# Clinical Efficacy and Safety of Newer Antibiotics for Carbapenem-Resistant Enterobacterales Infections: A Systematic Review

Khalid Salah Al-Juhani[1], Reem Salem Al-Saedi[1], Ibrahim Saud Al-Oufi[1], Khalid Eissa Hussein Al-Harbi[1], Ghalba Ghalib Almutiri[1], Hind Salem Wasel Alharbi[2], Maher Salem Musallam Aljohani[3], Nader Saud Al-Oufi[4], Naser Abdullah Al-Jabri[5], Fayzah Eid Alenzi[6*], Abdulrahman Abbad Almutairi[7], Fahad Farah Almutiry[8], Khaled Abdullah Owaidh Al-Mutairi[9], Mutaz Salem Mustafa Alhamed[10], Jabri Zuwayyid Obaid Almutairi[11]

[1]Ministry of Health- Madinah Health Cluster, King Fahd, Al Barakah, Madinah 42332, Saudi Arabia
[2]Midwife, Al Safiyah Primary Healthcare Center-Urgent Care, Al Haram, Madinah 42311, Saudi Arabia
[3]Pharmacy Technician, Al-Madinah Al-Munawwarah General Hospital, Mahzur, Madinah 42319, Saudi Arabia
[4]Nursing Technician, Al-Miqat Hospital, Madinah Health Cluster, Madinah Province, Saudi Arabia
[5]Pharmacy Technician, Health Centers Affairs Administration in Wadi Al-Far', Madinah Province, Saudi Arabia
[6]Maternity and Children Hospital, King Salman Medical City, Madinah Health Cluster, Madinah, Saudi Arabia
[7]King Fahad Madinah Hospital, 3177 Khalid Ibn Al Waleed Branch Rd, Al Jamiah, Madinah 42351, Saudi Arabia
[8]Nursing, Almazraa Primary Healthcare Center, Saudi Arabia
[9]Al-Jayasir Primary Healthcare Center, Al-Madinah Health Cluster, Madinah, Saudi Arabia
[10]Nursing Technician, Ministry of Health branch in the Medina, Madinah Province, Saudi Arabia
[11]Al-Salam Endowment Hospital- Madinah Health Cluster-Pilgrims Affaris, Madinah 42311, Saudi Arabia
***Corresponding author**
Fayzah Eid Alenzi
[6]Maternity and Children Hospital, King Salman Medical City, Madinah Health Cluster, Madinah, Saudi Arabia

**ABSTRACT**

Background. Carbapenem-resistant Enterobacterales (CRE) is a major public-health and clinical challenge because they cause severe infections and are associated with limited treatment options and high mortality. Newer antibiotics have expanded therapeutic choices, but activity varies by resistance mechanism. Objective. To review the clinical efficacy and safety of newer antimicrobial agents used to treat CRE infections, focusing on clinical cure, mortality, microbiological response, adverse events, and resistance emergence. Methods. A PubMed-only search-export audit was available (five CSV batches; 50 records, 16 duplicates, 34 unique PMIDs). Five full-text PDFs supplied for eligibility adjudication were assessed against the review's stated PICOS/design criteria. This adjudication is scoped to the supplied files; comprehensive database searching and independent dual-review validation are not represented as completed. Results. Of the five supplied full-text reports, four comparative clinical studies met the specified clinical population, intervention/outcome, and cohort-design criteria (Ackley et al. 2020; van Duin et al. 2018; Falcone et al. 2021; Hu et al. 2025). One uncontrolled retrospective case series (Zhang et al. 2021; n=15) was excluded from the primary comparative synthesis because case series were not among the.

specified eligible designs. Findings are heterogeneous and synthesized narratively. Conclusion. Treatment should be selected according to carbapenemase mechanism, susceptibility testing, infection site, severity, and patient-specific factors. Stewardship, surveillance, and high-quality comparative trials are essential.
**Keywords**: Carbapenem-resistant Enterobacterales; Antimicrobial resistance; Ceftazidime-avibactam; Meropenem-vaborbactam; Cefiderocol; Clinical efficacy; Safety.

## 1.INTRODUCTION

Antimicrobial resistance is a major challenge in contemporary healthcare. Carbapenem-resistant Enterobacterales (CRE) is of particular concern because they cause bloodstream infections, hospital-acquired pneumonia, urinary tract infections, intra-abdominal infections, and other healthcare-associated conditions. Clinically important organisms include Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae complex, and Citrobacter species [1-2]. Carbapenems have historically been relied upon for severe infections caused by multidrug-resistant Gram-negative bacteria. Their widespread use, however, has contributed to selection and dissemination of carbapenem-resistant organisms. Resistance may arise through carbapenemase production, altered outer-membrane permeability, increased efflux, or combinations of these mechanisms. Carbapenemase genes may be carried on mobile genetic elements and spread between species [1,3].

Major carbapenemase families include KPC, OXA-48-like enzymes, and metallo-β-lactamases (MBLs), such as NDM, VIM, and IMP. Their substrate profiles and susceptibility to β-lactamase inhibitors differ. Thus, CRE status alone is not sufficient to predict whether a given antimicrobial will be active [1,2,4]. Older therapeutic choices included polymyxins, aminoglycosides, tigecycline, and selected combination regimens. These drugs have limitations including nephrotoxicity, ototoxicity, inadequate serum exposure for some infection sites, and increasing resistance. Newer agents—such as ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, cefiderocol, and aztreonam-avibactam—have expanded options [1-3]. Clinical outcomes vary according to resistance mechanism, infection site, severity, timing of effective therapy, and patient factors. Resistance may also emerge during treatment. This review discusses clinical efficacy, safety, comparative evidence, and implications for clinical pharmacy and antimicrobial stewardship [5-7].

## 2. MATERIALS AND METHODS

Review design and research question

The review is intended as a systematic evidence synthesis of clinical efficacy and safety of newer antimicrobial agents in confirmed CRE infections, reported according to PRISMA 2020. The research question is: What efficacy and safety outcomes are associated with newer antibiotics used to treat CRE infections? [8].

PICOS framework

Table 1. PICOS framework.

| Component | Description |
|---|---|
| Population | Patients with confirmed CRE infections |
| Intervention | Newer antibiotics or novel β-lactam/β-lactamase inhibitor regimens |
| Comparator | Best available therapy, conventional antibiotics, or alternative newer antibiotics |
| Outcomes | Clinical cure, mortality, microbiological response, adverse events, resistance emergence |
| Study design | Randomized controlled trials and observational clinical studies |

Information sources and search strategy

The supplied PubMed CSV set was combined with the supplementary targeted-search candidate log and expanded screening records. The PubMed batches contained 50 raw records (16 within-batch duplicate records removed; 34 unique records). The supplementary curated log contained 11 entries, with one repeated Lee et al. Korean CRE bacteremia cohort entry removed, leaving 10 unique candidate records. Cross-matching the five PMID identifiers in the original supplementary search-results file against the 34 unique

PubMed CSV records found no exact PMID matches. The combined captured record set is therefore 61 entries

less 17 within-source repeats (16 PubMed duplicates and one supplementary repeat), yielding 44 unique tracked records. The targeted-search set is a curated candidate capture rather than a complete Google Scholar result

export; the figure reports this captured record set and does not imply exhaustive raw Google Scholar hit counts.

[("Carbapenem-Resistant Enterobacterales" OR "Carbapenem-Resistant Enterobacteriaceae" OR CRE OR "KPC-producing" OR "NDM-producing") AND (ceftazidime-avibactam OR meropenem-vaborbactam OR imipenem-relebactam OR cefiderocol OR aztreonam-avibactam OR "ceftazidime-avibactam plus aztreonam") AND ("clinical efficacy" OR "clinical cure" OR mortality OR "microbiological eradication" OR safety OR "adverse events")]. The review focused on literature published from January 2015 through November 2026, while retaining landmark earlier studies where clinically essential. Search records were derived from the PubMed export files supplied for this review.

Eligibility criteria

Inclusion criteria: (1) patients with confirmed CRE infection; (2) evaluation of one or more agents of interest; (3) at least one clinical efficacy or safety outcome; (4) randomized, prospective observational, or retrospective cohort design; (5) full-text peer-reviewed article; and (6) English language.

Exclusion criteria: in vitro or animal studies without patient outcomes; studies without a separately extractable CRE subgroup; editorials and narrative reviews without original data; case reports unless planned as a separate descriptive supplement; reports lacking extractable outcomes; and duplicate publications of the same dataset.

### Study selection, extraction, and risk of bias

Across the captured record set, 50 PubMed CSV records and 11 supplementary candidate-log entries were identified (n=61). Duplicate records removed within sources were 16 from the PubMed CSV batches and one repeated candidate entry in the supplementary log (n=17), leaving 44 unique tracked records (34 PubMed records and 10 supplementary candidates). In the PubMed screening branch, 26 title-stage exclusions left 8 records for abstract review; 3 abstract-stage exclusions left 5 reports assessed at full text. One full-text report was excluded because it was an uncontrolled case series, leaving 4 comparative reports in the primary synthesis. The supplementary candidate branch comprised 10 unique records: 2 were provisionally excluded for insufficiently separable CRE-specific outcomes, while 8 remain under candidate-level eligibility review; these are not yet all confirmed as eligible for the primary synthesis. The supplementary branch is integrated into the record accounting but is not yet treated as independent included studies.

Risk of bias was assessed using the ROBINS-I framework for the four comparative studies. The domain-level judgements are presented in Supplementary Table S2 and were carried forward from the previously completed assessment. The principal concern is confounding by indication, including differences in infection severity, resistance mechanism, source control, baseline renal function, prior effective therapy, and treatment selection. The ROBINS-I domain judgements for the four comparative reports are summarized in Table S2 (Supplementary).

Table S2 (Supplementary). ROBINS-I domain-level risk-of-bias assessment.

| Study | Confounding | Selection | Intervention classification | Deviations | Missing data | Outcome measurement | Reported result selection |
|---|---|---|---|---|---|---|---|
| Ackley et al. (2020) | Serious | Moderate | Low | Moderate | Low | Low | Moderate |
| van Duin et al. (2018) | Serious | Moderate | Low | Moderate | Low | Low | Moderate |
| Falcone et al. (2021) | Serious | Moderate | Low | Moderate | Low | Low | Moderate |
| Hu et al. (2025) | Moderate | Moderate | Low | Moderate | Low | Low | Moderate |

Residual confounding is the principal concern, particularly from illness severity, resistance mechanism, source control, prior effective therapy, renal function, and treatment selection. Hu et al.'s target-trial emulation may reduce some design-related concerns but cannot eliminate residual confounding. Domain judgements are reported separately; no summed risk-of-bias score is calculated.

## 3. DATA SYNTHESIS

Figure 1 combines the captured record accounting: 61 source entries, 17 within-source repeats removed, and 44 unique tracked records. The PubMed branch proceeds through documented title/abstract and supplied-full-text screening (34 screened; 26 title-stage exclusions; 8 abstract reviews; 3 abstract-stage exclusions; 5 full texts assessed; 1 excluded case series; 4 comparative reports retained). The supplementary targeted candidate branch has 10 unique tracked records, with 2 provisional exclusions and 8 candidate records at varying stages of eligibility confirmation. Candidate dispositions remain provisional where full-text eligibility or CRE-specific outcome extractability has not been established. The Huespe and EMBARCAR reports are treated as distinct cohorts, based on reviewer clarification; no overlap is assumed. The flow is based on the captured records and candidate log, not an exhaustive raw Google Scholar result count.

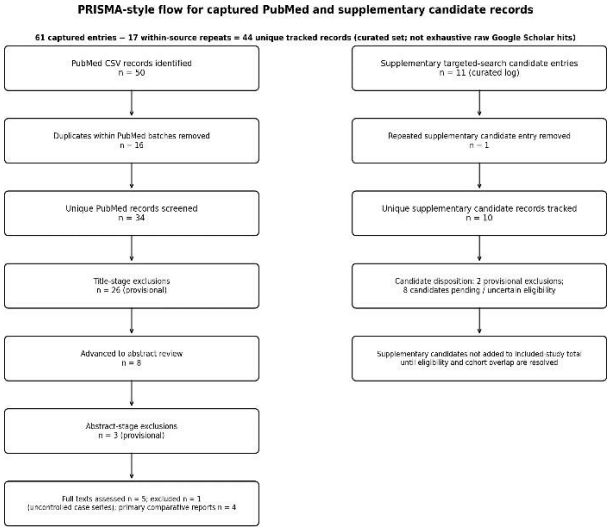


Figure 1. PRISMA flow diagram of the eligible studies selection process (Presents the combined captured record accounting, with separate PubMed screening and supplementary candidate branches to

**preserve the provisional status of targeted-search records).**

Full-text eligibility adjudication (accessible report set)

Five supplied full-text reports were checked against the eligibility criteria in Section 2.4. Four reports were retained in the primary comparative synthesis of that supplied report set: Ackley et al. (2020), van Duin et al. (2018), Falcone et al. (2021), and Hu et al. (2025) [5-7,9]. Zhang et al. (2021) [10] was excluded from the primary synthesis because it is a retrospective uncontrolled case series (n=15), whereas the protocol specifies randomized trials and prospective or retrospective cohort studies. The expanded targeted-search candidates are incorporated in the supplementary narrative evidence section; Huespe and EMBARCAR are treated as distinct patient cohorts based on reviewer clarification. For the supplied-PDF set, five reports underwent full-text assessment: one uncontrolled case series was excluded and four comparative reports were retained. The supplementary log contains 10 unique candidates, of which two are provisionally excluded; the remaining records await varying degrees of eligibility confirmation and are not counted as confirmed inclusions.

Supplementary evidence synthesis (candidate reports; not pooled)

A multicenter matched cohort from Turkiye included 180 patients with OXA-48- or KPC-producing Enterobacterales infections. Ceftazidime-avibactam was associated with lower 30-day mortality than other appropriate antimicrobial therapy (35.6% [32/90] vs 56.7% [51/90]; P=.004) and higher 21-day clinical response (50.0% [45/90] vs 26.7% [24/90]; P=.002); adjusted odds ratios were 0.37 (95% CI, 0.19–0.71) for mortality and 3.32 (1.68–6.53) for clinical response. A single-centre cohort of 19 patients with MBL-producing Enterobacterales bloodstream infection treated with cefiderocol reported day-14 clinical cure in 15/19 (78.9%), day-14 mortality in 2/19 (10.5%), and treatment-emergent cefiderocol resistance in 3/19 (15.8%). These results are descriptive candidate evidence and are not included in the four-study supplied-PDF

comparative synthesis pending protocol eligibility and full-text adjudication.

## 4. MECHANISMS OF CARBAPENEM RESISTANCE AND THERAPEUTIC IMPLICATIONS

KPC enzymes

KPC enzymes are serine β-lactamases that hydrolyze penicillins, cephalosporins, and carbapenems.

Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam can be active against many KPC-producing isolates. Resistance may arise through KPC variants, increased enzyme expression, or permeability changes [1,2,4].

Metallo-β-lactamases

NDM, VIM, and IMP enzymes require zinc and hydrolyze most β-lactams, including carbapenems. Avibactam, vaborbactam, and relebactam do not directly inhibit MBLs. Aztreonam is stable to MBL hydrolysis, but co-produced serine β-lactamases may inactivate it; avibactam can inhibit many such enzymes. This supports aztreonam-avibactam and ceftazidime-avibactam plus aztreonam. Cefiderocol may also be active against selected MBL-producing isolates, subject to susceptibility testing [2,4,7,11].

OXA-48-like enzymes

OXA-48-like carbapenemases are class D enzymes identified in Enterobacterales. Ceftazidime-avibactam is an important option for susceptible OXA-48-like-producing CRE. Meropenem-vaborbactam and imipenem-relebactam may not provide reliable activity against these organisms [1,2,4].

Non-carbapenemase mechanisms

Some CRE display resistance through ESBL or AmpC production combined with reduced permeability. Therapeutic decisions should be based on the specific resistance profile and susceptibility results; molecular characterization may be useful when phenotypic findings are difficult to interpret [1,2,4].

## 5. CLINICAL EFFICACY OF NEWER ANTIBIOTICS

Ceftazidime-avibactam

Ceftazidime-avibactam combines a third-generation cephalosporin with avibactam, which inhibits several class A and C β-lactamases and selected class D enzymes. It is an important option for KPC- and OXA-48-like-producing CRE but is not active alone against MBL-producing CRE. Clinical observational studies report favorable outcomes in bloodstream and other serious infections compared with older, often polymyxin-based regimens, although observational designs are vulnerable to confounding. Dose adjustment according to renal function, susceptibility testing, and monitoring for resistance emergence are important [5,6,12].

Meropenem-vaborbactam

Meropenem-vaborbactam combines meropenem with vaborbactam, a boronic acid β-lactamase inhibitor with activity against KPC and selected serine β-lactamases, but not MBLs. In TANGO II, clinical cure at test of cure in the confirmed CRE population was 59.4% with meropenem-vaborbactam versus 26.7% with best available therapy. Day-28 mortality was 15.6% versus 33.3%, a numerically favorable difference that was not statistically significant. Renal-related adverse events were less frequent with the newer regimen. The trial was relatively small, and findings should be interpreted accordingly [5,13].

Imipenem-cilastatin-relebactam

This combination includes imipenem, cilastatin to inhibit renal metabolism of imipenem, and relebactam, a β-lactamase inhibitor active against selected class A and C enzymes. It can restore imipenem activity against certain KPC-producing organisms. RESTORE-IMI 1 compared the combination with imipenem-cilastatin plus colistin in imipenem-nonsusceptible Gram-negative infections and demonstrated a favorable safety profile, especially concerning nephrotoxicity. The CRE-specific evidence remains less extensive than that for some other agents, and it should not be relied on against MBL producers [2,14].

Cefiderocol

Cefiderocol is a siderophore cephalosporin that binds iron and uses bacterial iron transport systems to enter Gram-negative organisms. It may be active against selected KPC-, OXA-48-like-, and MBL-producing CRE. Susceptibility is not universal, and resistance may involve iron transport changes and β-lactamase mechanisms. Interpretation should account for CREDIBLE-CR findings, which raised mortality concerns in some subgroups, particularly carbapenem-resistant non-fermenters; these observations should not be extrapolated directly to CRE alone [2, 15-16].

Aztreonam-avibactam

Aztreonam is stable against MBL hydrolysis, while avibactam inhibits co-produced serine β-lactamases. In the ASSEMBLE phase III study of MBL-producing Gram-negative infections, clinical cure at test of cure in the microbiological intention-to-treat population was reported in 5/12 (41.7%) with aztreonam-avibactam and 0/3 with best available therapy; day-28 mortality was 8% and 33%, respectively. The very small sample limits inference; results are supportive rather than definitive [4,11, 17].

Ceftazidime-avibactam plus aztreonam

This combination is a clinically important strategy for MBL-producing Enterobacterales. Aztreonam is not hydrolyzed by MBLs, and avibactam inhibits many co-produced serine β-lactamases. Observational evidence supports use in severe infections, including bloodstream infections caused by NDM-producing organisms.

Coordinated administration, renal adjustment, and monitoring are needed; randomized head-to-head evidence remains limited [2,4,7].

Table 2. Expected activity patterns by carbapenemase mechanism.

| Antibiotic | KPC | OXA-48-like | NDM/other MBL |
|---|---|---|---|
| Ceftazidime-avibactam | Usually active if susceptible | Important option | Not active alone |
| Meropenem-vaborbactam | Important option | Not reliably active | Not active |
| Imipenem-cilastatin-relebactam | May be active | Not reliably active | Not active |
| Cefiderocol | Potentially active | Potentially active | Variable; test susceptibility |
| Aztreonam-avibactam | Potentially active | Potentially active | Mechanistically important option |
| Ceftazidime-avibactam + aztreonam | Potentially active | Potentially active | Mechanistically important option |

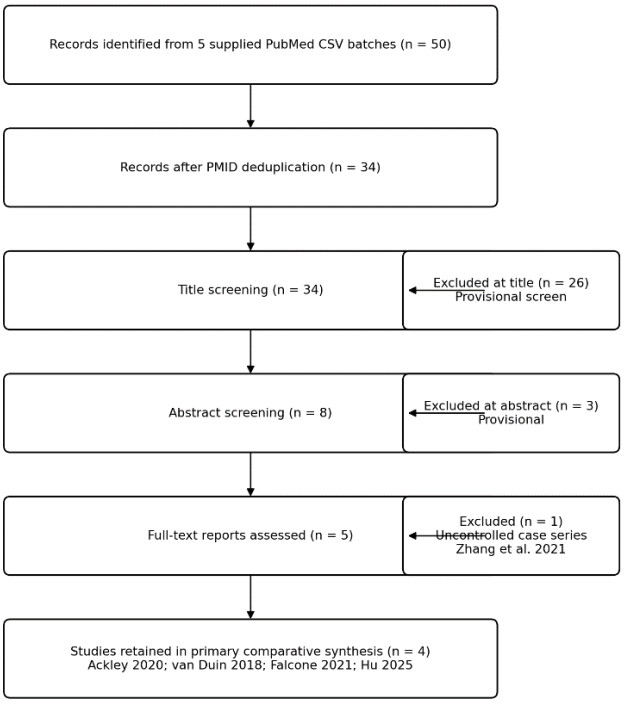


Figure 2. Full-text eligibility PRISMA flow diagram for the five accessible reports adjudicated against the review criteria. Note: Activity patterns are broad expectations and do not replace isolate-specific susceptibility testing.

## 6. COMPARATIVE CLINICAL EFFICACY

Supplementary comparative clinical evidence identified by targeted searching

The targeted supplementary search broadened the evidence discussed beyond the five supplied full-text reports. Karaba et al. reported similar 30-day mortality in a propensity-score-weighted cohort of 73 patients with KPC-producing Enterobacterales infections treated with ceftazidime-avibactam or meropenem-vaborbactam, while emergence of resistance was more frequent with ceftazidime-avibactam (12% vs 0%). Lee et al. reported an association between early ceftazidime-avibactam and lower 14-day mortality in a Korean CRE bacteremia cohort (n=194; 12.5% vs 32.1%; adjusted HR 0.34, 95% CI 0.12–0.98). The same Korean report appeared twice in the

candidate log and is counted once [18-19].

In MBL-producing Enterobacterales bacteremia, Huespe et al. used a multicenter target-trial emulation (n=243) to compare ceftazidime-avibactam plus aztreonam (n=93) with other active antibiotics (n=150). Reported 30-day mortality was 35% versus 47% (adjusted OR 0.63, 95% CI 0.43–0.91); clinical failure and adverse events also favored the combination. EMBARCAR's 2026 MBL-E subanalysis (n=140) is treated as a distinct cohort from Huespe et al., following reviewer clarification, and is considered separately in the supplementary evidence synthesis [20].

Aslan et al. reported a multicenter retrospective matched cohort [21] of OXA-48- or KPC-producing Enterobacterales infections in Türkiye (ceftazidime-avibactam n=90 versus other appropriate therapy n=90); 30-day mortality was 35.6% versus 56.7% (P=.004), and 21-day clinical response was 50.0% versus 26.7% (P=.002). A Romanian CPE bloodstream-infection cohort (n=308) was also identified, but its CPE definition and separately extractable CRE-specific subgroup require protocol-based adjudication before inclusion in the primary CRE synthesis [22].

Table 3. The list of Candidate study, Reported outcomes with Potential issue and current status.

| Candidate study | Design /sample | Comparison | Reported outcomes (source-derived) | Potential issue | Status |
|---|---|---|---|---|---|
| Karaba et al., 2026 | Prospective observational; propensity-weighted n=73; KPC-CRE | CZA vs MVB | 30-day mortality similar; resistance emergence 12% CZA vs 0% MVB | Full exact outcome extraction and bias assessment needed | Candidate |
| Lee et al., 2026 | Retrospective cohort; CRE bacteremia n=194 (CZA 32; BAT 162) | CZA vs BAT | 14-day mortality 12.5% vs 32.1%; P=.043; adjusted HR .34 (95% CI .12–.98); 30-day mortality not significant | MBL excluded; validate endpoint model from full text | Candidate |
| Huespe et al., 2025 | Multicenter target-trial emulation; MBL-E BSI n=243 (93 vs 150) | CZA+ ATM vs other active agents | 30-day mortality 35% vs 47%; adjusted OR .63 (95% CI .43–.91); clinical failure HR .65 (.44–.97); AEs 9.6% vs 22.8% | Potential cohort overlap with EMBARCAR 2026 | Candidate |
| Aslan et al., 2026 | Multicenter retrospective matched cohort n=180 (90 vs 90); OXA-48/KPC | CZA vs other appropriate therapy | Report describes improved clinical response and lower 30-day mortality with CZA; exact values pending complete extraction | Not included in primary quantitative synthesis | Candidate |

| | | | | | |
|---|---|---|---|---|---|
| Romanian CPE cohort, 2026 | Retrospective BSI cohort n=308 | CZA± ATM vs colistin/other | Mortality: 66.3% CZA±ATM, 79.3% colistin, 67.1% other; IPTW OR .48 (.26–.93), calendar-adjusted OR .72 (.37–1.42), nonsignificant | Effect attenuates after calendar-time adjustment; mixed regimen/carbapenemase population | Candidate |
| CRE BSI cohort, 2025 (PMID 40149038) | Retrospective cohort n=169 | CZA n=107 vs BAT | Adjusted mortality HR .86 (.40–1.83); microbiological cure OR 1.31 (.46–3.67); clinical response OR 1.39 (.35–5.43); AKI OR .56 (.11–2.80), no significant differences | Full-text data validation and coadministration details needed | Candidate |
| Boán et al., 2026 | Retrospective single-arm MBL-E BSI n=19 | Cefiderocol | Day-14 clinical cure 15/19 (78.9%); mortality 2/19 (10.5%); resistance emerged 3/19 (15.8%) | Include only if protocol permits noncomparative cohorts in descriptive synthesis | Candidate |
| EMBARCAR subanalysis, 2026 | Matched subanalysis n=140 | CZA+ ATM vs comparator | Reported mortality OR .18 (.05–.58), P=.005 | Possible overlap with Huespe; hold to prevent double counting | Hold |

Other candidates in the targeted-search lo including ASSEMBLE, GAME CHANGER, CEFI-SITA, and a mixed multidrug-resistant Gram-negative cohort were retained in screening notes as uncertain or provisionally excluded where CRE-specific outcome extractability was not established. These records are incorporated as candidate-level evidence tracking, not as confirmed independent studies. No pooled effect estimate is calculated because designs, populations, treatment comparators, and outcome definitions are heterogeneous and full eligibility adjudication is incomplete.

Four comparative reports from the five supplied full-text reports were retained in the PubMed-scope set. Ackley et al. compared ceftazidime-avibactam (CZA) with meropenem-vaborbactam (MVB) in 131 adults with CRE infection and reported clinical success of 61.9% and 69.2%, respectively (P=0.49). Falcone et al. observed 30-day mortality of 19.2% with CZA plus aztreonam versus 44.0% with other active antibiotics among 102 patients with MBL-producing Enterobacterales bloodstream infection (adjusted HR 0.37, 95% CI 0.13–0.74). van Duin et al. reported IPTW-adjusted 30-day hospital mortality of 9% with CZA-first treatment versus 32% with colistin-first treatment in a 137-patient CRE cohort. Hu et al. [9] reported higher clinical cure with CZA than polymyxin B in a single-center retrospective target-trial emulation (mITT 67.7% vs 43.8%; mortality difference not statistically significant; AKI was less frequent with CZA). Additional reports identified through supplementary citation searching are discussed as contextual evidence only and are not counted in the primary synthesis because their eligibility, full-text extraction, and potential cohort overlap have not been fully adjudicated [18,19,21–23]. Zhang et al. [10]'s 15-patient uncontrolled case series was excluded from the primary comparative synthesis by design criteria. These supplementary reports provide contextual evidence only. Their eligibility, outcome extraction, and potential cohort overlap remain under review; accordingly, they are not treated as independent confirmed studies in the primary synthesis.

Clinical cure

Clinical cure generally reflects resolution of signs and symptoms without additional antimicrobial therapy. Rates differ across studies because of infection type, severity, definitions, and follow-up. TANGO II supports meropenem-vaborbactam in confirmed CRE, while observational evidence supports ceftazidime-avibactam for selected KPC and OXA-48-like infections. Evidence for MBL-focused therapies is promising but less robust [5-7,13].

Mortality

Mortality in CRE infection is influenced by severity, septic shock, delay to active therapy, source control, comorbidity, renal dysfunction, and inappropriate empiric treatment. TANGO II mortality numerically favored meropenem-vaborbactam, but direct comparisons between newer agents are scarce and

trials may be underpowered [5-7,13].

Microbiological eradication

Microbiological response is usually assessed through follow-up cultures. It may not align exactly with clinical cure, and interpretation should account for infection site, indwelling devices, source control, colonization, and availability of repeat cultures [5,13,15].

Emergence of resistance

Resistance can arise during therapy. Ceftazidime-avibactam resistance may involve KPC variants and permeability changes; meropenem-vaborbactam resistance can involve KPC and porin alterations; cefiderocol resistance may involve iron transport and β-lactamase mechanisms. Clinical failure should prompt reassessment of susceptibility, source control, and microbiological diagnosis [2,5,7,15,24]. The table 4 presents the principal clinical outcomes extracted from the supplied full texts and supplementary evidence records. Comparisons are observational except where otherwise specified; estimates should not be interpreted as direct causal effects.

Table 4. Clinical outcome summary of comparative studies.

| Study(design;population) | Intervention vscomparator | Efficacy / mortality outcomes | Safety / caveats |
|---|---|---|---|
| Ackley et al., 2020 (retrospective multicenter cohort; CRE n=131) | CZA n=105 vs MVB n=26 | Clinical success 61.9% vs 69.2% (P=.49); 30-day mortality 19.1% vs 11.5% (P=.57); 90-day mortality 28.6% | AEs 34.3% vs 23.1% (P=.27); nephrotoxicity 29.2% vs 14.3% among baseline non-RRT (P=.16). Small MVB arm; CZA more often combined with other |

| | | | |
|---|---|---|---|
| | | vs 26.9% (P=.48). | agents. |
| van Duin et al., 2018 (CRACKLE multicenter observational cohort; n=137) | CZA-first n=38 vs colistin-first n=99 | IPTW-adjusted 30-day hospital mortality 9% vs 32%; P=.001. Adjusted probability of better 30-day disposition 64% (95% CI 57–71%). | Safety categories showed incident renal failure 5% with CZA vs 13% with colistin among safety set. Confounding by indication remains. |
| Falcone et al., 2021 (prospective observational MBL-E bloodstream infection; n=102) | CZA+ATM n=52 vs other active antibiotics n=50 | 30-day mortality 19.2% vs 44.0% (P=.007); adjusted HR .37 (95% CI .13–.74). Day-14 clinical failure 25.0% vs 52.0% (P=.005); adjusted HR .30 (95% CI .14–.65). | Comparative detailed AE extraction was not available in the transcription set; mechanism-defined cohort, nonrandomized treatment. |
| Hu et al., 2025 (target-trial emulation; mITT n=176 CRE) | CZA n=96 vs polymyxin B n=80 | Clinical cure 67.7% vs 43.8% (P=.001); microbiological eradication 75.0% vs 43.8% (P<.001). 28-day mortality 18.8% vs 25.0% (P=.316). | AKI 4.2% vs 16.3% (P=.007); GI events 13.5% vs 3.8% (P=.024). Weighted analysis; residual confounding persists. |
| Huespe et al., 2025 (multicenter target-trial emulation; MBL-E bacteremia n=243; supplementary candidate) | CZA+ATM n=93 vs other active antibiotics n=150 | 30-day mortality 35% vs 47%; adjusted OR .63 (95% CI .43–.91). Clinical failure 46% vs 53%; adjusted HR .65 (95% CI .44–.97). | AEs 9.6% vs 22.8%. Possible overlap with EMBARCAR subset; do not count latter as independent. |

| | | | |
|---|---|---|---|
| Aslan et al., 2026 (matched cohort;OXA-48/KPC infections n=180; supplementary candidate) | CZA n=90 vs other appropriate therapy n=90 | 21-day response 50.0% vs 26.7% (P=.002); 30-day mortality 35.6% vs 56.7% (P=.004); adjusted mortality OR .37 (95% CI .19–.71). | Contextual report; not included in primary synthesis |
| Lee et al., 2026 (retrospective CRE bacteremia cohort n=194; supplementary candidate; MBL excluded) | CZA n=32 vs best available therapy n=162 | 14-day mortality 12.5% vs 32.1% (P=.043); adjusted HR .34 (95% CI .12–.98). 30-day group-specific exact estimates not extracted. | Abstract-level extraction; requires full-text safety and adjustment validation. |

Integrated interpretation of clinical outcomes

Across the four supplied full-text comparative studies, outcome direction generally favored newer β-lactam-based regimens over polymyxin or older active comparators in selected cohorts, while direct comparison between ceftazidime-avibactam and meropenem-vaborbactam did not show a statistically significant clinical-success difference in Ackley et al. The strongest mechanism-specific signals in the supplied cohort evidence were observed for ceftazidime-avibactam plus aztreonam in MBL-producing Enterobacterales bloodstream infection (Falcone et al.) and for ceftazidime-avibactam versus polymyxin B in the target-trial emulation (Hu et al.). These findings are not pooled because populations, endpoints, comparators, and adjustment approaches differ. Supplementary comparative cohorts from 2025–2026 also report favorable selected outcomes for CZA-containing regimens, including in MBL bacteremia and OXA-48/KPC infections. Their results are considered supportive contextual evidence while candidate eligibility and full-text outcome extraction are being finalized. Huespe and EMBARCAR are treated as distinct cohorts, based on reviewer clarification, and their reports are considered separately.

Newer antibiotics have improved the therapeutic options for CRE infections, but their clinical value is dependent on carbapenemase mechanism, isolate susceptibility, infection site, illness severity, timely active therapy, and source control. Ceftazidime-avibactam and meropenem-vaborbactam are important options for susceptible KPC-producing CRE; ceftazidime-avibactam is also relevant to OXA-48-like producers. For MBL-producing Enterobacterales, ceftazidime-avibactam plus aztreonam and aztreonam-avibactam are mechanistically appropriate options where susceptibility and access support use, while cefiderocol may be considered for susceptible isolates. Available comparative evidence is mostly observational and heterogeneous; therefore, treatment recommendations should be individualized and guided by susceptibility testing and current infectious-disease guidance. Antimicrobial stewardship, renal-dose optimization, toxicity monitoring, and surveillance for resistance emergence remain central.

## 7. SAFETY AND ADVERSE DRUG REACTIONS

Safety is central because CRE patients often have critical illness, comorbidities, renal dysfunction, and polypharmacy. Newer β-lactam-based regimens generally avoid some toxicity associated with polymyxins, but they still require dose optimization and surveillance [13-15].

Nephrotoxicity

Polymyxins and aminoglycosides have important renal toxicity risks. TANGO II reported fewer renal-related adverse events with meropenem-vaborbactam than with best available therapy. All newer agents require renal assessment and dose adjustment where indicated [6,13-14].

Gastrointestinal effects

Nausea, vomiting, diarrhea, abdominal discomfort, and antibiotic-associated colitis may occur. Monitor symptoms and consider duration and concurrent medications [11, 13-15,17].

Hypersensitivity

β-lactams can cause reactions from rash to severe allergy. Assess prior reaction type, timing, and severity before prescribing [11,13-15,17].

Hepatic effects

Liver enzyme abnormalities may occur with some regimens. Consider monitoring in patients with liver disease or prolonged therapy, and review agent-specific labeling [11,13-15,17].

Neurological effects

Elevated β-lactam concentrations, particularly with renal impairment, may cause confusion, encephalopathy, myoclonus, or seizures. Reassess dosing and neurological status in vulnerable patients. [1,2]

Table 5. Safety considerations and monitoring.

| Agent | Key considerations |
|---|---|
| Ceftazidime-avibactam | Renal dose adjustment, hypersensitivity, gastrointestinal effects |
| Meropenem-vaborbactam | Renal adjustment, gastrointestinal effects, neurological toxicity in susceptible patients |
| Imipenem-cilastatin-relebactam | Renal adjustment, seizure risk, gastrointestinal effects |
| Cefiderocol | Renal adjustment, hypersensitivity, gastrointestinal effects; assess clinical response |
| Aztreonam-avibactam | Renal adjustment, hypersensitivity, hepatic enzyme abnormalities |
| Ceftazidime-avibactam + aztreonam | Renal adjustment of both agents, hypersensitivity, gastrointestinal effects, liver enzyme monitoring |

## 8. ROLE OF CLINICAL PHARMACY IN CRE MANAGEMENT

Antimicrobial selection

Selection should consider carbapenemase type, susceptibility results, infection site and severity, renal function, prior antibiotic exposure, allergy history, and local availability. Pharmacists can support interpretation and regimen optimization [1-3].

Dose optimization

Assess creatinine clearance, renal replacement therapy, changing renal function, pharmacokinetic variability, and infusion strategy where relevant. Reassess dosing frequently in critical illness [1,2].

Antimicrobial stewardship

Stewardship includes confirming infection rather than colonization, obtaining appropriate cultures, reviewing susceptibility results, de-escalating where possible, limiting duration, avoiding unnecessary combination therapy, and monitoring resistance [1-3].

Therapeutic monitoring

Monitor renal function, hepatic tests when appropriate, blood counts, vital signs, microbiological cultures, hypersensitivity, neurological status, and clinical response [1-2].

Table 6. Suggested monitoring parameters.

| Parameter | Purpose |
|---|---|
| Serum creatinine / creatinine clearance | Renal assessment and dose adjustment |
| Liver function tests | Detect hepatic abnormalities where relevant |
| Complete blood count | Identify hematological changes |
| Follow-up cultures | Evaluate pathogen persistence or eradication |
| Temperature and vital signs | Assess response and deterioration |
| Hypersensitivity signs | Early recognition of allergic reactions |
| Neurological status | Identify possible neurotoxicity |

## 9. DISCUSSION

The evidence summarized in this manuscript supports the expanded role of newer antibiotics in CRE infection, while underscoring that drug choice should be driven by resistance mechanism and susceptibility rather than the CRE label alone. KPC, OXA-48-like, and MBL producers differ materially in susceptibility profiles [7,11,13–15,17,25].

A recent 2026 systematic review and meta-analysis has already evaluated mortality with selected β-lactam/β-lactamase inhibitor combinations versus best available therapy in CRE. The present review's intended added value is a broader agent scope and a focused synthesis of clinical cure, microbiological response, adverse effects, and resistance emergence, with outcomes interpreted by carbapenemase mechanism. This distinction must be supported by a completed search and explicit comparison of overlapping review scopes before submission [25]. Meropenem-vaborbactam and ceftazidime-avibactam are important options for susceptible KPC-producing organisms. Ceftazidime-avibactam is particularly relevant to OXA-48-like producers. Imipenem-cilastatin-relebactam offers another option for selected isolates, although CRE-specific clinical evidence is comparatively limited. Cefiderocol and aztreonam-based approaches have value against selected MBL-producing pathogens [1,2,5–7,13,25].

Safety is a meaningful advantage of newer β-lactam-based agents over polymyxin-heavy regimens, especially regarding renal injury. However, the TANGO II safety result should not be generalized indiscriminately across all agents or clinical contexts. Individual drug dosing and monitoring remain necessary [6,13,14]. Appropriate early therapy is important in severe CRE infections. Empiric decisions in sepsis should incorporate previous cultures, local resistance epidemiology, prior antimicrobial exposure, and patient risk. Once microbiology becomes available, definitive treatment should be optimized and unnecessary breadth reduced [1-3].

Routine combination therapy is not automatically required when a newer β-lactam is active. Ceftazidime-avibactam plus aztreonam is a specific mechanistically complementary approach for selected MBL-producing Enterobacterales. Other combinations should be justified by clinical and microbiological evidence [1,2,7]. Interpretation is constrained by small CRE-specific trial populations, mixed infection sites, inconsistent outcome definitions, observational confounding, and few head-to-head comparisons. Carbapenemase distribution also varies by region. The PRISMA flow and primary synthesis reflect the supplied PubMed exports and accessible reports, not an exhaustive multi-database search

## 10. LIMITATIONS

The evidence base is heterogeneous in design, infection type, comparator, resistance mechanism, and endpoint definition. Small trial subgroups limit precision, while observational estimates may be affected by illness severity, timing of active therapy, source control, and baseline renal function. Direct comparisons among newer agents remain scarce; findings should be interpreted within the documented search and report-availability scope.

## 11. FUTURE RESEARCH DIRECTIONS

Conduct adequately powered head-to-head trials in confirmed CRE infections.

Expand clinical evidence for MBL-producing organisms, especially NDM-producing Enterobacterales.

Perform surveillance for resistance emergence and changing susceptibility patterns. Study dosing in critical illness, renal replacement therapy, and altered drug clearance. Evaluate stewardship interventions and duration optimization.

Assess cost-effectiveness in healthcare systems with differing resources.

## 12. CONCLUSION

Newer antibiotics have improved the therapeutic options for CRE infections, but their clinical value depends on carbapenemase mechanism, isolate susceptibility, infection site, illness severity, timely active therapy, and source control. Ceftazidime-avibactam and meropenem-vaborbactam are important options for susceptible KPC-producing CRE; ceftazidime-avibactam is also relevant to OXA-48-like producers. For MBL-producing Enterobacterales, ceftazidime-avibactam plus aztreonam and aztreonam-avibactam are mechanistically appropriate options where susceptibility and access support use, while cefiderocol may be considered for susceptible isolates. Available comparative evidence is predominantly observational and heterogeneous; treatment should be individualized and guided by susceptibility testing and current infectious-disease guidance. Antimicrobial stewardship, renal-dose optimization, toxicity monitoring, and surveillance for resistance emergence remain central.

Conflict of Interest

Conflict of Interest: The authors declare that they have no known conflicts of interest.

Funding

There is no external funding for this research.

Ethics Approval

Ethics Approval: Not applicable to a review of published literature.

Author contributions

The first author drafted the initial manuscript, leading the literature synthesis, methodology design, and primary text development. The corresponding author supervised the project, providing structural direction, technical validation, and critical review. All co-authors contributed to identifying data sources, extracting and validating evidence, constructing comparison tables, and conducting detailed manuscript revisions. All authors reviewed and approved the final manuscript for publication.

## 13. ACKNOWLEDGEMENT

The authors gratefully acknowledge the invaluable contributions of various academic platforms and open-access databases specifically PubMed, PubMed Central, Cochrane Library, BMJ Clinical Evidence, DOAJ, Google Scholar, Embase, and MEDLINE for facilitating transparent, unrestricted access to scholarly literature, peer-reviewed clinical evidence, and biomedical research that made this study possible.

## REFERENCES

1. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections. Clin Infect Dis. 2024. doi:10.1093/cid/ciae403.
2. Tamma PD, Bonomo RA, et al. Infectious Diseases Society of America 2026 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections. IDSA; published July 30, 2026. Available at: https://www.idsociety.org/practice-guideline/amr-guidance/.
3. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European Society of Clinical Microbiology and Infectious Diseases guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European Society of Intensive Care Medicine). Clin Microbiol Infect.

4. 2022;28(4):521–547. doi:10.1016/j.cmi.2021.11.025.
5. Tan X, Kim HS, Baugh K, Huang Y, Kadiyala N, Wences M, et al. Therapeutic options for metallo-β-lactamase-producing Enterobacterales. Infect Drug Resist. 2021;14:125–142. doi:10.2147/IDR.S246174.
6. Ackley R, Roshdy D, Meredith J, et al. Meropenem-vaborbactam versus ceftazidime-avibactam for treatment of carbapenem-resistant Enterobacteriaceae infections. Antimicrob Agents Chemother. 2020;64(5):e02313-19. doi:10.1128/AAC.02313-19.
7. van Duin D, Lok JJ, Earley M, et al; Antibacterial Resistance Leadership Group. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis. 2018;66(2):163–171. doi:10.1093/cid/cix783.
8. Falcone M, Daikos GL, Tiseo G, et al. Efficacy of ceftazidime-avibactam plus aztreonam in patients with bloodstream infections caused by metallo-β-lactamase-producing Enterobacterales. Clin Infect Dis. 2021;72(11):1871–1878. doi:10.1093/cid/ciaa586.
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
10. Hu N, Xiao F, Chen Y, Gu Q, Liang P, Xu Y, et al. Efficacy, safety, and cost-effectiveness analysis of ceftazidime-avibactam versus polymyxin B in the treatment of carbapenem-resistant Enterobacteriaceae
1. infections: a target trial emulation. Infect Dis Ther. 2025;14(7):1419–1437. doi:10.1007/s40121-025-01164-9.
11. Zhang HL, Cressman L, Lautenbach E. Real-world clinical outcomes of meropenem/vaborbactam for treatment of carbapenem-resistant Enterobacterales infections. J Glob Antimicrob Resist. 2021;27:299–302. doi:10.1016/j.jgar.2021.09.015.
12. Daikos GL, Cisneros JM, Carmeli Y, et al. Aztreonam-avibactam for the treatment of serious infections caused by metallo-β-lactamase-producing Gram-negative pathogens: a phase 3 randomized trial (ASSEMBLE). JAC Antimicrob Resist. 2025;7(4):dlaf131. doi:10.1093/jacamr/dlaf131.
13. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa infections: the REPRISE trial. Lancet Infect Dis. 2016;16(6):661–673.
14. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II randomized clinical trial. Infect Dis Ther. 2018;7:439–455. doi:10.1007/s40121-018-0214-1.
15. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. Clin Infect Dis. 2020;70(9):1799–1808. doi:10.1093/cid/ciz530.
16. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomized, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis. 2021;21(2):226–240. doi:10.1016/S1473-3099(20)30796-9.
17. Boán J, Aizpurúa C, Chacón S, et al. Cefiderocol for the treatment of bloodstream infection due to MBL-producing Enterobacterales: a single-center retrospective cohort. Int J Antimicrob Agents. 2026; article 108053. doi:10.1016/j.ijantimicag.2026.108053.
18. Carmeli Y, Cisneros JM, Paul M, et al. Aztreonam-avibactam versus meropenem for the treatment of serious infections caused by Gram-negative bacteria (REVISIT): a descriptive, multinational, open-label, phase 3, randomised trial. Lancet Infect Dis. 2025;25(2):218–230. doi:10.1016/S1473-3099(24)00499-7.
19. Karaba SM, Hareza DA, Munita JM, et al. Comparative outcomes of ceftazidime-avibactam versus meropenem-vaborbactam for KPC-producing Enterobacterales infections. Antimicrob Agents Chemother. 2026;70(5):e01602-25. doi:10.1128/aac.01602-25.
20. Lee Y, Seong JE, Lee JA, et al. Ceftazidime-avibactam effectiveness in carbapenem-resistant Enterobacterales bacteremia: a retrospective cohort study in Korea. J Korean Med Sci. 2026;41(26):e183.
21. doi:10.3346/jkms.2026.41.e183.
22. Huespe IA, Huaier Arriazu EF, Sanchez M, et al. Mortality of metallo-β-lactamase-producing Enterobacterales bacteremias with combined ceftazidime-avibactam plus aztreonam vs. other active antibiotics: a multicenter target trial emulation. Lancet Reg Health Am. 2025;49:101175. doi:10.1016/j.lana.2025.101175.
23. Aslan AT, Tanriverdi ES, Yıldız Kaya S, et al. Comparison of ceftazidime-avibactam with other appropriate antimicrobial therapy for the treatment of OXA-48- or KPC-producing Enterobacterales infections in Türkiye: a multi-centre retrospective matched-cohort study. Int J Antimicrob Agents. 2026;67(1):107650. doi:10.1016/j.ijantimicag.2025.107650.
24. Ormeneanu VP, Zanfirescu A, Andrei C, Dumitru F, Anghel F, Adam R, Negreș S. Ceftazidime-avibactam versus colistin-based regimens for carbapenem-resistant Enterobacterales bloodstream infections: a six-year retrospective cohort and 30-day mortality analysis. Microorganisms. 2026;14(9):2102.
25. doi:10.3390/microorganisms14092102. PMID:42795681.

26. Arboleda D, Buitrago C, Vergara EP, Nocua-Báez LC, Saavedra CH, Cortés JA. Impact of antibiotic therapy with ceftazidime-avibactam vs. best available therapy in adult patients with bacteremia caused by carbapenem-resistant Enterobacterales. Antibiotics (Basel). 2025;14(3):226. doi:10.3390/antibiotics14030226. PMID:40149038.
27. Shields RK, Potoski BA, Haidar G, Hao B, Doi Y, Chen L, et al. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis. 2016;63(12):1615–1618. doi:10.1093/cid/ciw636.
28. Al Shammari BR. Novel β-lactam/β-lactamase inhibitors versus best available therapy on the mortality-related carbapenem-resistant Enterobacterales infection: a systematic review and meta-analysis. Antibiotics (Basel). 2026;15(9):928. doi:10.3390/antibiotics15090928