg/mL): median (IQR)	32 (16-64)	16 (16-40)	**0.005**
MEM MIC (μg/mL): median (IQR)	1.0 (0.3-2.0)	32 (32-32)	/
MVB MIC (μg/mL): median (IQR) [available in 54]	0.5 (0.1-1.0)	2.0 (0.5-4.0)	**0.008**
Time (days) from isolation of CZA-S to isolation of CZA-R: median (IQR)	50.0 (23.5-82.5)	32.0 (15.5-74.3)	0.116
Time (days) from sample collection to start of empiric therapy: median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-2.5)	0.668
Time (days) from sample collection to start of definitive therapy: median (IQR)	3.0 (1.0-4.0)	3.0 (1.0-4.0)	0.860
Definitive therapy: n (%)			
- **Older generation antibiotics (MEM excluded)**	12 (16.9)	8 (12.1)	**0.028**
- **MEM-based**	30 (42.3)	15 (22.7)	
- **CFDC-based**	4 (5.6)	2 (3.0)	
- **IMR-based**	1 (1.4)	4 (6.1)	
- **MVB-based**	24 (33.8)	37 (56.1)	
Combination therapy: n (%)	36 (50.7)	33 (50.0)	0.934
Appropriate empiric therapy: n (%)	28 (39.4)	19 (28.8)	0.190
Appropriate definitive therapy: n (%)	48 (67.6)	42 (63.6)	0.625
Extended or continuous infusion: n (%)	46 (64.8)	43 (65.2)	0.965
Source control performed: n (%) [required in 78 (57.5%)]	22 (61.1)	31 (81.6)	0.071
Duration of definitive therapy (days): median (IQR) [excluded patients dead within 30 days from start]	15 (10-20)	15 (10-20)	0.853
Clinical cure: n (%)	51 (71.8)	49 (74.2)	0.848
Colonisation by CZA-R after treatment of infection: n (%) [evaluable in 118 cases]	13 (22.4)	15 (26.3)	0.669
Relapse of infection: n (%) [evaluable in 113 cases]	9 (16.4)	21 (38.2)	**0.018**
Secondary infection between 3 and 30 days from start of definitive therapy: n (%) [evaluable in 138 patients]	36 (51.4)	29 (44.6)	0.492
Type of secondary infection: n (%) [evaluable in 67 cases]			
- **UTI**	3 (8.3)	1 (3.4)	
- **LRTI**	6 (16.7)	8 (27.6)	0.594
- **BSI**	14 (38.9)	12 (41.4)	
- **Candidemia**	13 (36.1)	8 (27.6)	
Positive BCs 72 hours after start of definitive therapy: n (%) [performed in 75.4% of BSIs]	11 (37.9)	7 (41.2)	0.828
Positive BCs 7 days after start of definitive therapy: n (%) [performed in 49.2% of BSIs]	6 (33.3)	2 (16.7)	0.419
Positive BCs 14 days after start of definitive therapy: n (%) [performed in 36.1% of BSIs]	3 (23.1)	1 (11.1)	0.616
AR to definitive therapy: n (%)	1 (1.4)	5 (7.6)	0.078
Type of AR: n (%) [evaluable in 11 cases]			
- **Allergic**	0	1 (20.0)	

- **Kidney toxicity** - **Haematological toxicity**	0 1 (100.0)	2 (40.0) 2 (40.0)	0.549
Development of CDI during definitive treatment: n (%)	1 (1.4)	4 (6.1)	0.146
Cumulative mortality at 7 days from index sample collection: n (%)	7 (9.9)	6 (9.1)	0.878
Cumulative mortality at 14 days from index sample collection: n (%)	11 (15.5)	7 (10.6)	0.455
Cumulative mortality at 30 days from index sample collection: n (%)	14 (19.7)	11 (16.7)	0.665
Overall in-hospital mortality: n (%)	29 (40.8)	24 (36.4)	0.604
LOS from sample collection (days): median (IQR)	39.0 (18.0-70.0)	44.0 (20.0-79.8)	0.375
LOS from start of definitive therapy (days): median (IQR)	35.0 (12.0-67.0)	39.0 (19.0-77.0)	0.342
Overall LOS (days): median (IQR)	108.0 (56.0-143.0)	94.5 (48.8-142.8)	0.394

Abbreviations: AR, adverse reaction; BC, blood cultures; BSI, bloodstream infection; CCI, Charlson comorbidity index; CDI, Clostridioides difficilis infection; CFDC, cefiderocol; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CVC, central venous catheter; CZA, ceftazidime/avibactam; CZA-R, ceftazidime/avibactam resistant; IAI, intrabdominal infection; ICS, Increment CPE score; ICU, intensive care unit; IMR, imipenem/relebactam; IQR, interquartile range; KPC-Kp, KPC producing K. pneumoniae; LOS, length of stay; LRTI, lower respiratory tract infection; MEM, meropenem; MVB, meropenem/vaborbactam; PCT, procalcitonin; PICC, peripherally inserted central catheter; UTI, urinary tract infection; VAP, ventilator associated pneumonia.

Table 3. Subgroup analysis of mortality in patients with a meropenem-sensitive pathogen: comparison between meropenem/vaborbactam and meropenem				
	Outcome	**Meropenem (N=30)**	**Meropenem/vaborbactam (N=24)**	**p**
	Cumulative mortality at 7 days from index sample collection: n (%)	2 (6.7)	4 (16.7)	0.245
	Cumulative mortality at 14 days from index sample collection: n (%)	4 (13.3)	4 (16.7)	0.732
	Cumulative mortality at 30 days from index sample collection: n (%)	6 (20.0)	4 (16.7)	0.754
	Overall in-hospital mortality: n (%)	14 (46.7)	9 (37.5)	0.498
	Clinical cure	22 (73.3)	19 (79.2)	0.753
Subgroup	**Outcome**	**Meropenem**	**Meropenem/vaborbactam**	***p***
Septic shock (N=9)	Cumulative mortality at 7 days from index sample collection: n (%)	1 (16.7)	2 (25.0)	0.707
	Cumulative mortality at 14 days from index sample collection: n (%)	3 (50.0)	2 (25.0)	0.334
	Cumulative mortality at 30 days from index sample collection: n (%)	3 (50.0)	2 (25.0)	0.334
	Overall in-hospital mortality: n (%)	6 (100)	3 (37.5)	**0.016**
	Clinical cure	2 (33.3)	5 (62.5)	0.592
ICS≥8 (N=23)	Cumulative mortality at 7 days from index sample collection: n (%)	2 (18.2)	4 (33.3)	0.640
	Cumulative mortality at 14 days from index sample collection: n (%)	4 (36.4)	4 (33.3)	0.879
	Cumulative mortality at 30 days from index sample collection: n (%)	4 (36.4)	4 (33.3)	0.879
	Overall in-hospital mortality: n (%)	8 (72.7)	6 (50.0)	0.400
	Clinical cure	6 (54.5)	7 (58.3)	0.855
VAP (N=7)	Cumulative mortality at 7 days from index sample collection: n (%)	1 (100)	2 (28.6)	0.168
	Cumulative mortality at 14 days from index sample collection: n (%)	1 (100)	2 (28.6)	0.168
	Cumulative mortality at 30 days from index sample collection: n (%)	1 (100)	2 (28.6)	0.168
	Overall in-hospital mortality: n (%)	1 (100)	4 (57.1)	0.408
	Clinical cure	0	5 (71.4)	0.375
LRTIs (N=14)	Cumulative mortality at 7 days from index sample collection: n (%)	1 (14.3)	2 (28.6)	0.515
	Cumulative mortality at 14 days from index sample collection: n (%)	1 (14.3)	2 (28.6)	0.515
	Cumulative mortality at 30 days from index sample collection: n (%)	1 (14.3)	2 (28.6)	0.515
	Overall in-hospital mortality: n (%)	4 (57.1)	4 (57.1)	0.999
	Clinical cure	5 (71.4)	5 (71.4)	0.999
BSIs (N=34)	Cumulative mortality at 7 days from index sample collection: n (%)	1 (5.0)	2 (14.3)	0.347
	Cumulative mortality at 14 days from index sample collection: n (%)	3 (15.0)	2 (14.3)	0.954
	Cumulative mortality at 30 days from index sample collection: n (%)	5 (25.0)	2 (14.3)	0.447
	Overall in-hospital mortality: n (%)	10 (50.0)	4 (28.6)	0.211
	Clinical cure	14 (70.0)	11 (78.6)	0.704
Definitive therapy within 24 hours (N=18)	Cumulative mortality at 7 days from index sample collection: n (%)	1 (12.5)	1 (10.0)	0.867
	Cumulative mortality at 14 days from index sample collection: n (%)	2 (25.0)	1 (10.0)	0.396
	Cumulative mortality at 30 days from index sample collection: n (%)	3 (37.5)	1 (10.0)	0.163
	Overall in-hospital mortality: n (%)	6 (75.0)	2 (20.0)	**0.020**
	Clinical cure	5 (62.5)	9 (90.0)	0.275
Definitive therapy within 48 hours (N=27)	Cumulative mortality at 7 days from index sample collection: n (%)	1 (6.3)	1 (9.1)	0.782
	Cumulative mortality at 14 days from index sample collection: n (%)	2 (12.5)	1 (9.1)	0.782
	Cumulative mortality at 30 days from index sample collection: n (%)	4 (25.0)	1 (9.1)	0.296
	Overall in-hospital mortality: n (%)	9 (56.3)	2 (18.2)	**0.048**

	Clinical cure	12 (75.0)	10 (90.9)	0.618
Definitive therapy within 72 hours (N=38)	Cumulative mortality at 7 days from index sample collection: n (%)	2 (8.7)	1 (6.7)	0.821
	Cumulative mortality at 14 days from index sample collection: n (%)	4 (17.4)	1 (6.7)	0.630
	Cumulative mortality at 30 days from index sample collection: n (%)	6 (26.1)	1 (6.7)	0.209
	Overall in-hospital mortality: n (%)	13 (56.5)	4 (26.7)	0.100
	Clinical cure	17 (73.9)	13 (86.7)	0.440

Abbreviations: BSI, bloodstream infection; ICS, Increment CPE score; LRTI, lower respiratory tract infection; VAP, ventilator associated pneumonia.

Table 4. Survival analysis: 30 days after index sample collection			
Variable	**Survived at 30 days (N=112)**	**Deceased at 30 days (N=25)**	***p***
Gender male: n (%)	75 (67.0)	15 (60.0)	0.496
Age: median (IQR)	65.7 (54.0-75.0)	67.2 (54.9-78.1)	0.346
Isolation occurred in ICU: n (%)	64 (57.1)	20 (80.0)	**0.041**
CCI: median (IQR)	5.0 (3.0-6.0)	6.0 (4.0-9.0)	**0.014**
CCI ≥3: n (%)	92 (82.1)	21 (84.0)	0.825
Diabetes: n (%)	29 (25.9)	8 (32.0)	0.619
Cardiovascular disease: n (%)	63 (56.3)	17 (68.0)	0.371
Neurovascular disease: n (%)	47 (42.0)	9 (36.0)	0.657
COPD: n (%)	27 (24.1)	6 (24.0)	0.991
CKD: n (%)	29 (25.9)	8 (32.0)	0.619
Chronic liver disease: n (%)	5 (4.5)	1 (4.0)	0.918
Neoplasia (solid and/or haematologic): n (%)	20 (17.9)	4 (16.0)	0.825
Solid neoplasia: n (%)	15 (13.4)	3 (12.0)	0.852
Haematologic neoplasia: n (%)	6 (5.4)	2 (8.0)	0.638
Obesity: n (%)	19 (17.0)	4 (16.0)	0.907
Immunodeficiency: n (%)	12 (10.7)	6 (24.0)	0.099
Solid transplant: n (%)	4 (3.6)	3 (12.0)	0.114
CVC or PICC carrier at the time of infection onset: n (%)	68 (60.7)	15 (60.0)	0.947
Rectal colonization by KPC-Kp at the time of infection onset: n (%)	91 (81.3)	18 (72.0)	0.288
Time (days) from hospitalization to start of a large spectrum antibiotic therapy: median (IQR)	1.0 (0-3.0)	1.0 (0-3.0)	0.737
Previous CZA MIC (μg/mL): median (IQR)	2.0 (1.0-4.0)	2.0 (0.5-4.0)	0.562
Previous MEM MIC (μg/mL): median (IQR)	32 (32-32)	32 (32-32)	0.951
Previous CZA treatment: n (%)	63 (56.3)	12 (48.0)	0.509
Indication for previous CZA treatment: n (%)			
- **BSI**	17 (27.0)	4 (33.3)	0.858
- **LRTI**	21 (33.3)	4 (33.3)	
- **UTI**	5 (7.9)	0	
- **IAI**	1 (1.6)	0	
- **Empirical for sepsis in KPC-Kp colonization**	19 (30.2)	4 (33.3)	
Previous daily dose (g) of CZA received: median (IQR)	7.5 (7.5-7.5)	7.5 (7.5-7.5)	0.709
Number of days of CZA treatment previously received: median (IQR)	20.0 (10.3-32.0)	22.5 (16.0-31.0)	0.304
Cycles of CZA therapy received: median (IQR)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	0.416
Previous CZA received as monotherapy: n (%)	24 (37.5)	1 (8.3)	**0.048**
Index infection by CZA-R KPC-Kp: n (%)			
- **BSI**	50 (44.6)	11 (44.0)	0.445
- **LRTI**	36 (32.1)	11 (44.0)	
- **UTI**	16 (14.3)	1 (4.0)	
- **IAI**	4 (3.6)	0	
- **Other**	6 (5.4)	2 (8.0)	
VAP (confirmed or probable) out of 47 respiratory tract infection	14 (38.9)	9 (81.8)	**0.017**

Time (days) from hospitalization to infection by CZA-R KPC-Kp: median (IQR)	47 (21-78)	34 (12-79)	0.442
CRP (mg/dL): median (IQR)	12.3 (7.2-20.8)	13.0 (7.1-17.8)	0.862
PCT (ng/mL): median (IQR)	1.3 (0.4-7.2)	1.8 (0.5-10.3)	0.600
CRRT required during infection: n (%)	10 (8.9)	8 (32.0)	**0.005**
Vasoactive drugs required during infection: n (%)	25 (22.3)	13 (52.0)	**0.005**
Septic shock: n (%)	23 (20.5)	11 (44.0)	**0.021**
Pitt score at infection onset: median (IQR)	2.0 (1.0-4.0)	4.0 (3.0-5.5)	**<0.001**
ICS at infection onset: median (IQR)	6.0 (5.0-8.0)	11.0 (8.0-13.0)	**<0.001**
ICS ≥ 8 at infection onset: n (%)	43 (38.4)	21 (84.0)	**<0.001**
CZA MIC of (μg/mL): median (IQR)	16 (16-88)	24 (16-32)	0.493
MEM MIC (μg/mL): median (IQR)	8 (1-32)	4 (1-32)	0.950
MEM susceptible: n (%)	57 (50.9)	14 (56.0)	0.665
MVB MIC (μg/mL): median (IQR) [available in 54]	0.8 (0.4-2.0)	1.0 (0.1-4.0)	0.705
Time (days) from isolation of CZA-S to isolation of CZA-R KPC-Kp: median (IQR)	36.0 (20.0-76.0)	37.0 (17.3-92.8)	0.800
Time (days) from sample collection to start of empiric therapy: median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.265
Time (days) from sample collection to start of definitive therapy: median (IQR)	3.0 (1.0-4.0)	3.0 (0-4.5)	0.585
Definitive therapy: n (%) - **Older generation antibiotics (MEM excluded)** - **MEM-based** - **CFDC-based** - **IMR-based** - **MVB-based**	 16 (14.3) 36 (32.1) 3 (2.7) 5 (4.5) 52 (46.4)	 4 (16.0) 9 (36.0) 3 (12.0) 0 9 (36.0)	0.214
Combination therapy: n (%)	52 (46.4)	17 (68.0)	0.076
Appropriate empiric therapy: n (%)	42 (37.5)	5 (20.0)	0.108
Appropriate definitive therapy: n (%)	80 (71.4)	10 (40.0)	**0.005**
Extended or continuous infusion: n (%)	75 (67.0)	14 (56.0)	0.356
Source control performed: n (%) [required in 78 (57.5%)]	48 (76.2)	5 (45.5)	**0.038**
Duration of definitive therapy (days): median (IQR) [excluded patients dead within 30 days from start]	16 (12-20)	7 (3-12)	/
Positive BCs 72 hours after start of definitive therapy: n (%) [performed in 75.4% of BSIs]	15 (38.5)	3 (42.9)	0.826
Positive BCs 7 days after start of definitive therapy: n (%) [performed in 49.2% of BSIs]	7 (28.0)	1 (20.0)	0.712
Positive BCs 14 days after start of definitive therapy: n (%) [performed in 36.1% of BSIs]	4 (20.0)	0	0.484
AR to definitive therapy: n (%)	5 (4.5)	1 (4.0)	0.918
Type of AR: n (%) [evaluable in 11 cases] - **Allergic** - **Kidney toxicity** - **Haematological toxicity**	 1 (20.0) 1 (20.0) 3 (60.0)	 0 1 (100.0) 0	 0.301
Development of CDI during definitive treatment: n (%)	4 (3.6)	1 (4.0)	0.917

Abbreviations: AR, adverse reaction; BC, blood cultures; BSI, bloodstream infection; CCI, Charlson comorbidity index; CDI, Clostridioides difficilis infection; CFDC, cefiderocol; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CVC, central venous catheter; CZA, ceftazidime/avibactam; CZA-R, ceftazidime/avibactam resistant; IAI, intrabdominal infection; ICS, Increment CPE score; ICU, intensive care unit; IMR, imipenem/relebactam; IQR, interquartile range; KPC-Kp, KPC producing K.

pneumoniae; LRTI, lower respiratory tract infection; MEM, meropenem; MVB, meropenem/vaborbactam; PCT, procalcitonin; PICC, peripherally inserted central catheter; UTI, urinary tract infection; VAP, ventilator associated pneumonia.

Table 5. Multivariable analysis of 30-day mortality risk factors			
Variable	**Hazard Ratio**	**95% confidence interval**	***p* value**
Index infection occurring in ICU	1.368	0.326-5.739	0.668
ICS ≥ 8	6359	1.486-27.221	**0.013**
VAP	3.900	0.391-38.948	0.246
Appropriate definitive therapy	0.144	0.034-0.615	**0.009**
Source control performed when needed	0.180	0.044-0.734	**0.017**
Meropenem resistant phenotype	0.738	0.180-3.033	0.674
Meropenem/vaborbactam containing regimen	0.563	0.128-2.481	0.447

Abbreviations: ICS, Increment CPE score; ICU, intensive care unit; VAP, ventilator associated pneumonia.

Table 6. Comparison of meropenem/vaborbactam with older treatment options (included meropenem, excluded cefiderocol and imipenem/relebactam). N=126 patients			
Variable	**MVB (N=61)**	**Older treatments (N=65)**	*p*
Gender male: n (%)	41 (67.2)	40 (61.5)	0.578
Age: median (IQR)	69.0 (57.7-76.5)	62.2 (51.6-75.1)	0.214
Isolation occurred in ICU: n (%)	34 (55.7)	41 (63.1)	0.469
CCI: median (IQR)	6.0 (4.0-7.0)	5.0 (3.0-6.0)	**0.041**
CCI ≥3: n (%)	53 (86.9)	51 (78.5)	0.247
Diabetes: n (%)	20 (32.8)	14 (21.5)	0.166
Cardiovascular disease: n (%)	40 (65.6)	34 (52.3)	0.150
Neurovascular disease: n (%)	23 (37.7)	29 (44.6)	0.472
COPD: n (%)	15 (24.6)	16 (24.6)	0.997
CKD: n (%)	21 (34.4)	12 (18.5)	**0.046**
Chronic liver disease: n (%)	4 (6.6)	1 (1.5)	0.197
Neoplasia (solid and/or haematologic): n (%)	9 (14.8)	12 (18.5)	0.638
Solid neoplasia: n (%)	7 (11.5)	10 (15.4)	0.607
Haematologic neoplasia: n (%)	3 (4.9)	3 (4.6)	0.936
Obesity: n (%)	12 (19.7)	10 (15.4)	0.640
Immunodeficiency: n (%)	9 (14.8)	8 (12.3)	0.796
Solid transplant: n (%)	4 (6.6)	3 (3.1)	0.429
CVC or PICC carrier at the time of infection onset: n (%)	39 (63.9)	37 (56.9)	0.469
Rectal colonization by KPC-Kp at the time of infection onset: n (%)	48 (78.7)	52 (80.0)	0.856
Time (days) from hospitalization to start of a large spectrum antibiotic therapy: median (IQR)	1.0 (0-3.5)	1.0 (0-2.5)	0.382
Previous CZA MIC (μg/mL): median (IQR)	4.0 (0.8-5.5)	2.0 (1.0-4.0)	0.389
Previous MEM MIC (μg/mL): median (IQR)	32 (32-32)	32 (32-32)	0.701
Previous CZA treatment: n (%)	28 (45.9)	39 (60.0)	0.153
Indication for previous CZA treatment: n (%)			
- **BSI**	9 (32.1)	9 (23.1)	0.446
- **LRTI**	7 (25.0)	17 (43.6)	
- **UTI**	3 (10.7)	2 (5.1)	
- **IAI**	0	1 (2.6)	
- **Empirical for sepsis in KPC-Kp colonization**	9 (32.1)	10 (25.6)	
Previous daily dose (g) of CZA received: median (IQR)	7.5 (7.5-7.5)	7.5 (7.5-7.5)	0.436
Number of days of CZA treatment previously received: median (IQR)	19.5 (10.0-28.0)	24.0 (15.0-35.0)	0.098
Cycles of CZA therapy received: median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.519
Previous CZA received as monotherapy: n (%)	9 (32.1)	14 (35.9)	0.799
Index infection by CZA-R KPC-Kp: n (%)			
- **BSI**	27 (44.3)	32 (49.2)	**0.018**
- **LRTI**	24 (39.3)	17 (26.2)	
- **UTI**	2 (3.3)	13 (20.0)	
- **IAI**	2 (3.3)	1 (1.5)	
- **Other**	6 (9.8)	2 (3.1)	
VAP (confirmed or probable) out of 41 respiratory tract infection	14 (58.3)	4 (23.5)	**0.027**

Time (days) from hospitalization to infection by CZA-R KPC-Kp: median (IQR)	36 (16-70)	49 (27-84)	0.078
CRP (mg/dL): median (IQR)	11.5 (7.1-21.8)	12.4 (7.1-18.3)	0.915
PCT (ng/mL): median (IQR)	2.0 (0.5-8.4)	1.2 (0.4-8.3)	0.293
CRRT required during infection: n (%)	8 (13.1)	8 (12.3)	0.892
Vasoactive drugs required during infection: n (%)	17 (27.9)	18 (27.7)	0.982
Septic shock: n (%)	16 (26.2)	15 (23.1)	0.836
Pitt score at infection onset: median (IQR)	3.0 (2.0-4.0)	2.0 (1.0-4.0)	0.261
ICS at infection onset: median (IQR)	8.0 (5.0-11.0)	6.0 (5.0-10.0)	0.279
ICS ≥ 8 at infection onset: n (%)	32 (52.5)	24 (36.9)	0.106
CZA MIC (μg/mL): median (IQR)	16 (16-176)	32 (16-48)	0.943
MEM MIC (μg/mL): median (IQR)	32.0 (2.0-32.0)	2.0 (1.0-16.0)	**<0.001**
MEM susceptible: n (%)	24 (39.3)	42 (64.6)	**0.007**
MVB MIC (μg/mL): median (IQR) [available in 47]	0.8 (0.5-2.0)	0.4 (0.1-1.0)	0.064
Time (days) from isolation of CZA-S to isolation of CZA-R KPC-Kp: median (IQR)	34.5 (15.5-76.8)	39.5 (22.8-83.0)	0.433
Time (days) from sample collection to start of empiric therapy: median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-2.0)	0.157
Time (days) from sample collection to start of definitive therapy: median (IQR)	2.0 (1.0-4.0)	3.0 (1.5-4.0)	0.311
Definitive therapy: n (%) - **Older generation antibiotics (MEM excluded)** - **MEM-based** - **MVB-based**	 0 0 61 (100)	 20 (30.8) 45 (69.2) 0	/
Combination therapy: n (%)	15 (24.6)	46 (70.8)	**<0.001**
Appropriate empiric therapy: n (%)	24 (39.3)	19 (29.2)	0.263
Appropriate definitive therapy: n (%)	43 (70.5)	40 (61.5)	0.349
Extended or continuous infusion: n (%)	56 (91.8)	28 (43.1)	**<0.001**
Source control performed: n (%) [required in 69]	30 (85.7)	21 (61.8)	**0.030**
Duration of definitive therapy (days): median (IQR) [excluded patients dead within 30 days from start]	15 (10-21)	15 (11-20)	0.506
Clinical cure: n (%)	47 (77.0)	48 (73.8)	0.686
Colonisation by CZA-R KPC-Kp after treatment of infection: n (%) [evaluable in 107 cases]	10 (19.2)	16 (29.1)	0.266
Relapse of infection: n (%) [evaluable in 104 cases]	12 (23.5)	17 (31.2)	0.385
Secondary infection between 3 and 30 days from start of definitive therapy: n (%) [evaluable in 124 patients]	22 (36.7)	38 (59.4)	**0.013**
Type of secondary infection: n (%) [evaluable in 60 cases] - **UTI** - **LRTI** - **BSI** - **Candidemia**	 0 6 (27.3) 11 (50.0) 5 (22.7)	 4 (10.5) 7 (18.4) 13 (34.2) 14 (36.8)	0.207
Positive BCs 72 hours after start of definitive therapy: n (%) [performed in 74.6% of BSIs]	9 (42.9)	9 (39.1)	0.802
Positive BCs 7 days after start of definitive therapy: n (%) [performed in 50.9% of BSIs]	4 (26.7)	4 (26.5)	0.998
Positive BCs 14 days after start of definitive therapy: n (%) [performed in 37.3% of BSIs]	3 (30.0)	1 (8.3)	0.293
AR to definitive therapy: n (%)	3 (4.9)	3 (4.6)	0.697
Type of AR: n (%) [evaluable in 11 cases] - **Allergic** - **Kidney toxicity**	 0 1 (33.3)	 1 (33.3) 1 (33.3)	0.513

- **Haematological toxicity**	2 (66.7)	1 (33.3)	
Development of CDI during definitive treatment: n (%)	2 (3.3)	3 (4.6)	0.700
Cumulative mortality at 7 days from index sample collection: n (%)	6 (9.8)	5 (7.7)	0.758
Cumulative mortality at 14 days from index sample collection: n (%)	7 (11.5)	9 (13.8)	0.792
Cumulative mortality at 30 days from index sample collection: n (%)	9 (14.8)	13 (20.0)	0.488
Overall in-hospital mortality: n (%)	22 (36.1)	27 (41.5)	0.586
LOS from sample collection (days): median (IQR)	44.0 (20.0-81.5)	43.0 (19.5-71.5)	0.803
LOS from start of definitive therapy (days): median (IQR)	39.0 (17.0-79.0)	40.0 (15.0-65.0)	0.803
Overall LOS (days): median (IQR)	101.0 (50.5-136.5)	108.0 (56.0-155.0)	0.641

Abbreviations: AR, adverse reaction; BC, blood cultures; BSI, bloodstream infection; CCI, Charlson comorbidity index; CFDC, cefiderocol; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CVC, central venous catheter; CZA, ceftazidime/avibactam; CZA-R, ceftazidime/avibactam resistant; IAI, intrabdominal infection; ICS, Increment CPE score; ICU, intensive care unit; IMR, imipenem/relebactam; IQR, interquartile range; KPC-Kp, KPC producing K. pneumoniae; LOS, length of stay; LRTI, lower respiratory tract infection; MEM, meropenem; MVB, meropenem/vaborbactam; PCT, procalcitonin; PICC, peripherally inserted central catheter; UTI, urinary tract infection; VAP, ventilator associated pneumonia.

Table 7. Subgroup analysis of mortality in the comparison between MVB and older treatment options (N=126)				
Subgroup	**Outcome**	**Older treatment options**	**Meropenem/vaborbactam**	**p**
Septic shock (N=31)	Cumulative mortality at 7 days from index sample collection: n (%)	1 (6.7)	3 (18.8)	0.316
	Cumulative mortality at 14 days from index sample collection: n (%)	4 (26.7)	3 (18.8)	0.598
	Cumulative mortality at 30 days from index sample collection: n (%)	5 (33.3)	5 (31.3)	0.901
	Overall in-hospital mortality: n (%)	10 (66.7)	8 (50.0)	0.347
VAP (N=18)	Cumulative mortality at 7 days from index sample collection: n (%)	2 (50.0)	2 (14.3)	0.130
	Cumulative mortality at 14 days from index sample collection: n (%)	2 (50.0)	2 (14.3)	0.130
	Cumulative mortality at 30 days from index sample collection: n (%)	3 (75.0)	3 (21.4)	**0.045**
	Overall in-hospital mortality: n (%)	3 (75.0)	7 (50.0)	0.375
LRTIs (N=29)	Cumulative mortality at 7 days from index sample collection: n (%)	0	3 (27.3)	0.369
	Cumulative mortality at 14 days from index sample collection: n (%)	1 (5.6)	3 (27.3)	0.175
	Cumulative mortality at 30 days from index sample collection: n (%)	2 (11.1)	3 (27.3)	0.178
	Overall in-hospital mortality: n (%)	7 (38.9)	6 (54.5)	0.177
BSIs (N=20)	Cumulative mortality at 7 days from index sample collection: n (%)	0	1 (9.1)	0.224
	Cumulative mortality at 14 days from index sample collection: n (%)	0	1 (9.1)	0.796
	Cumulative mortality at 30 days from index sample collection: n (%)	1 (11.1)	1 (9.1)	0.488
	Overall in-hospital mortality: n (%)	5 (55.6)	2 (18.2)	0.264
Definitive therapy within 24 hours (N=42)	Cumulative mortality at 7 days from index sample collection: n (%)	3 (18.8)	2 (7.7)	0.283
	Cumulative mortality at 14 days from index sample collection: n (%)	6 (37.5)	2 (7.7)	**0.017**
	Cumulative mortality at 30 days from index sample collection: n (%)	7 (43.8)	3 (11.5)	**0.017**
	Overall in-hospital mortality: n (%)	11 (68.8)	6 (23.1)	**0.003**
Definitive therapy within 48 hours (N=63)	Cumulative mortality at 7 days from index sample collection: n (%)	4 (13.3)	2 (6.1)	0.326
	Cumulative mortality at 14 days from index sample collection: n (%)	7 (23.3)	2 (6.1)	**0.050**
	Cumulative mortality at 30 days from index sample collection: n (%)	9 (30.0)	3 (9.1)	**0.035**
	Overall in-hospital mortality: n (%)	16 (53.3)	9 (27.3)	**0.043**
Definitive therapy within 72 hours (N=85)	Cumulative mortality at 7 days from index sample collection: n (%)	5 (10.9)	2 (5.1)	0.231
	Cumulative mortality at 14 days from index sample collection: n (%)	9 (19.6)	2 (5.1)	0.069
	Cumulative mortality at 30 days from index sample collection: n (%)	12 (26.1)	3 (7.7)	**0.029**
	Overall in-hospital mortality: n (%)	22 (47.8)	11 (28.2)	0.050

Abbreviations: BSI, bloodstream infection; ICS, Increment CPE score; LRTI, lower respiratory tract infection; VAP, ventilator associated pneumonia.