Clinical Efficacy of Ceftazidime/Avibactam for Treating Infections Caused by Carbapenem-Resistant *Klebsiella pneumoniae*: A Systematic Review and Meta-Analysis

Nehad Jaser Ahmed

Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia.; n.ahmed@psau.edu.sa. https://orcid.org/0000-0003-4215-6225

* Corresponding Author: Nehad Ahmed, Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam bin Abdulaziz University. Email: n.ahmed@psau.edu.sa

Abstract

Carbapenem-resistant Klebsiella pneumoniae (CRKP) infections are difficult to treat because of high-level resistance, limited treatment options, and inconsistent treatment duration. Ceftazidime-avibactam (CAZ-AVI) has emerged as a potential option for carbapenem-resistant Enterobacterales infections, but comparative evidence specific to CRKP remains limited. This meta-analysis compared clinical cure, microbiological cure, and mortality associated with CAZ-AVI versus other antimicrobial regimens for CRKP infections. PubMed was searched for English-language human studies from the past five years using the terms "Ceftazidime/Avibactam" and "carbapenem-resistant Klebsiella pneumoniae." Of 206 eligible human records screened, seven observational comparative studies comprising 988 patients were included: 415 received CAZ-AVI-containing

regimens, and 573 received comparator regimens. Given study heterogeneity, pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using a random-effects (DerSimonian-Laird) model, with heterogeneity quantified via the I^2 statistic. CAZ-AVI was associated with higher clinical cure (64.9% vs 42.2%; OR 2.98, 95% CI 1.90–4.67, p<0.0001; I^2=21%), higher microbiological cure (70.4% vs 41.2%; OR 3.77, 95% CI 1.67–8.53, p=0.001; I^2=69%, attenuating to OR 5.18, 95% CI 2.61–10.27, I^2=41% after excluding one outlying study in sensitivity analysis), and lower mortality (26.8% vs 43.9%; OR 0.40, 95% CI 0.27–0.61, p<0.0001; I^2=19%). As all included studies were non-randomized with heterogeneous comparators, these findings support—but do not establish—a benefit of CAZ-AVI for CRKP infections; randomized studies are needed to confirm these results and guide antimicrobial stewardship.

Keywords: antimicrobial; carbapenem-resistant: ceftazidime-avibactam; cure rate; *Klebsiella pneumoniae*; mortality rate

1. Introduction

Enterobacterales are a gram-negative bacterial order that can cause several healthcare-associated infections, including meningitis, bloodstream infections, surgical-site infections, and pneumonia. Bacteremia caused by Enterobacterales has increased worldwide, particularly that caused by resistant *Klebsiella pneumoniae* (*K. pneumoniae*) strains [1]. Drug resistance among *K. pneumoniae* isolates is rising, particularly within the carbapenem class [2]. Carbapenems are typically reserved as a last-resort option for gram-negative infections resistant to conventional antibiotics [2]. Carbapenems are also widely used to treat infections caused by Enterobacterales that produce extended-

spectrum beta-lactamase (ESBL) [3]; however, overuse and inappropriate use of these agents have driven the emergence of carbapenem-resistant isolates.

Antibiotic resistance poses a severe and growing threat to human health, with antibiotic-resistant illnesses projected to cause millions of deaths globally each year by 2050 [4]. Carbapenem-resistant *K. pneumoniae* (CRKP) infections are difficult to manage because of high-level antibiotic resistance, restricted therapeutic alternatives, and inconsistent recommended treatment duration [5,6]. The World Health Organization classifies *K. pneumoniae* as a key priority antibiotic-resistant pathogen, accounting for a significant proportion of hospital- and community-acquired infections [7].

Carbapenem resistance is a global issue, affecting clinical, urban, and agricultural settings [8-13]. Patients with carbapenem-resistant Klebsiella pneumoniae (CRKP) infections have substantially higher mortality than those infected with carbapenem-susceptible strains, with the impact particularly pronounced among patients with bloodstream infections [14-18]. According to the 2019 CDC antibiotic resistance study and the China Antimicrobial Surveillance Network, the majority of carbapenem-resistant Enterobacterales are CRKP, with lower respiratory infections being the most common kind [19,20]. Notably, CRKP is linked to a higher death rate, with a nearly 2-fold increase in mortality when compared to carbapenem-susceptible enterobacterial infections [19,21].

Currently available penicillins, cephalosporins, and carbapenems generally lack in vitro activity against this resistant bacterium, including CRKP bloodstream infections [22]. CAZ-AVI combines the third-generation cephalosporin ceftazidime with avibactam, a non-β-lactam, β-lactamase inhibitor that irreversibly binds and inactivates the target

enzyme. This combination restores ceftazidime activity against organisms producing class A (including *K. pneumoniae* carbapenemase, KPC), class C (AmpC), and class D (OXA-48-like) β-lactamases, but it has no activity against class B metallo-β-lactamases (e.g., NDM, VIM) [23]; this spectrum is clinically important because it defines which CRKP isolates can be expected to respond to CAZ-AVI. There is increasing evidence that CAZ-AVI can be used to treat infections caused by resistant gram-negative bacteria, particularly carbapenem-resistant Enterobacterales infections [24-28]. Systematic reviews provided clinical evidence for the efficacy of CAZ-AVI in hospitalized patients with multidrug-resistant *K. pneumoniae* and carbapenem-resistant Enterobacterales [29,30]. Real-world studies report that this β-lactam/β-lactamase inhibitor combination reduces clinical failure, 14-day microbiological failure, and 30-day mortality in carbapenem-resistant Enterobacterales bacteremia compared with other available regimens [31,32].

Carbapenem-resistant Enterobacterales have shown strong antimicrobial and synergistic bacteriostatic/bactericidal activity when CAZ-AVI is administered alone or in combination with aztreonam [33]. For example, Abu Jaber et al. reported favorable outcomes with CAZ-AVI added to standard therapy in patients with infections caused by CRKP carrying blaOXA-48-like genes. The clinical success rate was significantly higher with CAZ-AVI ($p = 0.028$), and the intervention group also had higher microbiological eradication (68.8% versus 42.0%; $p = 0.007$), lower 30-day all-cause mortality (50.0% versus 70.0%; $p = 0.036$), and lower infection recurrence (7.8% versus 24.0%; $p = 0.019$) than the comparison group [33]. A previous systematic review and meta-analysis by Karampatakis et al. evaluated the efficacy and safety of ceftazidime-avibactam compared with other antimicrobial agents for infections caused by carbapenem-resistant Klebsiella

pneumoniae [34]. However, additional comparative studies have been published subsequently, including studies involving critically ill patients, hematological populations, and solid-organ transplant recipients [35–39]. The present systematic review and meta-analysis was therefore undertaken to provide an updated quantitative synthesis of comparative evidence specifically in CRKP infections. In addition to clinical cure and mortality, the present analysis evaluates microbiological cure and includes a sensitivity analysis addressing heterogeneity in microbiological outcomes. The inclusion of more recent observational evidence and the assessment of these outcomes provide an updated perspective on the comparative effectiveness of CAZ-AVI in CRKP infections.

2. Methods

The review methodology was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy and study selection. A systematic literature search was conducted in PubMed from database inception to December 1, 2025, to identify studies evaluating ceftazidime/avibactam (CAZ-AVI) for infections caused by carbapenem-resistant Klebsiella pneumoniae (CRKP). The search strategy combined controlled vocabulary (MeSH) and free-text terms related to K. pneumoniae, carbapenem resistance, and ceftazidime/avibactam. The following search string was used in PubMed:

("Klebsiella pneumoniae"[MeSH Terms] OR "Klebsiella pneumoniae"[Title/Abstract] OR "Klebsiella"[Title/Abstract]) AND ("Carbapenem-Resistant Enterobacteriaceae"[MeSH Terms] OR carbapenem-resistant[Title/Abstract] OR carbapenem resistance[Title/Abstract] OR carbapenemase-producing[Title/Abstract] OR

CRKP[Title/Abstract]) AND ("ceftazidime-avibactam"[Title/Abstract] OR "ceftazidime avibactam"[Title/Abstract] OR "ceftazidime/avibactam"[Title/Abstract] OR CAZ-AVI[Title/Abstract] OR CAZ/AVI[Title/Abstract])

The search was limited to human studies published in English during the five years preceding December 1, 2025. No additional filters were applied. The complete search strategy, including the search terms, field tags, MeSH terms, Boolean operators, and applied limits, is provided in Supplementary Table S1 to facilitate reproducibility.

Eligibility criteria. Studies were eligible if they: (1) enrolled patients with microbiologically confirmed CRKP infection; (2) directly compared CAZ-AVI, given alone or in combination with another agent (e.g., aztreonam), against any other antimicrobial regimen (e.g., polymyxins, tigecycline, other β-lactams, or best-available therapy); (3) reported, for both groups, at least one of clinical cure, microbiological cure/eradication, or all-cause mortality; (4) were published in English within the last five years; and (5) involved human participants. Studies were excluded if they lacked a comparator group, reported only pooled or aggregated outcomes that could not be disaggregated into 2×2 contingency data, were case reports, conference abstracts, or reviews without original comparative data, or were not in English. Of the 206 human, English-language studies identified, 199 were excluded for these reasons (most commonly, absence of a comparator arm or non-extractable outcome data), leaving seven studies for quantitative synthesis.

Review registration. This systematic review was not prospectively registered in a systematic review registry.

Data extraction. For each eligible study, the following information was extracted: first author and publication year; country/region and study design; infection site(s) and patient population (Table 1); the number of patients and the number of events for clinical cure, microbiological cure, and mortality in the CAZ-AVI and comparator groups; comparator regimen(s); and, when reported, antimicrobial dosing regimens, treatment frequency, treatment duration, and renal-dose adjustments. Dosing and renal-dose information was extracted descriptively when explicitly reported in the eligible publications but was not used as a criterion for study inclusion and was not incorporated into the quantitative meta-analysis, because these details were inconsistently reported across studies and were not sufficiently comparable. When dosing, renal-dose adjustment, treatment duration, or combination-therapy status was incompletely reported, these variables were recorded as "not reported" and were not inferred or imputed.

Handling of missing and non-uniformly reported data: Outcome data were extracted as reported in the eligible publications. When event counts and corresponding group totals were available, these data were entered directly into the meta-analysis. Studies that did not report an eligible outcome or did not provide sufficient information to derive the required 2 × 2 contingency data were not included in the corresponding outcome-specific meta-analysis. No unpublished data were requested or imputed, and no event counts were estimated from percentages. Where study characteristics such as dosing regimen, renal-dose adjustment, treatment duration, or combination therapy were incompletely reported, the information was recorded as not reported and was not inferred.

Risk of bias. The methodological quality and risk of bias of the included observational cohort studies were assessed using the Newcastle–Ottawa Scale (NOS) for

cohort studies. The NOS evaluates three domains: selection of study groups (maximum four stars), comparability of cohorts (maximum two stars), and ascertainment of outcomes and adequacy of follow-up (maximum three stars), yielding a maximum score of nine stars. Each included study was assessed at the study level according to the published NOS criteria. A conservative approach was used whereby stars were awarded only when the relevant methodological information was explicitly reported in the original publication; missing or insufficiently reported information was not inferred. The individual item-level assessments and total NOS scores are presented in Supplementary Table S2.

Statistical analysis. Outcomes (clinical cure, microbiological cure, and mortality) were summarized as odds ratios (OR) with 95% confidence intervals (CI) comparing the CAZ-AVI group with the comparator group in each study, and forest plots were generated for each outcome. Because all included studies were observational and clinically heterogeneous with respect to patient population, infection site, and comparator regimen, we used a random-effects model (DerSimonian-Laird) as the primary method for pooling effect estimates; we also calculated a fixed-effect model for comparison. Heterogeneity was quantified with the I^2 statistic, with $I^2 \geq 50\%$ considered indicative of substantial statistical heterogeneity. Because of the small number of studies contributing to each outcome (four to seven), formal statistical tests for publication bias (e.g., Egger's test) were not performed; funnel plots were therefore interpreted only as a qualitative, exploratory check for asymmetry suggestive of small-study effects or publication bias, rather than as evidence of study homogeneity. For the microbiological cure outcome, a sensitivity analysis was performed excluding the study identified as the principal source

of heterogeneity (Gu et al. [28]), to assess the robustness of the pooled estimate to this single study; subgroup analyses stratified by infection site or patient population were not performed because of the small number of available studies. No statistical transformations or imputations were applied to missing outcome data before pooling. The reported event counts and denominators were used directly for calculation of odds ratios. Outcome-specific analyses therefore included only studies for which sufficient comparative data were available.

A two-sided $p<0.05$ was considered statistically significant. Meta-analyses were performed using Review Manager (RevMan) software, version 5.4 (The Cochrane Collaboration); random-effects pooled estimates were cross-checked using the DerSimonian-Laird method implemented in Python.

3. Results

The PubMed database search identified 450 records. Of these, 78 records were excluded because they were published outside the predefined five-year period, leaving 372 records. A further eight records were excluded because they were published in languages other than English, resulting in 364 records. The search included studies involving human participants; therefore, 158 records involving non-human studies were excluded, leaving 206 studies for screening and retrieval. These 206 studies were subsequently screened for eligibility, and 199 studies were excluded because they did not contain the required comparative outcome data for the meta-analysis. Ultimately, seven observational studies met the eligibility criteria and were included in the systematic review and quantitative synthesis (Table 1 and Figure 1). Across the seven included observational studies, 988

patients were enrolled, including 415 patients who received CAZ-AVI-containing regimens and 573 who received comparator antimicrobial regimens. Outcome-specific denominators varied because not all studies reported every outcome and because the number of evaluable patients differed across outcomes.

Table 1: Characteristics of the observational studies included in the systematic review and meta-analysis, including publication year, journal, sample size, infection characteristics, and antimicrobial regimens in the CAZ-AVI and comparator groups.

Study	Year	Journal	Number of patients	
			Intervention	Control
Shi et al. [35]	2021	Infectious Diseases and Therapy	43	62
Abu Jaber et al. [33]	2024	Antibiotics	64	50
Sree et al. [36]	2024	Infection	22	65
Zhang et al. [37]	2023	Annals of Clinical Microbiology and Antimicrobials	28	66
Pérez-Nadales et al. [38]	2023	American Journal of Transplantation	149	149
Hu et al. [39]	2024	International Journal of Antimicrobial Agents	67	133
Gu et al. [28]	2021	Journal of Global Antimicrobial Resistance	42	48

The infection sites and patient populations varied across the seven included studies: Shi et al. enrolled critically ill patients with CRKP-induced pneumonia; Abu Jaber et al. [33] enrolled patients with infections caused by CRKP carrying blaOXA-48-like genes; Sree et al. enrolled patients with CRKP nosocomial infections at mixed sites; Zhang et al. enrolled hematology patients with carbapenem-resistant Enterobacteriaceae bloodstream infections; Pérez-Nadales et al. [38] enrolled solid-organ transplant recipients with bloodstream infections caused by carbapenemase-producing K. pneumoniae; Hu et al. [39] enrolled patients, including solid-organ transplant recipients, with CRKP infections; and Gu et al. [28] enrolled general patients with CR-KP infections. This diversity in infection site and patient population is an important source of clinical heterogeneity among the pooled studies.

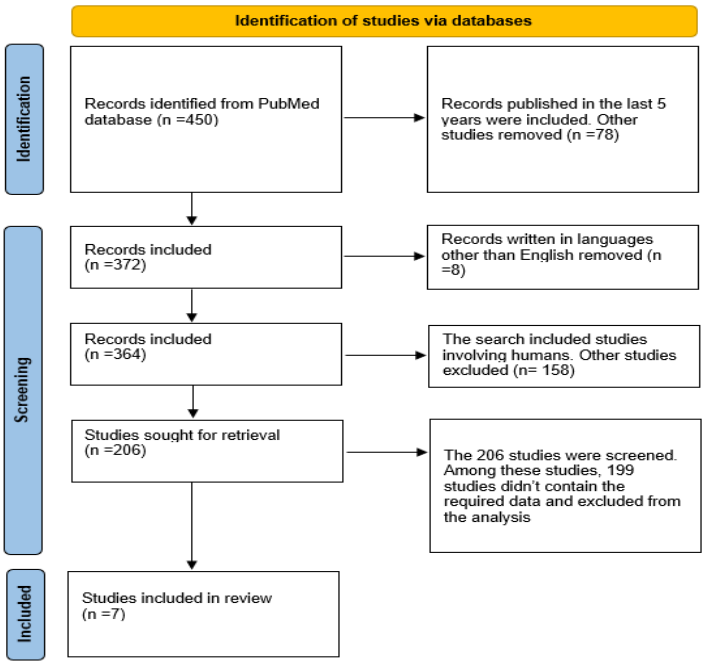

Figure 1. PRISMA flow diagram of study identification, screening, eligibility assessment, and inclusion in the systematic review**.**

The methodological quality and risk of bias of the seven included observational cohort studies were assessed using the Newcastle–Ottawa Scale. Overall, the studies demonstrated moderate-to-high methodological quality, with NOS scores ranging from 6 to 8 of 9 stars. Five studies—Shi et al. [35], Sree et al., Zhang et al., Pérez-Nadales et al. [38], and Gu et al. [28]—received 8 stars, whereas Abu Jaber et al. [33] and Hu et al. [39] received 6 stars. The main methodological limitation identified across the studies was incomplete reporting of follow-up adequacy, for which a star was not awarded when the completeness of follow-up was not explicitly documented. In addition, the Abu Jaber et al. and Hu et al. [39] studies did not provide sufficient evidence of adjustment for the principal confounding factors in the comparative treatment analysis, resulting in no stars for the NOS comparability domain. Detailed item-level assessments are provided in Supplementary Table S2.

Across the five studies reporting this outcome (n=508; 245 CAZ-AVI, 263 comparator), CAZ-AVI was associated with a higher clinical cure rate than other regimens (64.90% versus 42.21%, respectively) (Table 2).

Table 2: Clinical cure outcomes among patients with carbapenem-resistant Klebsiella pneumoniae infections treated with ceftazidime-avibactam or comparator antimicrobial regimens.

Study	Intervention			Control		
	Event	Total	%	Event	Total	%
Shi et al. [35]	22	43	51.16%	18	62	29.03%
Abu Jaber et al. [33]	27	64	42.19%	11	50	22.00%
Pérez-Nadales et al. [38]	55	66	83.33%	50	83	60.24%
Hu et al. [39]	27	30	90.00%	8	20	40.00%
Gu et al. [28]	28	42	66.67%	24	48	50.00%
Total	159	245	64.90%	111	263	42.21%

Figure 2 displays the clinical cure rate among patients infected with CRKP. CAZ-AVI treatment was associated with a higher clinical cure rate than other regimens (random-effects OR: 2.98; 95% CI: 1.90-4.67; $p < 0.0001$; fixed-effect OR: 2.96, 95% CI: 2.00-4.37).

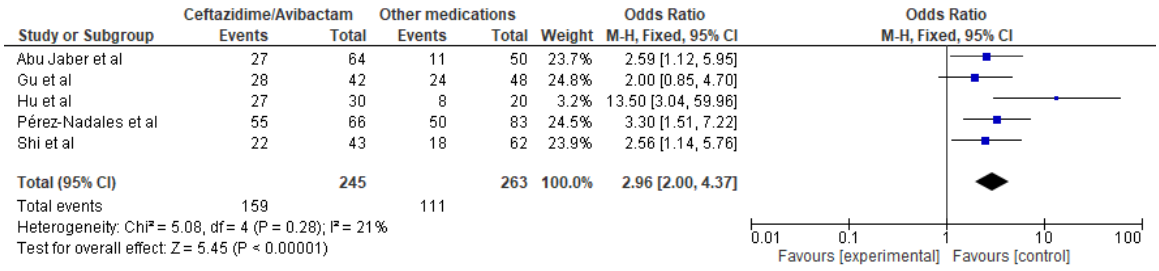

Figure 2. Forest plot comparing clinical cure with ceftazidime-avibactam versus comparator antimicrobial regimens in patients with carbapenem-resistant Klebsiella pneumoniae infections. Pooled odds ratios were calculated using a random-effects model.

The I^2 statistic for clinical cure was 21% (below the 50% threshold), indicating a low degree of statistical heterogeneity among the five included studies. The funnel plot

(Figure 3) showed no marked asymmetry, which is reassuring against substantial small-study or publication-bias effects, although with only five studies this assessment is necessarily exploratory and of limited power.

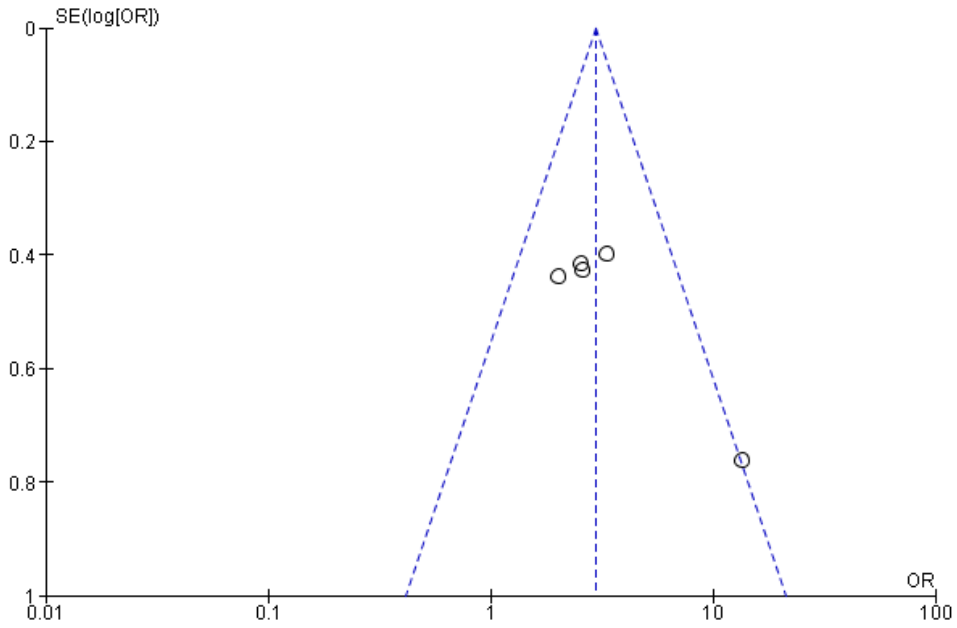

Figure 3. Funnel plot for studies reporting clinical cure, showing the distribution of study effect estimates around the pooled estimate as an exploratory assessment of potential small-study effects.

Across the four studies reporting this outcome (n=383; 189 CAZ-AVI, 194 comparator), CAZ-AVI treatment for CRKP infections resulted in a greater microbiological cure rate than other regimens (70.37% versus 41.24%, respectively) (Table 3).

Table 3: Microbiological cure outcomes among patients with carbapenem-resistant Klebsiella pneumoniae infections treated with ceftazidime-avibactam or comparator antimicrobial regimens.

Study	Intervention			Control		
	Event	Total	%	Event	Total	%
Shi et al. [35]	32	43	74.42%	21	62	33.87%
Abu Jaber et al. [33]	44	64	68.75%	21	50	42.00%
Hu et al. [39]	26	40	65.00%	5	34	14.71%
Gu et al. [28]	31	42	73.81%	33	48	68.75%
Total	133	189	70.37%	80	194	41.24%

Figure 4 shows the microbiological cure rate among patients with CRKP infections. CAZ-AVI was associated with a higher microbiological cure rate than other regimens (random-effects OR=3.77; 95% CI: 1.67-8.53; p=0.001; fixed-effect OR=3.59, 95% CI: 2.32-5.56).

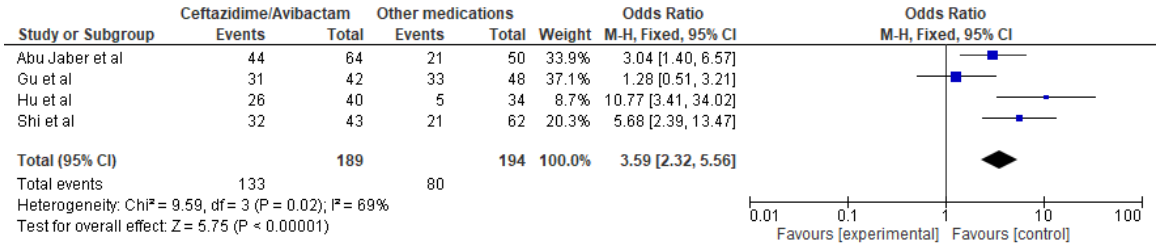

Figure 4. Forest plot comparing microbiological cure with ceftazidime-avibactam versus comparator antimicrobial regimens in patients with carbapenem-resistant Klebsiella pneumoniae infections. Pooled odds ratios were calculated using a random-effects model.

The I^2 statistic for microbiological cure was 69%, indicating substantial statistical heterogeneity among the four included studies, which is reflected in the wider confidence interval around the random-effects pooled estimate compared with clinical cure and mortality. The funnel plot (Figure 5) was visually inspected for asymmetry as an exploratory check for small-study or publication-bias effects, but with only four studies this assessment has very limited power and cannot itself establish or rule out homogeneity.

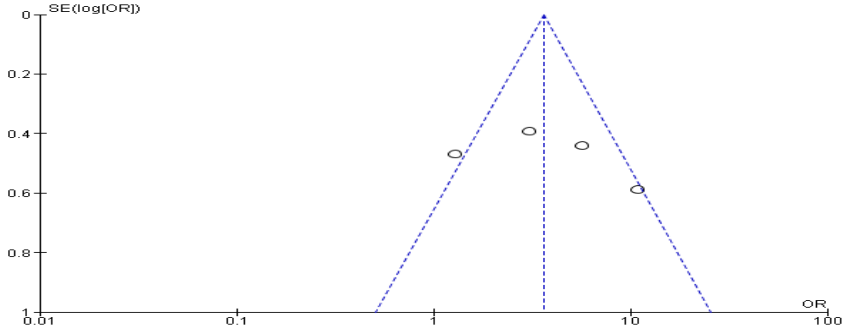

Figure 5. Funnel plot for studies reporting microbiological cure, presented as an exploratory assessment of potential small-study effects.

In a sensitivity analysis excluding the Gu et al. [28] study—identified as the principal source of heterogeneity in the full four-study analysis—the I^2 fell to 41%, below the 50% threshold used in this analysis, and the random-effects pooled estimate was correspondingly more precise. The forest plot in Figure 6 indicates that, in this three-study subset, CAZ-AVI was associated with a higher microbiological cure rate than other regimens (random-effects OR=5.18; 95% CI: 2.61-10.27; $p < 0.0001$; fixed-effect OR=4.96, 95% CI: 2.99-8.23). Because Gu et al. [28] enrolled a general CR-KP-infection population rather than the more homogeneous transplant, hematology, or ICU-pneumonia populations of the other three studies, this sensitivity analysis suggests that some of the heterogeneity in the full estimate reflects genuine clinical diversity across studies rather than a methodological artifact; the result should therefore be interpreted as an exploration of robustness rather than grounds for discarding the Gu et al. [28] data from the primary analysis.

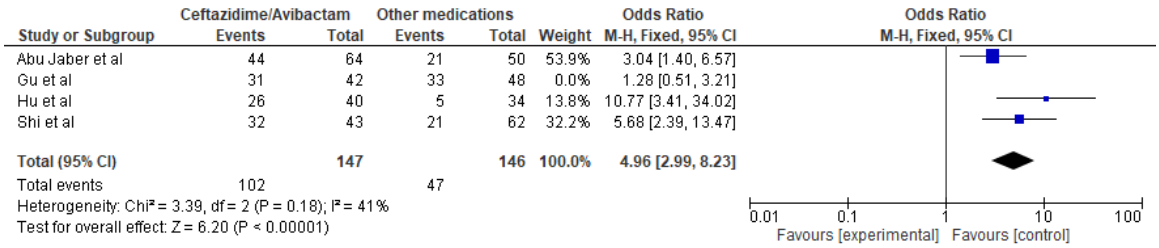

Figure 6. Sensitivity analysis of microbiological cure after exclusion of Gu et al., showing the random-effects pooled estimate and the corresponding reduction in statistical heterogeneity.

Across all seven studies (n=689; 295 CAZ-AVI, 394 comparator), CAZ-AVI treatment of CRKP infections was associated with a lower mortality rate than other regimens (26.78% versus 43.91%, respectively) (Table 4).

Table 4: All-cause mortality outcomes among patients with carbapenem-resistant Klebsiella pneumoniae infections treated with ceftazidime-avibactam or comparator antimicrobial regimens.

Study	Intervention			Control		
	Event	Total	%	Event	Total	%
Shi et al. [35]	13	43	30.23%	21	62	33.87%
Abu Jaber et al. [33]	32	64	50.00%	33	50	66.00%
Sree et al.	8	22	36.36%	37	65	56.92%
Zhang et al.	2	28	7.14%	25	66	37.88%
Pérez-Nadales et al. [38]	9	66	13.64%	23	83	27.71%
Hu et al. [39]	7	30	23.33%	12	20	60.00%
Gu et al. [28]	8	42	19.05%	22	48	45.83%
Total	79	295	26.78%	173	394	43.91%

Figure 7 shows the mortality rate of individuals with CRKP infections. CAZ-AVI was associated with lower mortality than other regimens (random-effects OR=0.40; 95% CI: 0.27-0.61; $p < 0.0001$; fixed-effect OR=0.40, 95% CI: 0.28-0.57).

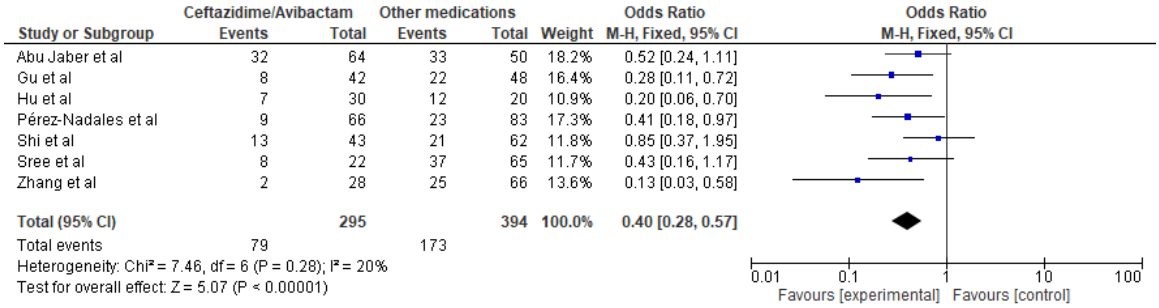

Figure 7. Forest plot comparing all-cause mortality between patients receiving ceftazidime-avibactam and those receiving comparator antimicrobial regimens for carbapenem-resistant Klebsiella pneumoniae infections. Pooled odds ratios were calculated using a random-effects model.

The I^2 for mortality was 19% (below the 50% threshold), indicating a low degree of statistical heterogeneity among the seven included studies. The funnel plot (Figure 8) showed no marked asymmetry, which is reassuring against substantial small-study or publication-bias effects, although, as with the other outcomes, this exploratory check has limited power given the small number of studies.

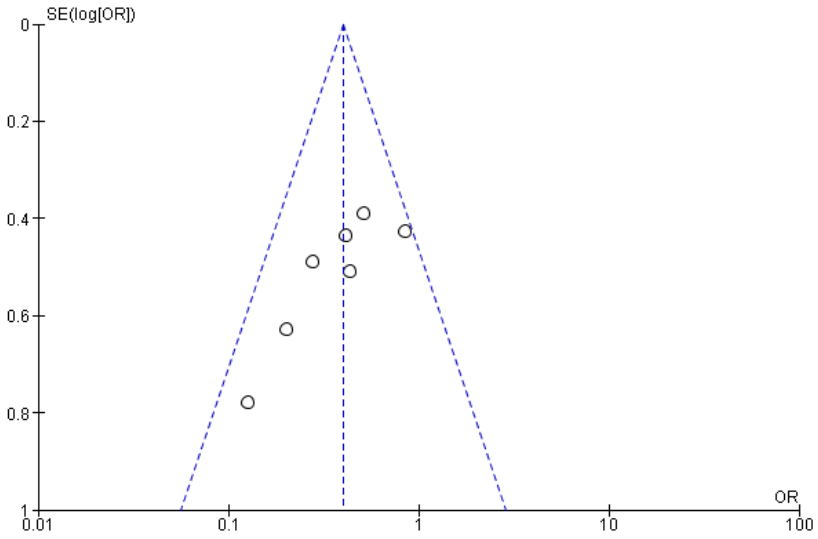

Figure 8. Funnel plot for studies reporting all-cause mortality, presented as an exploratory assessment of potential small-study effects.

4. Discussion

Carbapenem-resistant Klebsiella pneumoniae poses a significant healthcare challenge due to its limited treatment choices and high morbidity and mortality rates. Carbapenem-resistant Klebsiella pneumoniae infections are becoming more common globally due to their resistance to most existing antibiotics, including carbapenems, which are normally used as a last resort. The introduction of ceftazidime/avibactam has provided a potential remedy, however, clinical data on its efficacy in real-world settings is limited. The primary goal of this study was to determine the therapeutic efficacy of ceftazidime/avibactam in treating infections caused by carbapenem-resistant Klebsiella pneumoniae.

These pooled results are broadly consistent with findings from the individual included studies, although the included studies differed in the precise outcomes reported and in patient population. Abu Jaber et al. [33] reported higher clinical success and

microbiological eradication, and lower mortality and infection recurrence, with CAZ-AVI added to standard therapy for CRKP infections carrying blaOXA-48-like genes [33]. Shi et al. similarly reported higher clinical and microbiological success with CAZ-AVI than with tigecycline in critically ill patients with CRKP-induced pneumonia, although 28-day survival did not differ significantly between groups [35]. Sree et al. found a lower 30-day mortality rate with CAZ-AVI (with or without aztreonam) than with polymyxins, raising the possibility that aztreonam-containing combinations may offer particular benefit in CRKP infections, including those produced by metallo-β-lactamases for which CAZ-AVI alone lacks activity [36]. Taken together, these studies suggest that the benefit of CAZ-AVI observed in our pooled analysis is unlikely to be driven by any single study or population, although, as discussed below, the populations and comparator regimens involved were clinically heterogeneous.

Gu et al., whose general CR-KP population differed from the more specific transplant, hematology, and ICU-pneumonia populations of the other studies, also suggested that the benefit of CAZ-AVI may be more pronounced in severe than in moderate disease [28]; this is consistent with our finding that this study contributed disproportionately to the heterogeneity observed for microbiological cure, and our sensitivity analysis excluding it (I2 falling from 69% to 41%) supports clinical diversity, rather than a purely statistical artifact, as the more likely explanation. Pérez-Nadales et al. [38] and Hu et al. [39], both focused on solid-organ transplant recipients, and Zhang et al., focused on hematology patients, reported lower mortality and higher clinical success with CAZ-AVI than with best-available therapy or comparator regimens [37-39]. As in any observational comparison, confounding by indication cannot be excluded: depending

on local protocols and drug availability, CAZ-AVI may have been preferentially used in patients perceived as more (or less) likely to respond, and none of the included studies reported using methods such as propensity-score matching to address this. None of the included studies systematically reported the emergence of CAZ-AVI resistance during therapy; this is a recognized concern with this agent in the broader literature and represents an important outcome for future comparative studies to capture.

Our findings are consistent with the broader clinical evidence supporting the use of ceftazidime-avibactam against resistant Gram-negative infections. Karampatakis et al. previously conducted a systematic review and meta-analysis specifically evaluating CAZ-AVI versus other antimicrobials for CRKP infections [34]. The present findings are also directionally consistent with evidence from randomized phase 3 trials evaluating CAZ-AVI in serious Gram-negative infections. In the REPRISE trial, Carmeli et al. evaluated CAZ-AVI versus best available therapy in patients with complicated urinary tract or intra-abdominal infections caused by ceftazidime-resistant Gram-negative pathogens [40]. Similarly, the REPROVE trial by Torres et al. compared CAZ-AVI with meropenem for hospital-acquired pneumonia, including ventilator-associated pneumonia [41]. Although these randomized trials were not specific comparative trials of CRKP infections and were not included in the present meta-analysis, they provide important contextual evidence regarding the clinical efficacy of CAZ-AVI. Systematic reviews provided clinical evidence for the efficacy of CAZ-AVI in hospitalized patients with multidrug-resistant *K. pneumoniae* and carbapenem-resistant Enterobacterales (CRE) [29,30,34]. This meta-analysis nonetheless has several limitations that should inform how its findings are interpreted. First, the search was restricted to a single database (PubMed)

and to English-language publications, which may have missed eligible studies indexed elsewhere or published in other languages. Second, study selection, screening, and data extraction were performed by a single reviewer without duplicate independent assessment, as noted in the Methods. Third, risk of bias was formally assessed using the Newcastle–Ottawa Scale. Although most included studies demonstrated relatively strong methodological characteristics, all were observational, and residual confounding and selection bias cannot be excluded. In particular, the absence or limited use of adjusted comparative analyses in some studies and incomplete reporting of follow-up adequacy may have introduced uncertainty into the estimated treatment effects. In addition, treatment selection was determined by clinical practice rather than random allocation, making confounding by indication an important consideration when interpreting the pooled estimates. Fourth, the comparator ("other medications") group was clinically heterogeneous across studies (including tigecycline, polymyxins with or without aztreonam, and other best-available-therapy combinations), limiting the ability to attribute the observed benefit to any single alternative regimen. Fifth, the small number of studies contributing to each outcome (four to seven) limited the power of heterogeneity and small-study-effect assessments and precluded meaningful subgroup analyses by infection site or population. Finally, although dosing regimens, treatment duration, and renal-dose adjustments were extracted when explicitly reported, these parameters were inconsistently described across the included studies and therefore could not be reliably compared or incorporated into the quantitative analysis. This limits assessment of whether differences in dosing intensity, renal adjustment, or treatment duration may have contributed to the observed between-study differences in outcomes.

Despite the limitations above, the consistent direction of benefit observed across clinically distinct populations—including solid-organ transplant recipients, patients with hematologic malignancy, and critically ill patients with pneumonia—suggests that CAZ-AVI is a reasonable treatment option for CRKP infections in settings where susceptibility testing supports its use (i.e., where the resistance mechanism is not a class B metallo-β-lactamase), particularly given the limited alternatives currently available. Because CRKP infections are relatively uncommon and frequently arise in critically ill or immunocompromised patients, adequately powered randomized trials remain difficult to conduct; in the interim, use of CAZ-AVI within an antimicrobial stewardship framework, with attention to local resistance patterns, susceptibility testing, and the possibility of resistance emergence during therapy, appears warranted while higher-quality comparative evidence, including well-designed prospective studies with explicit confounding-control strategies, continues to accumulate.

5. Conclusion

In this meta-analysis of seven observational studies, a ceftazidime-avibactam (CAZ-AVI) regimen appears to be a promising option for treating infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP), with consistently higher clinical and microbiological cure rates and lower mortality than other regimens across clinically diverse populations. Because all included studies were observational and the comparator regimens were heterogeneous, these findings support, rather than definitively establish, a benefit of CAZ-AVI and should be interpreted in light of the limitations discussed above. CAZ-AVI nonetheless represents a meaningful addition to the management of multidrug-resistant bacterial infections, especially given the growing incidence of carbapenem-

resistant pathogens and the scarcity of therapeutic alternatives. Larger, well-designed prospective studies—randomized where feasible—are needed to confirm these findings, define optimal use (including dosing and combination strategies), and guide antimicrobial stewardship.

List of Abbreviations

AmpC: AmpC β-lactamase

CAZ-AVI: Ceftazidime-avibactam

CDC: Centers for Disease Control and Prevention

CI: Confidence interval

CRKP: Carbapenem-resistant *Klebsiella pneumoniae*

CRE: Carbapenem-resistant Enterobacterales

ESBL: Extended-spectrum β-lactamase

ICU: Intensive care unit

KPC: *Klebsiella pneumoniae* carbapenemase

NDM: New Delhi metallo-β-lactamase

OR: Odds ratio

OXA-48: Oxacillinase-48 carbapenemase

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RevMan: Review Manager

VIM: Verona integron-encoded metallo-β-lactamase

Author Contributions

N.J.A. is the sole author of the manuscript and was responsible for Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Data Curation,

Writing – Original Draft, Writing – Review & Editing, Visualization, and Project Administration. The author has read and approved the final version of the manuscript.

Availability of Data and Materials

All data generated and analyzed during the study are included in this article. The analytic files, including the RevMan 5.4 project file used for the primary meta-analysis and generation of forest and funnel plots, as well as the Python script used to cross-check the DerSimonian–Laird calculations, are available from the corresponding author upon reasonable request.

Ethics Committee Approval

This meta-analysis did not require ethical approval as it used publicly available data and previously conducted and published studies.

Consent for Publication

No consent for publication is required, as the manuscript does not involve any individual personal data, images, videos, or other materials that would necessitate consent.

Conflicts of Interest

The author declares no conflicts of interest.

Funding

The study did not receive any external funding and was conducted using only institutional resources.

Acknowledgments

None

AI-declaration:

The author acknowledges the use of ChatGPT (GPT-5, OpenAI, 2025) to assist in language refinement, grammar correction, and improvement of manuscript clarity. The author reviewed and verified all content generated by the AI tool. All figures are original and have not been reproduced or adapted from previously published materials.

Standards of Reporting

This systematic review was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.

References

1. ECDC. Surveillance of Antimicrobial Resistance in Europe 2018. 2018. Available online: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2018 (Accessed December 01, 2025).
2. Ioniță, O.E.; Cernat, R.C.; Militaru, N.M.; Vodarici, M.E.; Fulina, M.; Pițigoi, D.; Mocanu, E.; Severin, B.; Cambrea, C.S.; Dumitru, I.-M. Carbapenem-Resistant Klebsiella pneumoniae in Healthcare-Associated Infections: Global and Regional Epidemiology, Resistance Mechanisms, and Therapeutic Strategies, with Particular Attention to Romania and Eastern Europe (2020–2025). *Microorganisms*. **2026**, *14*, 1870.
3. Paterson, D.L.; Isler, B.; Harris, P.N.A. PRO: Carbapenems should be used for ALL infections caused by ceftriaxone-resistant Enterobacterales. *JAC Antimicrob Resist*. **2021**, *3*, dlab013.
4. Salam, M.A.; Al-Amin, M.Y.; Salam, M.T.; Pawar, J.S.; Akhter, N.; Rabaan, A.A.; Alqumber, M.A.A. Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. *Healthcare*. **2023**, *11*, 1946.
5. Chen, H.Y.; Jean, S.S.; Lee, Y.L.; Lu, M.C.; Ko, W.C.; Liu, P.Y.; Hsueh, P.R. Carbapenem-resistant enterobacterales in long-term care facilities: A global and narrative review. *Front Cell Infect Microbiol*. **2021**, *11*, 601968.
6. Zhang, Y.; Wang, Q.; Yin, Y.; Chen, H.; Jin, L.; Gu, B.; Xie, L.; Yang, C.; Ma, X.; Li, H.; *et al*. Epidemiology of carbapenem-resistant enterobacteriaceae infections: Report from the China CRE network. *Antimicrob Agents Chemother*. **2018**, *62*, 10–1128.
7. Tacconelli, E.; Carrara, E.; Savoldi, A.; Harbarth, S.; Mendelson, M.; Monnet, D.L.; Pulcini, C.; Kahlmeter, G.; Kluytmans, J.; Carmeli, Y.; *et al*. Discovery, research, and development of

new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. **2018**, *18*, 318-327.
8. Koli, S.V.; Mali, S.V.; Geevarghese, J. Global divide in carbapenem resistance and hypervirulence of Klebsiella pneumonia: comparing trends in India and developed nations"- a comprehensive review. *J Antibiot*. **2025**, *78*, 457–471.
9. Lin, X.C.; Li, C.L.; Zhang, S.Y.; Yang, X.F.; Jiang, M. The Global and Regional Prevalence of Hospital-Acquired Carbapenem-Resistant Klebsiella pneumoniae Infection: A Systematic Review and Meta-analysis. *Open Forum Infect Dis*. **2023**, *11*, ofad649.
10. Dropa, M.; Daoud, Z. The global threat of carbapenem-resistant gram-negative bacteria. *Front Cell Infect Microbiol.* **2022**, *12*, 974268.
11. Reyes, J.; Komarow, L.; Chen, L.; Ge, L.; Hanson, B.M.; Cober, E.; et al. Global epidemiology and clinical outcomes of carbapenem-resistant Pseudomonas aeruginosa and associated carbapenemases (POP): a prospective cohort study. *Lancet Microbe*. **2023**, *4*, e159-e170.
12. Wise, M.G.; Karlowsky, J.A.; Mohamed, N.; Hermsen, E.D.; Kamat, S.; Townsend, A.; et al. Global trends in carbapenem-and difficult-to-treat-resistance among World Health Organization priority bacterial pathogens: ATLAS surveillance program 2018–2022. *J Glob Antimicrob Resist*. **2024**, *37*, 168-175.
13. Ramkisson, T.; Rip, D. Carbapenem resistance in Enterobacterales from agricultural, environmental and clinical origins: South Africa in a global context. *AIMS Microbiol*. **2023**, *9*, 668–691.
14. Li, D.; Huang, X.; Rao, H.; Yu, H.; Long, S.; Li, Y.; Zhang, J. Klebsiella pneumoniae bacteremia mortality: a systematic review and meta-analysis. *Front Cell Infect Microbiol*. **2023**, *13*, 1157010.
15. Bhat, D.; Rajan, A.K.; Aditya, V.; Eshwara, V.K.; Varma, M.; Umakanth, S.; et al. Does carbapenem resistance influence clinical outcomes in ICU patients with Klebsiella pneumoniae bacteraemia? A comparative analysis of Carbapenem-resistant and susceptible isolates. *Acta Trop*. **2025**, *2025*, 107744.
16. Calderón-Parra, J.; Carretero-Henriquez, M.T.; Escudero, G.; Suances-Martin, E.; de la Fuente, M.M.; González-Merino, P.; et al. Current epidemiology, risk factors and influence on prognosis of multidrug resistance in Klebsiella spp. bloodstream infection. Insights from a prospective cohort. *Eur J Intern Med*. **2025**, *139*, 106369.
17. Zhang, Q.; Fang, Z.; Fang, B.; Zeng, H.; Xu, J. Clinical Epidemiological Analysis of the Genotypic Spectrum and Mortality Risk in Carbapenem-Resistant Klebsiella pneumoniae (CRKP) Infections. *Can J Infect Dis Med Microbiol*. **2026**, *2026*, 1529426.
18. Chen, J.; Hou, Y.; Shi, J.; Gao, X.; Liang, G. Mortality risk of carbapenem-resistant hypervirulent Klebsiella pneumoniae vs. classical CR-KP: a systematic review and meta-analysis. *Front Public Health*. **2025**, *13*, 1680292.
19. Kadri, S.S. Key takeaways from the U.S. Cdc's 2019 antibiotic resistance threats report for frontline providers. *Crit Care Med*. **2020**, *48*, 939–945.
20. Hu, F.P.; Guo, Y.; Zhu, D.M. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005–2014. *Clin Microbiol Infect*. **2016**, *22*, S9–S14.

21. Rodríguez, O.L.; Sousa, A.; Pérez-Rodríguez, M.T.; Martínez-Lamas, L.; Suárez, R.L.; Martínez, C.T.; Pino, C.P.; Vidal, F.V.; Pérez-Landeiro, A.; Casal, M.C. Mortality-related factors in patients with OXA-48 carbapenemase-producing Klebsiella pneumoniae bacteremia. *Medicine*. **2021**, *100*, e24880.
22. Neuner, E.A.; Yeh, J.Y.; Hall, G.S.; Sekeres, J.; Endimiani, A.; Bonomo, R.A.; Shrestha, N.K.; Fraser, T.G.; van Duin, D. Treatment and outcomes in carbapenem-resistant Klebsiella pneumoniae bloodstream infections. *Diagn Microbiol Infect Dis*. **2011**, *69*, 357–362.
23. Shields, R.K.; Nguyen, M.H.; Chen, L.; Press, E.G.; Potoski, B.A.; Marini, R.V.; Doi, Y.; Kreiswirth, B.N.; Clancy, C.J. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia. *Antimicrob Agents Chemother*. **2017**, *61*, 10-1128.
24. Krapp, F.; Grant, J.L.; Sutton, S.H.; Ozer, E.A.; Barr, V.O. Treating complicated carbapenem-resistant enterobacteriaceae infections with ceftazidime/avibactam: A retrospective study with molecular strain characterisation. *Int J Antimicrob Agents*. **2017**, *49*, 770–773.
25. Tumbarello, M.; Trecarichi, E.M.; Corona, A.; De Rosa, F.G.; Bassetti, M.; Mussini, C.; Menichetti, F.; Viscoli, C.; Campoli, C.; Venditti, M.; *et al*. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae. *Clin Infect Dis*. **2019**, *68*, 355–364.
26. Castón, J.J.; Lacort-Peralta, I.; Martín-Dávila, P.; Loeches, B.; Tabares, S.; Temkin, L.; Torre-Cisneros, J.; Paño-Pardo, J.R. Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing enterobacteriaceae in hematologic patients. *Int J Infect Dis*. **2017**, *59*, 118–123.
27. van Duin, D.; Bonomo, R.A. Ceftazidime/avibactam and ceftolozane/tazobactam: Second-generation β-lactam/β-lactamase inhibitor combinations. *Clin Infect Dis*. **2016**, *63*, 234–241.
28. Gu, J.; Xu, J.; Zuo, T.T.; Chen, Y.B. Ceftazidime-avibactam in the treatment of infections from carbapenem-resistant Klebsiella pneumoniae: Ceftazidime-avibactam against CR-KP infections. *J Glob Antimicrob Resist*. **2021**, *26*, 20–25.
29. Soriano, A.; Carmeli, Y.; Omrani, A.S.; Moore, L.S.P.; Tawadrous, M.; Irani, P. Ceftazidime-avibactam for the treatment of serious gram-negative infections with limited treatment options: A systematic literature review. *Infect Dis Ther*. **2021**, *10*, 1989–2034.
30. Zhen, S.; Wang, H.; Feng, S. Update of clinical application in ceftazidime-avibactam for multidrug-resistant gram-negative bacteria infections. *Infection*. **2022**, *50*, 1409–1423.
31. Mazuski, J.E.; Wagenlehner, F.; Torres, A.; Carmeli, Y.; Chow, J.W.; Wajsbrot, D.; Stone, G.G.; Irani, P.; Bharucha, D.; Cheng, K.; *et al*. Clinical and microbiological outcomes of ceftazidime-avibactam treatment in adults with gram-negative bacteremia: A subset analysis from the phase 3 clinical trial program. *Infect Dis Ther*. **2021**, *10*, 2399–2414.
32. Zheng, G.; Cai, J.; Zhang, L.; Chen, D.; Wang, L.; Qiu, Y.; Deng, H.; Bai, H.; Bian, X.; He, J. Ceftazidime/avibactam-based versus polymyxin b-based therapeutic regimens for the treatment of carbapenem-resistant Klebsiella pneumoniae infection in critically ill patients: A retrospective cohort study. *Infect Dis Ther*. **2022**, *11*, 1917–1934.
33. Abu Jaber, A.M.R.; Basgut, B.; Hawan, A.A.; Al Shehri, A.A.; AlKahtani, S.A.; Ahmed, N.J.; Abdi, A. The Clinical Efficacy of Adding Ceftazidime/Avibactam to Standard Therapy

in Treating Infections Caused by Carbapenem-Resistant Klebsiella pneumonia with blaOXA-48-like Genes. *Antibiotics*. **2024**, *13*, 265.
34. Karampatakis, T.; Tsergouli, K.; Lowrie, K. Efficacy and safety of ceftazidime-avibactam compared to other antimicrobials for the treatment of infections caused by carbapenem-resistant Klebsiella pneumoniae strains, a systematic review and meta-analysis. *Microb Pathog*. **2023**, *179*, 106090.
35. Shi, Y.; Hu, J.; Liu, P.; Wang, T.; Wang, H.; Liu, Y.; Cao, Q.; Zuo, X. Ceftazidime-Avibactam-Based Versus Tigecycline-Based Regimen for the Treatment of Carbapenem-Resistant Klebsiella pneumoniae-Induced Pneumonia in Critically Ill Patients. *Infect Dis Ther*. **2021**, *10*, 2721-2734.
36. Sree, R.A.; Gupta, A.; Gupta, N.; Veturi, S.; Reddy, L.S.K.; Begum, M.; Shravani, E.; Challa, H.R.; Reddy, S.S.; Singamsetty, A.; *et al*. Ceftazidime-avibactam alone or in combination with Aztreonam versus Polymyxins in the management of carbapenem-Resistant Klebsiella pneumoniae nosocomial Infections (CAPRI study): a retrospective cohort study from South India. *Infection*. **2024**, *52*, 429-437.
37. Zhang, L.; Zhen, S.; Shen, Y.; Zhang, T.; Wang, J.; Li, J.; Lin, Q.; Xiao, Z.; Zheng, Y.; Jiang, E.; *et al*. Bloodstream infections due to Carbapenem-Resistant Enterobacteriaceae in hematological patients: assessment of risk factors for mortality and treatment options. *Ann Clin Microbiol Antimicrob*. **2023**, *22*, 41.
38. Pérez-Nadales, E.; Fernández-Ruiz, M.; Natera, A.M.; Gutiérrez-Gutiérrez, B.; Mularoni, A.; Russelli, G.; Pierrotti, L.C.; Pinheiro Freire, M.; Falcone, M.; Tiseo, G.; et al. Efficacy of ceftazidime-avibactam in solid organ transplant recipients with bloodstream infections caused by carbapenemase-producing Klebsiella pneumoniae. *Am J Transplant*. **2023**, *23*, 1022-1034.
39. Hu, J.; Zha, L.; Yu, Y.W.; Su, Q.; Fang, X.L.; Ji, J.R.; Shen, P.; Chen, Y.B.; Zheng, X.; Xiao, Y.H. Efficacy of ceftazidime-avibactam in the treatment of carbapenem-resistant Klebsiella pneumoniae infections: Focus on solid organ transplantation recipients. *Int J Antimicrob Agents*. **2024**, *63*, 107152.
40. Carmeli, Y.; Armstrong, J.; Laud, P.J.; Newell, P.; Stone, G.; Wardman, A.; Gasink, L.B. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis*. **2016**, *16*, 661–673.
41. Torres, A.; Zhong, N.; Pachl, J.; Timsit, J.F.; Kollef, M.; Chen, Z.; Song, J.; Taylor, D.; Laud, P.J.; Stone, G.G.; Chow, J.W. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis*. **2018**, *18*, 285–295.