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REVIEW



An update on beta-lactam–beta-lactamase inhibitor combinations for the treatment of carbapenem-resistant Gram-negative pathogens

Ilias Karaiskos^a, Aikaterini Gkoufa^b, Evdoxia Kyriazopoulou^c, Eleni Polyzou^{d,e}, Vasiliki Rapti^f, Konstantinos Ioannidis^g, Evangelia Chrysanthopoulou^c, Zoe Athanassa^h, Karolina Akinosoglou^{d,e,i,*}, Garyphalia Poulakou^{f,*} and On behalf of the Study Group of the Hellenic Group for the Combat of Antimicrobial Resistance in Critically Ill Patients of the Hellenic Society of Chemotherapy

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ABSTRACT

Introduction: Carbapenem-resistant Gram-negative bacteria represent a major global health threat driven by diverse β -lactamase enzymes, particularly KPC, metallo- β -lactamases, and OXA-type carbapenemases, leading to limited treatment options and high mortality. The development of novel β -lactam/ β -lactamase inhibitor (BLBLI) combinations has significantly improved outcomes in resistant infections by restoring β -lactam activity against key resistance mechanisms, primarily among Enterobacterales.

Areas covered: This expert review summarizes the pharmacology, clinical efficacy, and safety of approved and emerging BLBLIs, including ceftolozane–tazobactam, cefepime–enmetazobactam, ceftazidime–avibactam, meropenem–vaborbactam, imipenem–relebactam, aztreonam–avibactam, and sulbactam–durlobactam. Emphasis is placed on activity against carbapenem-resistant Enterobacterales, difficult-to-treat *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii*. Evidence derives from clinical trials, real-world studies, and pharmacokinetic/pharmacodynamic (PK/PD) analyses from major databases (PubMed, Scopus, Web of Science) from inception through January 2026, focusing on dosing optimization and outcomes.

Expert opinion: BLBLIs have transformed the management of KPC-producing infections, markedly reducing mortality compared with legacy therapies. However, their impact is threatened by the rising prevalence of metallo- β -lactamases and the persistent therapeutic gap in carbapenem-resistant *A. baumannii*. Future success will depend on next-generation inhibitors with broader enzyme coverage, optimized dosing strategies guided by PK/PD principles, and robust antimicrobial stewardship to preserve long-term efficacy.

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β -lactam/ β -lactamase inhibitors; pharmacokinetics/pharmacodynamics; carbapenem-resistant Enterobacterales; difficult-to-treat *Pseudomonas aeruginosa*; avibactam; vaborbactam; relebactam; sulbactam–durlobactam

1. Introduction

Carbapenem-resistant Gram-negative bacteria (CR-GNB) represent a rapidly expanding global health threat driven by a complex resistome including class A carbapenemases (e.g. *Klebsiella pneumoniae* carbapenemase [KPC]), class B metallo- β -lactamases (MBLs) such as New Delhi metallo- β -lactamase (NDM), Verona integron-encoded metallo- β -lactamase (VIM), and Imipenemase (IMP), and class D oxacillinases (OXA-48-like enzymes), together with non-enzymatic mechanisms such as porin loss and efflux pump overexpression [1–3]. The World Health Organization has designated carbapenem-resistant Enterobacterales and carbapenem-resistant *Acinetobacter baumannii* as critical and carbapenem-resistant *Pseudomonas aeruginosa* as high priority pathogens because of high mortality, limited treatment options, and rapid global dissemination [4]. Historically, treatment relied on

polymyxins, tigecycline, fosfomycin, and aminoglycosides, agents limited by suboptimal pharmacokinetics, toxicity, and inferior clinical outcomes [5].

Novel β -lactam/ β -lactamase inhibitor (BLBLI) combinations have substantially expanded therapeutic options. Diazabicyclooctanes (DBOs; avibactam, relebactam) and cyclic boronates (vaborbactam) inhibit class A and C β -lactamases and selected class D enzymes, restoring activity of partner β -lactams against resistant pathogens [6,7]. Approved combinations, ceftazidime–avibactam (CAZ-AVI), meropenem–vaborbactam (MER-VAB), and imipenem–relebactam (IMI-REL), demonstrate improved clinical outcomes against KPC-producing Enterobacterales. Activity against OXA-48-like producers is primarily retained by CAZ-AVI. For difficult-to-treat *P. aeruginosa*, clinical efficacy is mainly supported by CAZ-AVI

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Article highlights

- The development of novel β -lactam/ β -lactamase inhibitor (BLBLI) combinations has transformed the management of carbapenem-resistant Enterobacterales, restoring β -lactam activity and significantly improving clinical outcomes compared with historical polymyxin-based regimens.
- Market-approved BLBLIs, including ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–relebactam, demonstrate consistent real-world effectiveness against KPC-producing organisms, with improved safety profiles and reduced nephrotoxicity; activity against OXA-48 producers remains largely confined to ceftazidime–avibactam.
- The introduction of sulbactam–durlobactam represents a major advance for carbapenem-resistant *Acinetobacter baumannii*, enabling effective, less toxic therapy and marking a shift away from polymyxin-based regimens for this historically difficult-to-treat pathogen.
- Agents such as ceftolozane–tazobactam and cefepime–enmetazobactam expand the therapeutic landscape, with ceftolozane–tazobactam playing a key role in difficult-to-treat *Pseudomonas aeruginosa*, and cefepime–enmetazobactam providing a carbapenem-sparing option for ESBL-producing Enterobacterales.
- Pharmacokinetic/pharmacodynamic optimization, particularly prolonged or continuous infusion strategies, is essential to achieve aggressive exposure targets and maximize therapeutic success in critically ill patients.
- Metallo- β -lactamase-producing pathogens represent the major unresolved resistance gap for current BLBLIs, with aztreonam–avibactam emerging as a targeted strategy supported by Phase III clinical evidence.
- Next-generation inhibitor platforms, including cyclic boronates and β -lactam enhancers, aim to broaden activity to both serine and metallo- β -lactamases, potentially redefining future resistance management.

and IMI-REL and an earlier BLBLI combination, ceftolozane–tazobactam (C-T). These regimens are also associated with substantially lower nephrotoxicity compared with polymyxin-based therapy [6–9]. These agents have effectively reclassified many carbapenem-resistant isolates into treatable phenotypes in clinical practice [10,11].

However, major therapeutic gaps remain for MBL-producing organisms and certain non-fermenters [6–9]. New BLBLI strategies aim to expand enzyme coverage and optimize pharmacokinetics/pharmacodynamics (PK/PD) exposure in critically ill patients [8]. Aztreonam–vibactam (ATM-AVI) overcomes MBL-mediated resistance by protecting aztreonam from co-produced serine β -lactamases [12], while sulbactam–durlobactam (SUL-DUR) represents a targeted approach for carbapenem-resistant *A. baumannii* (CRAB) [13]. Additional agents, including cefepime–taniborbactam, cefepime–zidebactam, and imipenem/cilastatin–funobactam further target emerging resistance mechanisms [8,14]. In parallel, newer BLBLI combinations, such as cefepime–enmetazobactam (FEP-ETZ) [15], and C-T [16], expand treatment options for infections caused by extended spectrum β -lactamase (ESBL)-producing Enterobacterales, although C-T remains particularly valuable for difficult to treat resistance (DTR) *P. aeruginosa* [17].

This narrative review was conducted through a structured literature search of PubMed, Scopus, Web of Science, and the Cochrane Library for English-language publications available from inception up to January 2026. Search terms included β -lactam– β -lactamase inhibitors, novel β -lactamase inhibitors, next-generation BLBLIs, ceftolozane–tazobactam, cefepime–

enmetazobactam, ceftazidime–avibactam, meropenem–vaborbactam, imipenem–relebactam, imipenem–cilastatin–relebactam, aztreonam–avibactam, sulbactam–durlobactam, cefepime–taniborbactam, cefepime–zidebactam, imipenem–cilastatin–funobactam, meropenem–parlubactam, meropenem–nacubactam, pharmacokinetics, pharmacodynamics, clinical outcomes, and real-world evidence. Original investigations, clinical trials, observational studies, systematic reviews, meta-analyses, and regulatory or guideline documents were included. Reference lists of key publications and recent expert commentaries in pharmacology-focused journals were manually screened to ensure comprehensive coverage of emerging agents.

This narrative review evaluates contemporary BLBLI combinations targeting carbapenem-resistant Enterobacterales, DTR *P. aeruginosa*, and *A. baumannii*, integrating inhibitor chemistry, β -lactamase coverage, PK/PD principles, and clinical outcomes to define the evolving therapeutic landscape and priorities for optimized use. In addition to approved agents, we highlight emerging intravenous BLBLIs designed to address key resistance gaps. Collectively, licensed and investigational intravenous BLBLIs are redefining the management of severe Gram-negative infections, enabling a shift from salvage therapy toward mechanism-driven, precision treatment, with ongoing clinical and real-world data essential to guide optimal use and stewardship.

2. Landscape of β -lactamases underpinning carbapenem resistance

Antimicrobial resistance among Gram-negative pathogens is primarily mediated by β -lactamases, including ESBLs, AmpC cephalosporinases, and carbapenemases (Ambler classes A–D) disseminated through mobile genetic elements and high-risk clones [18,19]. Carbapenemases currently account for most carbapenem resistance in Enterobacterales and non-fermenters and include serine enzymes (KPC, OXA-types) and MBLs (NDM, VIM, IMP) [2]. Resistance is further amplified by reduced outer membrane permeability and efflux overexpression, producing high-level resistance, cross-resistance, and therapeutic failure [20,21].

2.1. Class A carbapenemases: KPC family

Class A carbapenemases hydrolyze most β -lactams and are partially inhibited by classical inhibitors and boronic derivatives [3,22]. The most clinically relevant enzymes include KPC, SME, IMI, NMC-A, and selected GES variants, with KPC predominating in *K. pneumoniae* [21,22]. More than 200 KPC variants exist [23], with KPC-2 and KPC-3 most prevalent globally [24,25]. Carbapenem-hydrolyzing GES variants continue to evolve, reflecting expanding substrate profiles [26]. KPC-producing organisms remain endemic in Southern and Southeastern Europe, including Greece, with persistent ICU transmission, and have disseminated globally via clonal expansion and antimicrobial pressure-driven diversification [22,24,25].

2.2. Class B carbapenemases: metallo- β -lactamases

MBLs are zinc-dependent enzymes hydrolyzing most β -lactams while sparing aztreonam [3,18,22]. They are not

inhibited by currently available inhibitors and are frequently plasmid encoded within integrons, facilitating horizontal transfer and multidrug resistance [21,27]. Major families include NDM, VIM, and IMP, with more than 90 NDM, 96 VIM, and 110 IMP variants described [23]. NDM has expanded most rapidly worldwide; VIM remains prevalent in Southern Europe, particularly in *P. aeruginosa*, while IMP persists at lower levels [1,3,22]. European epidemiology is heterogeneous, with northern NDM predominance and Mediterranean coexistence of NDM and VIM [28]. Global dissemination remains strongly linked to South Asia with spread across the Middle East, Africa, and Southeast Asia [22].

2.3. Class D carbapenemases in Enterobacterales

Among Enterobacterales, class D carbapenemases are mainly OXA-48-like enzymes. Alone, they weakly hydrolyze carbapenems but confer resistance when combined with porin loss and ESBL co-production [3,18,24]. Variants include OXA-48, OXA-181, and OXA-232 [23]. They hydrolyze penicillins efficiently but poorly hydrolyze extended-spectrum cephalosporins and resist classical inhibitors [3,19,21,22]. OXA-48-like enzymes are endemic across Europe with reservoirs in North Africa and the Middle East facilitating transmission [21,22,24]. The *bla*_{OXA-48} gene, first identified in Turkey in 2001, has spread globally via plasmids and clonal expansion [29]. Detection is challenging due to modest carbapenem MIC elevation, contributing to silent dissemination and delayed infection control [24].

2.4. Class D carbapenemases in Acinetobacter baumannii

In *A. baumannii*, carbapenem resistance is driven primarily by class D oxacillinases, particularly OXA-23 and overexpressed intrinsic OXA-51-like enzymes. These are often accompanied by efflux pump overexpression and permeability defects, producing high-level multidrug resistance [30]. Unlike Enterobacterales, carbapenemase genes in *A. baumannii* are frequently chromosomally encoded or mobilized by insertion sequences, promoting stable clonal persistence in hospital environments.

OXA-23 is now the dominant carbapenemase worldwide, with endemic circulation across Europe, Asia, Africa, and South America and spread mediated by epidemic international clones [31]. This resistance architecture has rendered many conventional β -lactams ineffective and contributes substantially to the high mortality associated with CRAB infections.

3. Structural evolution of modern β -lactamase inhibitors

Limited activity of early β -lactam-derived inhibitors (clavulanate, sulbactam, tazobactam) against carbapenemases prompted development of non- β -lactam scaffolds with broader coverage, resulting in two principal platforms: diazabicyclooctanes (DBOs) and cyclic boronates [6,7].

DBO inhibitors (i.e. avibactam, relebactam, zidebactam, nacubactam) form reversible covalent complexes with class A and class C β -lactamases and variably inhibit selected class

D enzymes, particularly OXA-48-like carbapenemases [14,20,32]. Zidebactam and nacubactam additionally bind to penicillin-binding protein-2 (PBP2), providing intrinsic antibacterial activity and enhancing partner β -lactam efficacy [14,20,32].

Cyclic boronates, exemplified by vaborbactam, act as transition-state analogues with potent inhibition of class A carbapenemases, especially KPC, while retaining activity against class C enzymes [6,7]. Pralurbactam shows similar class A and C inhibition but limited class D activity and inconsistent efficacy against MBL-producing organisms and carbapenem-resistant *P. aeruginosa* [33]. Next-generation boronates such as taniborbactam and xeruborbactam extend activity to many class D enzymes and clinically relevant MBLs, addressing a major limitation of earlier BLBLI platforms [32,34].

4. Pharmacokinetic and pharmacodynamic (PK/PD) principles guiding BLBLI therapy

BLBLI efficacy depends on achieving simultaneous pharmacodynamic targets for both the β -lactam and inhibitor components. Traditional β -lactam targets required free drug concentrations above the MIC for 40–70% of the dosing interval, whereas critically ill populations often require more aggressive exposure, approaching 100% the fraction of the dosing interval that free drug concentrations exceed MIC ($fT > 4 \times \text{MIC}$) to optimize bacterial killing and suppress resistance [35–37]. Inhibitors demonstrate molecule-specific PK/PD drivers: avibactam correlates with time above a threshold concentration ($fT > CT$), while relebactam and vaborbactam relate more closely to exposure indices such as fAUC/MIC (free area under the curve (AUC) to MIC ratio) [38]. Durlobactam exhibits exposure-dependent activity best described by fAUC/MIC targets, complementing the time-dependent activity of sulbactam [39–41], whereas tazobactam [42] and enmetazobactam [43] primarily function through maintaining concentrations above inhibitory thresholds, sufficient to protect the partner β -lactam. Effective therapy therefore requires coordinated, joint PK/PD optimization.

Three principles consistently improve target attainment: loading doses to compensate for expanded volume of distribution, prolonged or continuous infusion to stabilize concentrations, and therapeutic drug monitoring where available [44]. For ATM-AVI, simulations show efficacy when aztreonam exceeds the MIC for ~60% of the interval and avibactam remains above 2.5 mg/L for $\geq 50\%$, supporting prolonged infusion every 6 h [45]. For SUL-DUR, translational PK/PD analyses demonstrate that achieving high sulbactam $fT > \text{MIC}$ together with adequate durlobactam exposure (fAUC/MIC targets) is critical for activity against CRAB, with extended infusion regimens improving probability of target attainment across renal function groups [39–41]. Similarly, C-T efficacy is driven by maintaining ceftolozane concentrations above the MIC for ≥ 50 –100% of the dosing interval, with tazobactam exposure ensuring sustained β -lactamase inhibition [42,46], while FEP-ETZ demonstrates optimal activity when cefepime achieves high $fT > \text{MIC}$ in conjunction with enmetazobactam concentrations sufficient to inhibit ESBL enzymes, supporting prolonged infusion strategies in severe infections [43].

Monte Carlo simulations demonstrate that intermittent dosing of CAZ-AVI and MER-VAB frequently fails aggressive PK/PD targets at contemporary MIC distributions, whereas extended or continuous infusion markedly improves joint probability of attainment [36,47]. Similar findings have been reported for C-T, where prolonged infusion enhances target attainment in infections due to *P. aeruginosa* with elevated MICs, and for FEP-ETZ in ESBL-producing Enterobacterales. Clinical studies consistently report reduced target failure and improved microbiological eradication with prolonged infusion, particularly in patients with high drug clearance [47].

Critical illness substantially alters pharmacokinetics through increased volume of distribution, hypoalbuminemia, and variable renal elimination. Augmented renal clearance (ARC) is strongly associated with subtherapeutic exposure, while renal replacement therapies variably remove both β -lactams and inhibitors depending on modality and effluent rate, necessitating individualized dosing strategies [48]. These effects are particularly relevant for agents such as ceftolozane, cefepime, and sulbactam, which are predominantly renally cleared [8]. Prolonged infusion consistently improves exposure reliability in these settings [37].

Pathogen-directed dosing further refines therapy. In MBL-producing Enterobacterales, aztreonam (ATM) stability combined with avibactam protection supports prolonged infusions ensuring synchronized target attainment across renal function groups and infection sites [42]. For KPC infections, MER-VAB administered as 3-h infusions optimizes exposure, particularly with augmented clearance [8,9,44], whereas prolonged (2–3 h) or continuous CAZ-AVI infusion maximizes activity against ESBLs, AmpC producers, KPC, OXA-48-like enzymes, and resistant *P. aeruginosa* [38]. For difficult-to-treat *P. aeruginosa*, C-T prolonged infusion (3 h) enhances PK/PD target attainment and microbiological response [42,46], while FEP-ETZ provides a rational option for ESBL-producing Enterobacterales with optimized exposure through extended infusion (2–4 h) [43]. In CRAB, SUL-DUR dosing strategies that ensure simultaneous attainment of sulbactam time-dependent targets and durlobactam exposure thresholds achieve bactericidal activity and support its role as a first-line or salvage therapy [39–41]. PK/PD parameters and dosage strategies of approved BLBLIs are depicted in Table 1 [5–9,12,14,32,35–48].

5. Ceftolozane–tazobactam

Ceftolozane–tazobactam (C-T) is a parenteral cephalosporin/ β -lactamase inhibitor combination approved by the U.S. Food and Drug Administration (FDA) [49] in 2014 and by the European Medicines Agency (EMA) [50] in 2015 for the treatment of complicated intra-abdominal infections (cIAI) with metronidazole, cUTI, including acute pyelonephritis and with subsequent label expansion to include hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) [49,50]. Ceftolozane binds PBP1b, PBP1c, and PBP3 and retains potent *in vitro* activity against multidrug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* because of enhanced membrane penetration, reduced efflux vulnerability, and stability against AmpC β -lactamases [51,52]. Tazobactam

expands activity to ESBL-producing Enterobacterales, although carbapenemase producers remain resistant; accordingly, guidelines mainly reserve C-T for carbapenem-resistant pathogens as a carbapenem sparing strategy, polymicrobial infections, and DTR *P. aeruginosa* [16,17,53].

Surveillance studies reported susceptibility rates of 94% for *P. aeruginosa* and 95% for Enterobacterales in Western Europe, versus 81% and 79%, respectively, in Eastern Europe, with similar findings in North America [54,55]. Randomized trials have established their efficacy across pneumonia, cUTI, and cIAI [56,57].

Real-world data supports findings from randomized clinical trials. In the SPECTRA study ($n=617$), the majority of isolates were *P. aeruginosa* (87.4%), with a high proportion of MDR strains (72.7%) [58]. Pneumonia was the most frequent clinical indication (29.5%), highlighting the predominance of respiratory infections in this cohort. All-cause in-hospital mortality was higher among patients with respiratory infections compared with non-respiratory infections (24.7% vs 18.1%), with the highest mortality observed in critically ill subgroups, including those requiring ICU admission [59]. These findings underscore the substantial burden and worse outcomes associated with severe respiratory infections caused by resistant Gram-negative pathogens in real-world settings [58,59]. SPECTRA sub-analysis supported real-world clinical effectiveness of C-T across patients with renal impairment and obesity, highlighting C-T as a component within treatment guidelines for resistant Gram-negative infections in this population [60]. In CEFTABUSE II ($n=153$), which included severely ill patients with ESBL-Enterobacterales infections, 30-day mortality was 9.8% and clinical failure 21.7% [17]. In a Greek retrospective study of ESBL bloodstream infections ($n=115$), C-T did not differ from meropenem in clinical cure or mortality [61]. In the outpatient setting, a U.S. multicenter study found only 4.5% clinical failure among 124 evaluable patients despite a high prevalence of MDR and carbapenem-resistant *P. aeruginosa* [62].

Evidence supporting the use of C-T is also favorable in immuno-compromised populations. In patients with febrile neutropenia, C-T demonstrated numerically higher clinical response rates compared with standard-of-care regimens (87% vs 70%), with comparable 30-day mortality (4%) [63]. In the ZENITH study, a matched cohort of neutropenic hematologic patients with *P. aeruginosa* bloodstream infection (BSI), C-T was associated with significantly improved outcomes, including lower 7-day (6.8% vs 34.1%) and 30-day mortality (22.7% vs 48.9%), as well as reduced need for mechanical ventilation (13.6% vs 33.3%) [64]. Multivariable analysis identified C-T therapy as an independent protective factor for survival (adjusted OR 0.19) [64]. Microbiological data in hematology and oncology patients further support the strong antipseudomonal activity of C-T, with high susceptibility rates among *P. aeruginosa* isolates (>90%), although comparatively reduced activity against certain Enterobacterales, including *K. pneumoniae*, *K. aerogenes*, and *Enterobacter cloacae* complex, underscores the importance of MIC-guided definitive therapy [65].

Comparative effectiveness studies consistently suggest a clinical advantage of C-T over alternative regimens for infections caused by MDR *P. aeruginosa*. In the CACTUS multi-center

Table 1. Pharmacokinetic/pharmacodynamic principles and dosing considerations of approved β -lactam/ β -lactamase inhibitor (BLBLI) combinations.

BLBLI combination	Key PK/PD targets	PK/PD parameters	General dosing strategies	Dosing in critically ill	Dosing in renal impairment
Cefazidime–Avibactam	Cefazidime $ft > MIC +$ avibactam $ft > CT$; concurrent attainment required.	C_{max} (mg/L): 90.4/14.6 $T_{1/2}$ (hours): 2.7/2.7 V_d (L): 17/22.2 $AUC_{0-24}(mg^*h/L)$: 291/38.2 CI (L/h): 6.9/13.1 Protein binding (%): 21/82 Elimination (%): Renal (83/>97)	2.5 g (2 g/0.5 g) q8h (commonly 2-h infusions); many centers use 3-h infusions in severe infection. Renal adjustment (add metronidazole for cAI)	Front-loaded then prolonged-continuous infusions in ARC/high MICs; consider TDM	CrCl >50: 2.5 g q8h CrCl 31–50: 1.25 g q8h CrCl 10–30: 0.94 g q12h CrCl <10: 0.94 g q48h CrCl 6–15 ($\pm$ HD): 0.94 g q24h CrCl ≤ 5 ($\pm$ HD): 0.94 g q48h CVWH: 1.25 g q8h CVHDF: 2.5 g q8h
Meropenem–Vaborbactam	Meropenem $ft > MIC +$ vaborbactam f_{AUC}/MIC ; regimen engineered for joint attainment	ELF penetration (%): 30/35 C_{max} (mg/L): 43.4/55.6 $T_{1/2}$ (hours): 1.22/1.68 V_d (L): 20.2/18.6 $AUC_{0-24}(mg^*h/L)$: 138/196 CI (L/h): 15.1/10.9 Protein binding (%): 2/33 Elimination (%): Renal (40–60 >75–95)	4 g (2 g/2 g) q8h as 3-h infusion. Renal adjustment	ARC/high MICs may require prolonged/continuous infusion with TDM to keep meropenem >MIC ($\approx$ up to 8 mg/L)	CrCl >50: 4 g q8h CrCl 30–49: 2 g q8h CrCl 15–29: 2 g q12h CrCl <15: 1 g q12h HD: 1 g q12h (AD) CRT: No data
Imipenem–Cilastatin–Relebactam	Imipenem $ft > MIC +$ relebactam f_{AUC}/MIC ; label supports targets at MIC ~1–2 mg/L	ELF penetration (%): 65/79 C_{max} (mg/L): 30.5/15.8 $T_{1/2}$ (hours): 1.13/1.68 V_d (L): 19.6/20.8 $AUC_{0-24}(mg^*h/L)$: 130/81.2 CI (L/h): 12.1/8.9 Protein binding (%): 20/20 Elimination (%): Renal(50/>95) ELF penetration (%): 55/54	1.25 g (0.5 g/0.5 g/0.25 g) q6h, 30-min infusion; Renal adjustment.	In ARC, keep standard dose but favor prolonged infusions & close monitoring	CrCl ≥ 90 : 1.25 g q6h CrCl 60–89: 1 g q6h CrCl 30–59: 0.75 g q6h CrCl 15–29: 0.5 g q6h CrCl <15: Not recommended HD: 0.5 g q6h (AD) CRT: No data
Aztreonam–Avibactam	Joint targets: aztreonam ~60% $ft > MIC +$ avibactam ~50% $ft > MIC$ or $ft > CT$; aim $\geq 90\%$ joint PTA (to MIC 8 mg/L).	C_{max} (mg/L): 59/11.3 $T_{1/2}$ (hours): 2.8/2.2 V_d (L): 19.6/23.7 $AUC_{0-24}(mg^*h/L)$: 982/175 CI (L/h): 12.1/8.9 Protein binding (%): 38/8 Elimination (%): Renal(70/>95) ELF penetration (%): 20–60/35	Loading dose 2.67 g (2 g/0.67 g), then 2 g (1.5 g/0.5 g) q6h (infusion 3 h); renal adjustment (add metronidazole for cAI). Each vial contains 1.5 g aztreonam and 0.5 g avibactam.	Prolonged –continuous infusion after full-vial loading in ARC/unstable clearance; TDM where available	CrCl >50: 2.67 g $\times$ 1, then 2 g q6h CrCl >30–50: 2.67 g $\times$ 1 then 1 g q6h CrCl >15–30: 1.8 g $\times$ 1, then 0.9 g q8h CrCl ≤ 15 : 1.33 g $\times$ 1, then 0.9 g q12h HD: 1.33 g $\times$ 1, then 0.9 g q12h (AD) CRT: No data
Ceftolozane–Tazobactam	Ceftolozane $ft > MIC +$ tazobactam exposure above a threshold concentration; concurrent target attainment preferred.	C_{max} (mg/L): 110/125 $t_{1/2}$ (hours): 3/1 V_d (L): 13.5/18.2 $AUC_{0-24}(mg^*h/L)$: 700/200 Protein binding (%): 16–21/30 Elimination (%): Predominantly renal (>90/>80) ELF penetration (%): 50/62	1.5 g (1 g/0.5 g) q8h over 1 h for cUTI/cAI; 3 g (2 g/1 g) q8h over 1 h for HAP/VABP. Renal adjustment required (add metronidazole for cAI).	In severe infection, many centers favor extended infusions (e.g. 3 h) and early TDM where available, especially with ARC or high MIC isolates.	CrCl >50: 1.5 g q8h (or 3 g q8h for HAP/VABP) CrCl 30–50: 750 mg q8h (or 1.5 g q8h for HAP/VABP) CrCl 15–29: 375 mg q8h (or 750 mg q8h for HAP/VABP) HD: 750mg LD, 150 mg q8h (dose AD) or 2.25 g LD, then 450 mg q8h dose AD for HAP/VABP CRT: 3 g $\times$ 1, then 750 mg q8h

(Continued)

Table 1. (Continued).

BLBLI combination	Key PK/PD targets	PK/PD parameters	General dosing strategies	Dosing in critically ill	Dosing in renal impairment
Cefepime– Ennetazobactam	Cefepime $fT > MIC$ + ennetazobactam exposure above a threshold concentration; joint attainment targeted.	C_{max} (mg/L): 100/20 $t_{1/2}$ (hours): 2.7/2.6 V_d (L): 20/25 AUC_{0-24} (mg·h/L): 1110/200 Protein binding (%): 20/ negligible Elimination (%): Predominantly renal(80/90) ELF penetration (%): 60/53	2.5 g (2 g/0.5 g) q8h over 2 h. Renal dose adjustment required.	Consider front-loaded prolonged infusion (for 4 h) and close renal reassessment mainly in ARC and sepsis; TDM may be helpful where available.	CrCL ≥ 130 : 2.5 g q8h CrCL 60–129: 2.5 g q8h CrCL 30–59: 1.25 g q8h CrCL 15–29: 1.25 g q12h CrCL < 15 : 1.25 g q24h HD: 1.25 g, then 0.625 g q24h dose AD CRR: No data
Sulbactam–Durlobactam	Sulbactam $fT > MIC$ + durlobactam f_{AUC}/fT above inhibitor threshold	C_{max} (mg/L): 50/25 $t_{1/2}$ (hours): ~1.5/2.0 V_d (L): 20/15 AUC_{0-24} (mg·h/L): 300/250 Protein binding (%): 38/45 Elimination (%): Renal (85/80) unchanged in urine ELF penetration (%): 40/50	1 g/1 g q6h infused over 3 h; co-administer imipenem– cilastatin (or meropenem if contraindication per label). Renal adjustment required.	In critical illness, maintain aggressive early exposure, reassess clearance frequently, and consider prolonged administration; in ARC shorter interval (q4h); TDM-informed optimization when available.	CrCL ≥ 130 : 2 g q4h CrCL 45–129: 2 g q6h CrCL 30–44: 2 g q8h CrCL 15–29: 2 g q12h CrCL < 15 : 2 g q12h $\times$ 3 doses, then q24h HD: 2 g q12h $\times$ 3doses (after AD), then q24h CRR: 2 g q6h (label-based)

AD, dose administered after dialysis; ARC, augmented renal clearance; AUC, area under the concentration–time curve; AUC_{0-24} , area under the curve over the dosing interval; BLBLI, beta-lactam/beta-lactamase inhibitor; CI, continuous infusion; Cl, clearance; C_{max} , peak serum concentration; CrCL, creatinine clearance; CRR, continuous renal replacement therapy; CT, critical threshold concentration; cIAI, complicated intraabdominal infections; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; ELF, epithelial lining fluid; f_{AUC}/MIC , free AUC to MIC ratio; $fT > CT$, fraction of time free above a critical threshold; $fT > MIC$, fraction of time free drug exceeds MIC; h, hours; HABP, hospital-acquired bacterial pneumonia; HD, hemodialysis; JTA, joint target attainment; LD, loading dose; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetics/pharmacodynamics; PTA, probability of target attainment; q4h, every 4 h; q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; q24h every 24 h; t $_{1/2}$, half-life; TDM, therapeutic drug monitoring; VABP, ventilator-associated bacterial pneumonia; V_d , volume of distribution.

matched cohort study, C-T was associated with higher rates of overall clinical success compared with CAZ-AVI (61% vs 52%; adjusted OR 2.07), without differences in 30-day mortality. This advantage was primarily driven by improved outcomes in pneumonia, where clinical success was higher with C-T (63% vs 51%) [66]. These findings are further supported by a recent meta-analysis of observational studies ($n = 1161$), which demonstrated higher clinical cure rates with C-T compared with CAZ-AVI (OR 1.82, 95% CI 1.10–2.99), without differences in mortality, microbiological failure, or resistance development, reinforcing a consistent efficacy signal across comparative analyses [67]. Additional real-world evidence from the PINC AI database showed that early C-T therapy was associated with lower recurrence of MDR *P. aeruginosa* pneumonia, fewer pneumonia-related readmissions, and a higher likelihood of discharge to home, with similar mortality [68]. In the PUMA study, which evaluated a composite ‘global outcome’ integrating survival, recurrence, need for renal replacement therapy, readmissions, and discharge disposition, treatment with C-T was more frequently associated with favorable overall outcomes compared with polymyxin-based regimens. Specifically, patients receiving C-T had a 61.3% probability of achieving a better overall outcome and were more often discharged home alive without complications (20.2% vs 9.8%) [69].

Resistance to C-T in *P. aeruginosa* has increasingly been reported following its clinical use and is primarily mediated by structural modifications of the Pseudomonas-derived cephalosporinases (PDC) AmpC β -lactamase, which enhance hydrolytic activity against ceftolozane [70,71]. These changes frequently involve mutations within the Ω -loop region of AmpC that expand the active site and improve substrate accommodation [70]. Overexpression of AmpC, often driven by mutations in regulatory genes such as *ampD*, *ampG*, *ampR*, or *dacB*, further contributes to reduced susceptibility [70]. Additional resistance mechanisms include mutations in the DNA polymerase subunits gamma and tau, alterations in PBP-3, as well as decreased outer membrane permeability and upregulation of efflux pumps, which together limit intracellular drug concentrations [70,72]. Importantly, the acquisition of class A β -lactamases, particularly Guiana extended-spectrum (GES)-type enzymes, represents an emerging mechanism of resistance to C-T. GES variants (e.g. GES-1, GES-5) can hydrolyze ceftolozane and are frequently identified among C-T-resistant isolates, often contributing to discordant susceptibility profiles, such as resistance to C-T with retained susceptibility to CAZ-AVI [73]. Resistance may emerge during therapy, particularly in prolonged treatment courses or high-inoculum infections, through stepwise accumulation of mutations under selective pressure [72,74,75]. Notably, such adaptive changes are frequently associated with cross-resistance to other β -lactams, including CAZ-AVI [76].

Overall, current guidance places C-T among the key agents for serious MDR Gram-negative infections. Infectious Diseases Society of America (IDSA) designates it as a preferred option for DTR *P. aeruginosa*, while stewardship-oriented recommendations advise thoughtful use of novel β -lactams in carbapenem-resistant *P. aeruginosa* that remain susceptible to traditional β -lactams [53]. Risk-stratified pneumonia algorithms also incorporate C-T for high-risk *P. aeruginosa* infection [77,78]. For cIAI, the

Surgical Infection Society in 2024 update rates C-T plus metronidazole a Grade 1-A recommendation in higher-risk patients and recognizes it as an empiric option alongside other newer β -lactams [79].

6. Cefepime–enmetazobactam

A novel combination to become available is cefepime–enmetazobactam (FEP-ETZ). Cefepime is a fourth-generation oximino–cephalosporin with broad bactericidal activity against a wide range of Gram-negative and Gram-positive pathogens, including *P. aeruginosa*, but with limited activity against enterococci and anaerobic bacteria [15]. Its structure, which includes an N-methyl-pyrrolidone group at the 3' position, confers zwitterionic properties that enhance penetration through the outer membrane of Gram-negative bacteria [80]. Cefepime targets primarily PBP2 and PBP3, contributing to its potent activity. Compared with other cephalosporins, it demonstrates increased stability against certain β -lactamases, particularly chromosomal and plasmid-mediated AmpC enzymes and some OXA-type enzymes, although it remains susceptible to hydrolysis by many ESBL-enzymes [15]. While these pharmacologic features improve its activity against some resistant Gram-negative organisms, clinical and *in vitro* data indicate limited efficacy against ESBL-producing strains, where elevated MIC and risk of treatment failure have been observed [81].

Enmetazobactam, a penicillanic acid sulfone β -lactamase inhibitor, exhibits potent activity against CTX-M, TEM, and SHV ESBLs, as well as other class A β -lactamases [43,82]. Its molecular design incorporates a methyl substitution on the triazole ring that confers zwitterionic characteristics, facilitating improved penetration into Gram-negative bacteria [43,82]. This structural feature also supports diverse hydrogen-bonding interactions within the active site of β -lactamases, enhancing binding affinity and inhibitory potency [43,82].

Like other β -lactamase inhibitors (BLIs), enmetazobactam has minimal intrinsic antibacterial activity; however, in combination with cefepime, it shields the antibiotic from enzymatic hydrolysis and thereby restores its efficacy against ESBL-producing organisms. Specifically, enmetazobactam inhibits selected serine β -lactamases, enhancing cefepime stability against certain class A, C, and D enzymes, and retaining activity against some KPC-producing strains, particularly those harboring omega-loop mutations [80,82]. However, it lacks activity against MBL-producing bacteria, as those enzymes are not inhibited by serine-based BLIs [80,82]. Its activity against CRAB is also limited and varies according to the specific resistance mechanisms involved. In particular, activity may be retained against isolates producing OXA-58 enzymes or those lacking oxacillinase production, while efficacy is reduced in the presence of other oxacillinases [80].

This regimen has recently been approved by both the FDA and the EMA for the treatment of complicated cUTIs, including pyelonephritis, as well as HAP and VAP, with or without concomitant bacteremia, caused by ESBL-producing Enterobacterales [83,84]. FEP-ETZ has been evaluated across early and late-phase clinical development, including two

phase I trials (NCT03680352 and NCT03775668) and one phase II study (NCT03680612) that primarily established its safety, tolerability, and pharmacokinetic/pharmacodynamic profile, although detailed results from these studies remain limited in the published literature [80]. The pivotal evidence derives from the phase III randomized, multicenter ALLIUM trial, which compared cefepime–enmetazobactam with piperacillin–tazobactam in patients with cUTIs, including acute pyelonephritis [85]. In this study, the combination demonstrated superior efficacy, achieving higher rates of composite clinical (resolution of baseline signs and symptoms) and microbiological (reduction in baseline urinary pathogen concentration to $<10^3$ CFU/mL) at day 14, including infections caused by ESBL-producing Enterobacterales [85]. Beyond cUTI, regulatory approval has been extended to include HAP and VAP, despite the absence of dedicated phase III clinical trials in this indication. This approval has been supported by robust PK/PD data, ELF penetration studies, and efficacy, demonstrated in preclinical murine infection models, reflecting a regulatory approach that considers the urgent need for new therapeutic options in the setting of escalating antimicrobial resistance [86]. Regarding safety profile, FEP-ETZ is generally well tolerated, with reported adverse events including mild elevations in transaminases, headache, diarrhea, and infusion-site reactions such as phlebitis [85]. Moreover, although no clinically significant drug–drug interactions have been clearly identified, caution is warranted due to the known risk of cefepime-associated neurotoxicity. This risk may be heightened when co-administered with other neurotoxic agents and in patients with impaired renal function, where drug accumulation can occur [80].

Concerning resistance patterns to FEP-ETZ, these may arise through several mechanisms, including the production of β -lactamases not inhibited by enmetazobactam, most notably MBLs, as well as reduced outer membrane permeability due to porin alterations, upregulation of efflux systems, and structural changes in PBPs that diminish target affinity [80,86,87].

Summarizing, this promising antibiotic may play an important role as a carbapenem-sparing option within antimicrobial stewardship strategies, as it may be administered in serious infections caused by ESBL-producing Enterobacterales and *P. aeruginosa*.

7. Ceftazidime–avibactam

CAZ-AVI has shown robust antibacterial activity against *P. aeruginosa* and Enterobacterales, including strains producing ESBLs and carbapenemases, since avibactam inhibits class A, class C, and some class D β -lactamases, thereby protecting ceftazidime from enzymatic degradation [88]. *In vitro* studies consistently demonstrate high activity of CAZ-AVI against carbapenemase-producing Enterobacterales (CRE) [89,90]. In a global surveillance study (2016–2018; $n = 1,992$), CAZ-AVI showed excellent activity against KPC-producing isolates (resistance $\sim 1.5\%$) [89]. Similarly, in a worldwide collection of 1,690 OXA-48-like-producing isolates (2016–2020), susceptibility exceeded 97–99% among MBL-negative strains, including major variants such as OXA-48, OXA-181, and OXA-232 [91]. More recent surveillance data from U.S. and European

hospitals (2020–2021) confirmed sustained activity, with susceptibility of 99.5% among KPC-producing carbapenem-non-susceptible Enterobacterales [90]. Activity against *P. aeruginosa* is also retained, although lower, with susceptibility rates of approximately 78% in MDR and 57% in DTR isolates [90].

Clinical comparative evidence indicates that CAZ-AVI is superior to best available therapy (BAT) for the treatment of infections caused by carbapenemase-producing Enterobacterales [92–97]. This was demonstrated in the multicenter CAVICOR retrospective cohort study, which included 339 patients with KPC- or OXA-48-producing infections and compared CAZ-AVI with BAT, defined as treatment with alternative *in vitro*-active agents including colistin, aminoglycosides, tigecycline, fosfomycin, and carbapenem-based combination regimens [92]. Treatment with CAZ-AVI was associated with significantly lower 30-day mortality than BAT (13.7% vs 22.0%) and remained independently associated with survival in multivariable analysis (OR 0.41, 95% CI 0.20–0.80, $p = 0.01$). CAZ-AVI was also associated with higher rates of 21-day clinical response (89.4% vs 79.3%) and microbiological eradication (83.3% vs 69.4%, $p = 0.02$). Survival benefit was most pronounced among patients with high INCREMENT-CPE severity scores [92].

Consistent findings have been reported in other real-world comparative studies evaluating CAZ-AVI against older therapeutic regimens for life-threatening infections caused by CR-GNB [93,94]. In a retrospective cohort study of critically ill, mechanically ventilated patients from two ICUs, treatment with CAZ-AVI was associated with significantly higher clinical success (80.5% vs 53%), higher microbiological eradication (94% vs 68%), lower relapse rates (5% vs 33%), and reduced 28-day mortality (14.6% vs 38.9%) compared with control regimens, which predominantly consisted of colistin-based combinations, tigecycline, aminoglycosides, fosfomycin, or trimethoprim-sulfamethoxazole. In multivariable analysis, receipt of CAZ-AVI was an independent predictor of 28-day survival [93]. Additional evidence from a national registry study of 147 patients with KPC- or OXA-48-producing *K. pneumoniae* infections further demonstrated favorable outcomes with CAZ-AVI, including high 14-day clinical success and microbiological response rates, low rates of resistance emergence during therapy, and a significantly lower 28-day mortality in patients with bloodstream infections compared with historical regimens not containing CAZ-AVI [94].

Further support comes from a multicenter retrospective cohort evaluating CAZ-AVI as salvage therapy for severe infections caused by KPC-producing *K. pneumoniae*. In this real-world study of 577 patients, predominantly with BSI (67.8%), CAZ-AVI-based regimens achieved a 73% clinical response rate with a 30-day all-cause mortality of 25.3%. Notably, among patients with KPC-*K. pneumoniae* bacteremia, treatment with CAZ-AVI was associated with significantly lower 30-day mortality compared with matched cohorts receiving alternative therapies (36.5% vs 55.8%; $p = 0.005$) [95].

Overall, accumulated clinical evidence indicates that the introduction of CAZ-AVI has transformed the therapeutic landscape of CRE infections, with important implications for

mortality [10,11,93,94,98–102]. Across several observational studies, CAZ-AVI treatment has been consistently associated with reduced mortality and favorable clinical outcomes [93,94,98–101]. Reported 28–30-day mortality rates remain relatively low, generally ranging between approximately 8% and 25%, while clinical cure rates frequently exceed 70–80% across cohorts [93,94,98–101]. These findings suggest that in CAZ-AVI era, carbapenem resistance may no longer be an independent predictor of mortality [10].

This concept is supported by a multicenter, retrospective Italian study of 427 patients with *K. pneumoniae* BSI. Although crude 30-day mortality was higher among patients with CR-GNB isolates compared with carbapenem-susceptible isolates, carbapenem resistance was not independently associated with mortality after adjustment for disease severity and comorbidities [10]. CAZ-AVI was the most frequently used therapy for CR-GNB infections, and in propensity-score-matched analyses, mortality did not differ between patients with CR-GNB infections treated with CAZ-AVI and those with carbapenem-susceptible infections treated with standard β -lactam regimens [10]. These findings indicate that appropriate CAZ-AVI therapy may effectively reduce the excess mortality historically associated with CR *K. pneumoniae* BSIs, restoring survival to levels comparable to those observed in carbapenem-susceptible infections [10].

Similarly, findings from the nationwide ALARICO Network study demonstrated that, although carbapenem resistance in BSIs remains associated with excess mortality, infections caused by KPC-producing Enterobacterales – predominantly treated with CAZ-AVI – were associated with a relatively limited attributable mortality compared with metallo- β -lactamase-producing Enterobacterales, which carried the highest risk of death [11]. These observations are further reinforced by a systematic review and meta-analysis including 11 studies and 1,213 patients, which demonstrated significantly lower 28-day and 30-day mortality with CAZ-AVI compared with alternative antimicrobial regimens for carbapenem-resistant *K. pneumoniae* infections, including BSIs [102].

CAZ-AVI has shown efficacy against carbapenemase-producing *P. aeruginosa*, with accumulating evidence continues to support its use in this setting [73,103,104]. In a collection of 160 of multi-drug resistant (MDR) and extensively drug-resistant (XDR) non-MBL *P. aeruginosa* clinical isolates obtained from nine Greek hospitals, CAZ-AVI exhibited higher *in vitro* activity than most other β -lactam agents, including ceftazidime, cefepime, piperacillin/tazobactam, and carbapenems. Only colistin exhibited higher overall activity, while CAZ-AVI retained activity against a substantial proportion of isolates resistant to other antipseudomonal agents [73]. Consistent findings from large global and European surveillance studies indicate that CAZ-AVI maintains clinically relevant *in vitro* activity against carbapenem-resistant, MBL-negative *P. aeruginosa*, including isolates resistant to other antipseudomonal β -lactams [103,104] and, in some cases, to C-T [104]. Across these surveillance programs, CAZ-AVI consistently ranks among the most active β -lactam agents against *P. aeruginosa* [103,104].

Real-world clinical data further confirm the effectiveness of CAZ-AVI for the treatment of MDR- and XDR *P. aeruginosa* [105,106]. In a multicenter U.S. retrospective cohort, predominantly involving respiratory tract infections, CAZ-AVI was associated with a 30-day mortality rate of 17.2%, with early initiation of therapy (within 48 h) was independently associated with improved outcomes [106]. Similarly, a retrospective cohort study from Spain reported a clinical cure rate of 54.1% by day 14, a 30-day all-cause mortality of 13.1%, and no emergence of CAZ-AVI resistance during follow-up. Early initiation of CAZ-AVI and its use in combination therapy were independently associated with clinical cure [105].

A systematic review comparing antimicrobial therapies for MDR *P. aeruginosa* infections indicate that CAZ-AVI is the only comparator with effectiveness non-inferior to C-T [107]. In contrast, aminoglycoside- or polymyxin-based regimens were associated with significantly lower clinical cure rates and higher all-cause mortality. Network meta-analysis demonstrated that aminoglycoside/polymyxin regimens were less likely to achieve clinical cure (OR = 0.31, 95% CI 0.17–0.52) and more likely to result in all-cause mortality (OR = 1.65, 95% CI 1.11–2.50) compared with ceftolozane–tazobactam [107]. No statistically significant differences were observed between ceftolozane–tazobactam and CAZ-AVI for clinical cure (OR = 0.92, 95% CI 0.57–1.60), all-cause mortality (OR = 0.83, 95% CI 0.62–1.12), microbiological cure (OR = 0.79, 95% CI 0.30–1.84), or length of hospital stay [107].

The role of combination therapy with CAZ-AVI remains controversial. A recent meta-analysis including 25 studies ($n = 2676$) found no significant difference between combination therapy and monotherapy in terms of 30-day mortality or clinical cure, although a modest improvement in microbiological eradication was observed in the combination arm [108]. Similarly, in a large multicenter observational study, no difference in 30-day mortality was observed between patients receiving CAZ-AVI monotherapy and those treated with combination regimens (26.1% vs 25.0%) [95]. These findings support the use of CAZ-AVI as monotherapy when *in vitro* susceptibility is confirmed, reserving combination strategies for selected high-risk clinical scenario, probably for patients with nosocomial pneumonia [109].

Together, these clinical and comparative effectiveness data, have led to the incorporation of CAZ-AVI into major international treatment guidelines. Both the IDSA and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) now recommend CAZ-AVI as a preferred option for the management of severe infections caused by CRE, including scenarios in which carbapenemase results are unavailable or negative [53,110]. Notably, CAZ-AVI is recommended as monotherapy when *in vitro* susceptibility is confirmed, reflecting growing confidence in its efficacy and safety profile and supporting a shift away from routine use of polymyxin-based or combination regimens [53,110]. In clinical practice, real-world data from a prospective UK-wide antimicrobial registry indicate that CAZ-AVI may be used empirically in selected high-risk scenarios, although its use remains largely targeted and informed by microbiological susceptibility data, particularly in patients with complex infections due to MDR Gram-negative pathogens [111].

CAZ-AVI resistance is increasingly reported, particularly among KPC-producing *K. pneumoniae*, with treatment-emergent resistance rates ranging from approximately 2% to 14% in clinical series [112]. Contemporary surveillance data from endemic settings such as Italy and Greece further corroborate these findings, demonstrating *in vitro* resistance rates of approximately 6.1% and 8.5%, respectively, among KPC-producing bloodstream isolates [113,114]. The predominant mechanism involves structural alterations in the Ω -loop of the *bla*_{KPC} enzyme, most notably the D179Y substitution (KPC-31), which reduces avibactam binding while preserving or enhancing ceftazidime hydrolysis [9,21,112]. In addition to these KPC-mediated mechanisms, non-KPC pathways are increasingly recognized, including the acquisition of Vietnamese extended-spectrum β -lactamase (VEB)-type extended-spectrum β -lactamases, particularly VEB-25, a VEB-1 variant harboring a Lys234Arg substitution that compromises avibactam inhibition and confers high-level resistance [115,116]. Furthermore, resistance may be augmented by concomitant non-enzymatic mechanisms, such as alterations in outer membrane porins (OmpK35/36), increased *bla*_{KPC} expression, and PBP modifications, which may act synergistically to enhance resistance and facilitate its emergence under antimicrobial pressure [9,21,112].

Table 2 summarizes real-world studies evaluating CAZ-AVI for severe Gram-negative infections across heterogeneous populations, including critically ill patients, hematological malignancy and transplant recipients, and solid tumor patients, with emphasis on disease severity, infection source, treatment strategy, and outcomes [66,75,92,117–161].

8. Meropenem–vaborbactam

Meropenem–vaborbactam (MER-VAB) combines the carbapenem meropenem with vaborbactam, a cyclic boronic acid β -lactamase inhibitor developed to restore meropenem activity against class A serine carbapenemases, particularly KPC enzymes (e.g. KPC-2, KPC-3) [162], as well as ESBL and Class C enzymes [163–165]. MER-VAB also remains active against isolates harboring KPC variants associated with CAZ-AVI resistance, such as KPC-8 and KPC-31 [166]. In the ARTEMIS surveillance study, which included more than 1,900 clinical Enterobacterales isolates collected from 49 sites across six European countries (Austria, France, Germany, Italy, Spain, UK), MER-VAB demonstrated high overall *in vitro* activity, with 97.4% susceptibility among all species, comparable to other approved BLBLI combinations. Although susceptibility to MER-VAB declined to 70.9% among meropenem-resistant Enterobacterales and further decreased to less than 16.7% in isolates resistant to both meropenem and other BLBLI combinations (e.g. CAZ-AVI, IMI-REL), MER-VAB retained high activity against KPC-producing isolates, with susceptibility reaching 93.6% [167]. Due to the selective inhibitory spectrum of vaborbactam, MER-VAB susceptibility is markedly reduced against MBL-producing CRE (e.g. NDM, VIM, IMP), and OXA-48-like carbapenemases, with susceptibility rates falling below 20% [165,167]. In addition, in difficult-to-treat resistant pathogens, such as *P. aeruginosa*, *Acinetobacter* spp., and *S. maltophilia*, MER-VAB activity is generally comparable to meropenem alone [165,168–170].

Table 2. Real-world evidence on ceftazidime–avibactam in severe Gram-negative infections across general, critically ill, and immunocompromised (hematological and oncologic) populations.

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with CAZ-AVI	Outcomes	Comments
Halacoglu et al. [117]	2024	Retrospective	80	CCI: 4 (mean) CCI ≥ 3 : 71/80 (88.75%) Neutropenia: prolonged in most patients Mechanical ventilation: 60% Septic shock: NR	<i>P. aeruginosa</i> (35%) <i>K. pneumoniae</i> (10%) <i>K. pneumoniae</i> (6.25%) <i>E. coli</i> (6.25%) Other: <i>Enterobacteriales</i> (26.25%)	RTI/bronchial secretions: 36% BSI: 32% UTI: 26% CVC-related: 15% SSTI: 7%	Combination therapy: 100% Combination with: – TGC (32%) – COL (polyin) (30%) – Amikacin (24%) – Fosfomycin (8%) – MER (6%)	Mortality: 28d: 57.5%	Hematologic population with profound immunosuppression, including patients with ALL, and 19.3% underwent HSCT (42.5% allo-HSCT; 21.25% auto-HSCT); remaining patients received chemotherapy only.
Sastre-Escobal et al. [118]	2022	Multicentre, international, retrospective descriptive study	54	Septic shock: 11%	<i>K. pneumoniae</i> (79.5%) Carbapenemase: KPC (52%)	BSI Mainly endogenous source (57.5%)	Combination therapy predominantly used. Combination with: – AG – COL – TGC	Mortality: 7-day: 11% 30-day: 24%	High-risk neutropenic hematological population. Nephrotoxicity (15%) attributed to AG or COL
Tumbarello et al. [119]	2023	Multicentre, retrospective, observational study	198	CCI > 4 in 39.4% Septic shock: 12.1%	<i>Enterobacteriales</i> (74.2%) <i>K. pneumoniae</i> (62.9%) 75.5% KPC CRPA (25.0%)	BSI (90.1%)	Monotherapy: 38.9% Combination therapy: 61.1% Combination with: – COL – Amikacin – TGC – Fosfomycin – AZT	Mortality: 30d: 17.7% Infection relapse: 2.0% CAZ/AVI resistance: 0.5%	Large real-world cohort of patients with hematological malignancies (neutropenia 81.3%, HSCT 24.7%), including MPls and FUO; no survival benefit of combination therapy over monotherapy
Pfäfflin et al. [120]	2025	Prospective, observational, single-center, investigator-initiated study	50 (46 evaluable for outcomes)	CCI: median 5.5 SOFA: median 7 APACHE: NR Septic shock: 3/50 (6%) ICU admission: 77% Mechanical ventilation ≤ 7 d: 76%	<i>P. aeruginosa</i> (48%) <i>K. pneumoniae</i> (28%) <i>K. aerogenes</i> (8%) <i>E. coli</i> (6%) <i>E. cloacae</i> complex (6%) <i>S. maltophilia</i> (2%) Other: <i>Enterobacteriales</i> ($\leq 2\%$ each)	HAP/VAP: 50% CMI: 28% BSI: 16% SSTI: 6% UTI: 2% Other: bone infection 2%	Monotherapy: 55% Combination therapy: 45% Combination with: – COL (IV/nebulized) – Ciprofloxacin – Gentamicin – TGC – AZT – Fosfomycin	Clinical success: Day 14: 59% Microbiological failure (30 d): 4% Mortality: 30 d: 9% 90 d: NR CAZ/AVI resistance: 0%	Critically ill ICU cohort with high mechanical ventilation burden.
Abi Freim et al. [121]	2009–2022	Retrospective, case-control study	339 CAZ/AVI arm: 39 episodes	CCI: mean 3.3 ± 1.8 MISCC score: 19.5 ± 4.1 (high-risk) qSOFA: 0.6 ± 0.6 ECOG: 0.3 ± 0.6 Septic shock: NR	Gram-negatives: 74.4% <i>E. coli</i> 53.8%; ESBL 80.9%; CRE 19.0% <i>Klebsiella</i> spp. (7.7%) <i>P. aeruginosa</i> (5.1%) <i>Acinetobacter</i> spp. (2.6%) <i>S. maltophilia</i> (2.6%) Gram-positives: 28.2% <i>K. pneumoniae</i> (100%) CR	Intravascular device: 33.3% RTI: 28.2% Gastrointestinal: 10.3% UTI: 10.3% Other: NR	CAZ/AVI mainly used as escalation after failure of first-/second-line therapy Monotherapy vs combination: NR	Sepsis: 59.0% ICU admission: 30.8% Respiratory failure: 28.2% Persistent bacteremia: 20.5% Mortality: 30 d (late): 23.1%	High-risk febrile neutropenia cohort (acute leukemia, HSCT)
Huang et al. [122]	2018–2023	Single-center, retrospective, observational study	101 patients CAZ/AVI: 47 CARB: 54	CCI: median 7 (IQR 3.5) in CAZ/AVI Shock: 93.6% (CAZ/AVI) ICU admission: 46.8% (CAZ/AVI)	<i>P. aeruginosa</i> (100%) DTR	BSI (100%) Nosocomial BSI	Monotherapy: CAZ/AVI only Combination therapy (CARB): 100% Combination with: – Amikacin – COL – TGC – Fluoroquinolones – Fosfomycin – TMP-SMX – Sulbactam	Mortality: 7-day: 8.5% (CAZ/AVI) vs 25.9% (CARB), 14-day: 19.2% vs 29.6% 28-day: 27.7% vs 33.3% All-cause mortality: ~49% vs 51% Microbiological cure (14 d): 72.3% vs 63.0%	Adult hospitalized patients predominantly critically ill, high comorbidity burden, and high rates of septic shock
Almangour et al. [123]	2017–2022	Retrospective, multicenter cohort study	200 CAZ/AVI: 100 C/T: 100	CCI: median 5 (IQR 3–8) APACHE II: median ~19–20 ICU admission: 56% Mechanical ventilation: 48% Septic shock: 37%	<i>P. aeruginosa</i> (100%) DTR	RTI (HAP/VAP): 49% Wound: 24% UTI: 10% IAI: 8% BSI: 19%	Monotherapy: 59% Combination therapy: 41% Combination with: – COL (IV/inhaled) – AZT – Fluoroquinolones – AG – Carbapenems	Clinical cure: 66% (CAZ/AVI) Mortality: In-hospital: 37% 30 d: 23% AKI: 17% No significant difference vs C/T	Adult hospitalized patients with severe infections caused by MDR <i>P. aeruginosa</i> , including ICU and non-ICU patients, with high rates of mechanical ventilation and septic shock
Harezzi et al. [75]	2018–2023	Multicenter, prospective observational study (IPW-adjusted cohort)	186 C/T: 102 CAZ/AVI: 84	CCI ≥ 5 : ~48% Median CCI: 4 ICU admission: 58% Immunocompromise: 34%	<i>P. aeruginosa</i> (100%) DTR	RTI: 55–57% BSI: 13% SSTI: 13% UTI: 9% IAI/biliary: 6%	Predominantly monotherapy Combination therapy: 14% (12/84) Combination with: – AG – Polymyxins – Fluoroquinolones	Mortality: 30 d: 17% (CAZ/AVI) vs 21% (C/T) Emergence of resistance (590 d): CAZ/AVI 25% (8/32) vs C/T 38% (14/37)	Immunocompromise: 34%. DTR <i>P. aeruginosa</i> population; IPW achieved balance for severity, immunocompromise, CRRT, and infection source.
Pérez-Nadales et al. [124]	2022	Multicentre, international, retrospective observational cohort study	210 SOT recipients with CPKP-BSI; treatment cohort $n = 149$ (CAZ/AVI $n = 83$, BAT $n = 66$)	CCI: median 6 (IQR 4–8); INCREMENT-SOT-CPE score: median 8 (IQR 3–12); Severe sepsis/septic shock: 47.7%; ICU admission: 51%	<i>K. pneumoniae</i> (100%); Carbapenemase: KPC 73.8%; OXA-48 26.2%	BSI: 100% UTI 24.8% IAI 18.8% Biliary tract 17.4% Vascular access 16.8% RTI 9.4%	Monotherapy: 80.7% Combination therapy: 19.3% Combination with TGC, COL, fosfomycin, ciprofloxacin	Clinical success: 14 d 80.7% (CAZ/AVI) vs 60.6% (BAT); 30 d 83.1% vs 60.6% Mortality: 30 d 13.3% vs 27.3%	Largest comparative SOT cohort with CPKP-BS

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Table 2. (Continued).

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with CAZ-AVI	Outcomes	Comments
Hakeam et al. [125]	2017–2020	Retrospective, multicenter cohort study	61 (CAZ/AVI: 32; COL: 29)	CCI: median 5 (IQR 3–6); CCI ≥ 3: 81.9%; Pitt score: median 3 (IQR 1–5.5); SOFA: median 10 (IQR 7–13); ICU onset: 37.7%	<i>K. pneumoniae</i> (78.7%); <i>E. coli</i> (11.5%); Other <i>Enterobacteriales</i> (≤10%); Carbapenemase genes: OXA-48 (62%), KPC (12%), NDM (26%)	BSI: 100%; Secondary BSI: 88.5%; IAI: 24.5%; CVC-related: 34.4%; RTI (HAP/VAP): 11.4%; UTI: 8.1%	Monotherapy: 28.1%; Combination therapy: CAZ/AVI vs COL 71.9% vs 100%; Combination with: – Carbapenems – TGC – AZT – AG – Fluoroquinolones	Clinical success: 46.8% (CAZ/AVI) vs 20.7% (COL); Microbiological eradication (72 h): 68.8% vs 44.8%; Mortality: 14 d 18.8% vs 31.0%; 30 d 37.5% vs 41.4%	First study comparing CAZ/AVI vs contemporary-dose COL for CRE BSI; CAZ/AVI independently reduced 14-day mortality (aHR 0.22); benefit mainly early; long-term outcomes driven by comorbidity and severity
Lima et al. [126]	2015–2019	Retrospective, single-center observational study	76 total CAZ/AVI: 33 BAT: 43	CCI > 3: 33% (CAZ/AVI) vs 56% (BAT) Pitt index > 2: 51% vs 44% INCREMENT-CPE ≥ 7: 49% vs 42% ICU admission: 61% (CAZ/AVI) vs 21% (BAT)	<i>K. pneumoniae</i> (100%) OXA-48 carbapenemase (100%)	BSI: 100%; UTI: 100% overall (CAZ/AVI 30% vs BAT 63%) Unknown source more frequent in CAZ/AVI	Monotherapy: 91% (30/33) Combination therapy: 9% CAZ/AVI used as targeted therapy in 88% Extended infusion ≥ 2 h	Clinical success: 91% (CAZ/AVI) vs 58% (BAT) Clinical cure: 97% vs 74% Mortality: 14-day: 3% vs 23% 30-day: 12% vs 26% Recurrence (90 d): 21% vs 3%	First study focused exclusively on CRKP-OXA-48 bacteremia
Zhen et al. [127]	2015–2019	Single-center, retrospective, observational study	56 patients 57 isolates	CCI: median 2 (IQR 2–3) Pitt bacteremia score: median 1 (IQR 0–2) Neutropenia > 14 days: 23.2% Shock: 8.9%	CBE (71.4%) – MBL-CRE: 42.9% – Serine β-lactamase CRE: 17.9% CRPA: 28.6%	BSI: 100%	Monotherapy: 14.3% Combination therapy: 85.7% Combination with: – TZT (all MBL-CRE) – AG (amikacin/etmiconin) – Ciprofloxacin – MER – Polymyxin	Clinical success: 76.8% Microbiological eradication: 83.9% Survival: 30-day: 83.9% overall CRP: 83.0% CRPA: 81.3% MBL-CRE + AZT: 91.7%	Hematological population (AML, ALL, HSCT); half post – allo-HSCT.
Yuan et al. [128]	2025	Phase 4, prospective, multi-center, open-label study (42 centers)	235 treated (safety set) 209 cMITT 80 mMITT	APACHE II: mean 15.6 (SD 4.38) 10–19: 81.7% 20–30: 17.9% Mechanical ventilation: 27.7% VAP: 4.7% ICU population: implied by HAP/VAP; ICU rate NR	<i>Enterobacteriales</i> (81.3% of mMITT) – <i>K. pneumoniae</i> : 61.3% <i>P. aeruginosa</i> : 20.0% Mixed GN/GP: 11.3%	RTI (HAP/VAP): baseline bacteremia: 6.4%	CAZ/AVI monotherapy per protocol Empiric background agents allowed (e.g. linezolid, vancomycin, amikacin) at investigator discretion	Clinical cure: TOC: 62.7% (cMITT) EOT: 75.1% Microbiological response: TOC: 51.3% (mMITT) Mortality: 5.7% at TOC and Day 28 (cMITT) 7.3% (mMITT)	Large real-world Asian cohort with high illness severity and comorbidity burden. Higher SOFA score, immunomodulator use, and <i>Enterobacter</i> spp. infection were associated with mortality. Early initiation of CAZ/AVI and CAZ/AVI monotherapy were independently associated with improved outcomes
Yang et al. [129]	2025	Multicenter, retrospective cohort study	472 adult patients	SOFA score: mean 8.4 CCI: ≥ 4 in 73.1% Population: elderly (mean age 70.6 y)	<i>K. pneumoniae</i> (64.4%) <i>P. aeruginosa</i> (17.8%) <i>E. coli</i> (8.3%) <i>Enterobacter</i> spp. (2.3%)	RTI (46.2%) CUTI (22.0%) CAI (14.0%) Primary BSI (10.0%)	CAZ/AVI predominantly as targeted therapy (≈90%) Both monotherapy and combination regimens used	Clinical success: 58.1% In-hospital mortality: 41.1% Microbiological cure: 57% (32/65) Clinical cure: 71.9% (microbiologic cure group) vs 50% (failure group) Recurrence (30 d): 6.3% vs 12.5% Mortality (30 d): 56.3% vs 41.7% (NS)	
El Nekidy et al. [130]	2018–2022	Retrospective, observational, single-center study	56	ICU admission: NR SOFA: NR APACHE: NR Septic shock: NR RRT: 100% (CVH or IHD)	<i>Enterobacteriales</i> (associated with cure) Other Gram-negative MDR organisms (NR by species)	RTI: 60.7% BSI: NR Other sources: NR	Monotherapy: NR Combination therapy: NR Dosing adapted to RRT: – CVH: 1.25 g q8h (most common) – IHD: 1.25 g q24h	Global success: 79.0% Therapeutic success: 63.4% Mortality (28 d / discharge): 20.2% Resistance emergence: 5.4% AEs related to CAZ/AVI: 17.4% Serious AEs: 6.2%	One of the largest prospective real-world CAZ/AVI cohorts. High effectiveness across infection sites and pathogens, including <i>P. aeruginosa</i> and <i>Enterobacter</i> spp. Demonstrates frequent monotherapy use and low resistance emergence. Supports CAZ/AVI + AZT for MBL producers.
Piroth et al. [131]	2019–2021	Prospective, multicenter, observational real-world study (41 French centers)	257	ICU admission: NR SOFA: NR APACHE: NR Septic shock: NR Immunocompromised: 31.1% Chronic renal failure: 25.7%	<i>P. aeruginosa</i> (52.4%) <i>Klebsiella</i> spp. (34.9%) <i>Enterobacter</i> spp. (18.4%) <i>E. coli</i> (12.9%) MBL producers: 19 cases	HAP/VAP: 34.2% CUTI: 17.5% dAI: 14.8% Bacteremia (other sites): 6.6% BSIs: 5.8% SSIs: 4.7%	Monotherapy: 77.8% Combination therapy: 22.2% Combination with: – AG (19%) – Fluoroquinolones (14.3%) – TMP-SMX (10.9%) – COL (10.5%) – AZT (10.1%) MBL infections: CAZ/AVI + AZT in 12/19	Global success: 79.0% Therapeutic success: 63.4% Mortality (28 d / discharge): 20.2% Resistance emergence: 5.4% AEs related to CAZ/AVI: 17.4% Serious AEs: 6.2%	One of the largest prospective real-world CAZ/AVI cohorts. High effectiveness across infection sites and pathogens, including <i>P. aeruginosa</i> and <i>Enterobacter</i> spp. Demonstrates frequent monotherapy use and low resistance emergence. Supports CAZ/AVI + AZT for MBL producers.
Sathe et al. [132]	2014–2015	Phase 3 randomized, double-blind, non-inferiority trial – post-hoc regional subset analysis	90 Indian patients enrolled 78 randomized (CAZ/AVI 36; MER 42)	APACHE II: majority 10–20 ICU setting: 100% Ventilation: NR Septic shock: NR Renal impairment (moderate-severe): 2.6%	<i>P. aeruginosa</i> (53.8%) <i>K. pneumoniae</i> (23.1%) Other <i>Enterobacteriales</i> (23.1%)	HAP: 100%	Comparator study CAZ/AVI vs MER All patients received concomitant antibiotics Mean duration CAZ/AVI: 8.9 d Mean duration MER: 10.2 d	Clinical cure (TOC, cMITT): CAZ/AVI 80.6% vs MER 71.8% Clinical cure (TOC, CE): CAZ/AVI 88.0% vs MER 77.1% EOT cure rates: consistent across all analysis sets Safety: comparable to MER; no new safety signals	Subgroup analysis of Indian patients from REPROVE. Demonstrates numerically higher cure rates with CAZ/AVI vs MER in HAP despite high prior antibiotic exposure. Reflects local resistance epidemiology with predominance of <i>P. aeruginosa</i> .

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Table 2. (Continued).

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with CAZ-AVI	Outcomes	Comments
Zhuang et al. [133]	2019–2021	Multicenter, retrospective observational study	183 CR-GNB – infected patients	APACHE II: median 21 (IQR 14–22) ICU admission: 68.9% Mechanical ventilation: 68.3% Septic shock/sepsis: 47.0%	<i>K. pneumoniae</i> (72.1%) <i>P. aeruginosa</i> (16.4%) <i>A. baumannii</i> co-infection (19.7%) Other <i>Enterobacteriales</i>	RTI (80.9%) BSI (33.3%) IAI (25.7%) UTI (16.9%) Multifocal infection: 61.7%	CAZ/AVI monotherapy: 79.5% CAZ/AVI + 1 agent: 39.3% CAZ/AVI + 2 agents: 31.1% Most common combinations: C (23.5%), polymyxin B (20.8%), carbapenem (19.7%) Dose adjusted for renal function; prolonged infusion in minority	Clinical success: 75.4% Microbiological clearance: 60.0% 7-day microbial efficacy: 43.7% 30-day mortality: 11.5% In-hospital mortality: 14.2%	Critically ill population with high ICU and ventilation rates. Renal dysfunction (C _{CR} <20 mL/min) independently associated with lower clinical efficacy. Dose adjustment and combination with carbapenem associated with improved bacterial clearance. Age and mechanical ventilation independently associated with mortality.
Arns et al. [134]	2020–2022	Multicenter, prospective cohort study	127 hospitalized adults	APACHE II: median 14 (IQR 9–20) ICU admission: 65.4% Mechanical ventilation: 56.7% Vasoactive drugs: 38.6% IHD: 33.9%	<i>K. pneumoniae</i> (66.9%) <i>S. marcescens</i> (29.1%) Chromosomal AmpC producers (33.1%): <i>Serratia</i> , <i>Enterobacter</i> spp., <i>K. aerogenes</i> , <i>P. aeruginosa</i>	RTI (53.5%) UTI (20.5%) BSI (15.7%) IAI (4.7%) Polymicrobial infection: 33.9%	CAZ/AVI ≥ 48 h in all patients Combination therapy: 45.7% Active combination therapy: 31.5% Median treatment duration: 10 days (IQR 7–13) Median time to CAZ/AVI initiation: 3 days	30-day mortality: 27.6% In-hospital mortality: 41.7% Microbiological persistence at 30 days: 32.8% Emergent CAZ/AVI resistance: 0.8% (1 patient)	Population: High-severity cohort with frequent ICU admission, organ support (mechanical ventilation, vasopressors, dialysis), and predominantly respiratory, MDR Gram-negative infections.
Shields et al. [66]	2016–2023	Multicenter, matched, retrospective observational study (28 hospitals)	420 total (CAZ/AVI n = 210; C/T n = 210)	CCI: CAZ/AVI: median 4 (IQR 3–6) C/T: median 5 (IQR 3–7) SOFA score: CAZ/AVI: median 7 (IQR 4–10) C/T: median 7 (IQR 4–10) Severe sepsis / septic shock: CAZ/AVI: 59% C/T: 59% ICU admission: CAZ/AVI: 79% C/T: 81% Mechanical ventilation: CAZ/AVI: 70% C/T: 71% Vasopressor use: CAZ/AVI: 40% C/T: 40% RRT: CAZ/AVI: 30% C/T: 30%	<i>P. aeruginosa</i> (100%) MDR / DTR CAZ/AVI: 59% C/T: 59% ICU admission: CAZ/AVI: 79% C/T: 81% Mechanical ventilation: CAZ/AVI: 70% C/T: 71% Vasopressor use: CAZ/AVI: 40% C/T: 40% RRT: CAZ/AVI: 30% C/T: 30%	RTI: 83% (balanced) • VAP 46–49% • HAP 13–15% • HAP 10–12% • CAP 10–11% Bacteremia: 17%	CAZ/AVI arm: Monotherapy: 73% Combination therapy: 27% Combination with IV and/or inhaled agents (AGs, polymyxins, others)	Clinical success (30 d): 52% (CAZ/AVI) vs 61% (C/T) 30-day mortality: 24% vs 23% 90-day mortality: 37% vs 38% Recurrence (30 d): 21% vs 15% Resistance emergence: 23% vs 22%	Critically ill, well-matched cohorts with comparable baseline severity across groups. High burden of ICU care, mechanical ventilation, vasopressor support, and RRT; outcomes strongly influenced by disease severity and pneumonia predominance.
Rodgers et al. [135]	2022	Prospective, randomized, multicenter, double-blind, phase 3 trial – Indian subset analysis (RECLAIM)	125 randomized CAZ/AVI + MET: 62 MER: 63	APACHE < 10: 91.3% 10–30: 8.7% ICU admission: implied (critical care) Bacteremia: 5.2% Renal impairment (moderate – severe): 7.8% Pitt bacteremia score: mean 4.1 (survivors) vs 7.0 (fatal) CCI: mean ~5 Severe neutropenia: 19.8% Septic shock: NR	<i>E. coli</i> (80.0%) <i>K. pneumoniae</i> (16.9%) <i>P. aeruginosa</i> (10.8%)	Complicated IAI (100%)	CAZ/AVI + metronidazole per protocol Comparator: MER Monotherapy vs combination: protocol-defined (CAZ/AVI always with metronidazole)	Clinical cure (ITOC): MITT: 89.3% (CAZ/AVI) vs 84.7% (MER) CE: 97.8% vs 93.5% MITT: 83.5% vs 77.1%	Indian subgroup from RECLAIM; younger population with lower comorbidity burden than global cohort. Demonstrates non-inferior efficacy of CAZ/AVI + metronidazole vs MER for CAI in ICU-relevant setting, supporting carbapenem-sparing strategy.
Mert et al. [136]	2024	Multicenter, retrospective, observational study	106 adults with CAZ/AVI – susceptible CRKP-BSI	ICU admission: 50% Vasopressor use: 34% Mechanical ventilation: 31% CCI: mean 5.5 (81% ≥ 3) Neutropenia: common (oncology population) Septic shock: NR	<i>K. pneumoniae</i> (100%) CR OXA-48 predominant (endemic setting)	BSI: 100%	Monotherapy only (study inclusion): CAZ/AVI 2.5 g q8h (dose-adjusted for renal function) Used as first-line or salvage after last-resort regimens	Mortality: 30 d: 33% overall First-line CAZ/AVI: 14.3% vs salvage: 37.7% Relapse: 0% Resistance emergence: 0%	OXA-48–endemic multicenter cohort from Turkey. Demonstrates clear survival benefit of early CAZ/AVI initiation and supports CAZ/AVI monotherapy for CRKP-BSI. Early initiation (day of blood culture) independently reduced mortality (HR ~ 0.25).
Alghamdi et al. [137]	2024	Retrospective observational cohort study (single center)	32 cancer patients	ICU admission: 50% Vasopressor use: 34% Mechanical ventilation: 31% CCI: mean 5.5 (81% ≥ 3) Neutropenia: common (oncology population) Septic shock: NR	<i>K. pneumoniae</i> (88%) <i>E. coli</i> (6%) <i>Enterobacter</i> spp. (3%) OXA-48: 81% NDM: 9% OXA-48 + NDM: 9%	BSI: 44% Non-BSI: 56%	Non-BSI: 56% CAZ/AVI ≥ 72 h as targeted therapy Monotherapy: 53% Combination therapy: 47% (AGs, AZT, COL, TGC) AZT added for NDM-producing isolates	Mortality: 30 d: 47% In-hospital: 56% Clinical cure: 59% Relapse: 10.5% Reinfection: 23.5%	High-risk oncology cohort with frequent ICU admission and CRE risk factors. Mortality remains high despite CAZ/AVI. No mortality difference between monotherapy and combination therapy. Supports CAZ/AVI as a salvage/targeted option in cancer patients with OXA-48/NDM CRE.
Guimarães et al. [138]	2019	Multicenter case series (compassionate-use salvage therapy)	29 adults	ICU admission: 58.6% Renal impairment: 48.2% CCI: median 2 (21% ≥ 3) Pitt score (BSI only, n = 12): median 2; ≥ 4 in 16.6% Hypotension at diagnosis: 48% Septic shock: NR	<i>K. pneumoniae</i> (=97%) <i>S. marcescens</i> (rare) All isolates KPC-2 producers Carbapenem and polymyxin-resistant CAZ/AVI susceptibility: 100% (MIC50 1 µg/mL)	BSI: 41.4% UTI: 27.6% IAI: 13.8% Nosocomial RTI: 10.3% SSTI: 6.9%	CAZ/AVI used as salvage therapy under compassionate-use protocol Initial therapy: 41% Combination therapy: 48.3% (TGC, polymyxins, MER, AGs, fosfomycin)	Clinical cure: 82.7% Microbiological cure (BSI): 100% 14-day mortality: 31% 30-day mortality: 51.7% Adverse events: 13.7%	Extremely high-risk cohort with XDR KPC-2 <i>Enterobacteriales</i> , including polymyxin resistance. Despite severity, high clinical success observed. Mortality remained substantial, particularly in renal impairment. Supports CAZ/AVI as a last-resort salvage option in carbapenem- and polymyxin-resistant infections.

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Table 2. (Continued).

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with CAZ-AVI	Outcomes	Comments
Boattini et al. [139]	2017–2021	Retrospective, single-center observational cohort	196 (182 evaluable for 30-day mortality)	CCI ≥ 3 : CAZ/AVI monotherapy 83.3% vs CAZ/AVI combination 59.8% vs other regimens 70.5% ($p = 0.04$) INCREMENT-CPE ≥ 8 : CAZ/AVI monotherapy 44.4% vs CAZ/AVI combination 43.9% vs other regimens 51.6% ($p = 0.50$) Critically ill (ICU admission): CAZ/AVI monotherapy 69.4% vs CAZ/AVI combination 45.6% vs other regimens 70.5% ($p = 0.18$)	<i>K. pneumoniae</i> (100%)	BSI: 100%	CAZ/AVI used as targeted therapy Monotherapy and combination therapy used Combination mainly with polymyxin or other active agents	In-hospital mortality: 27.8% (CAZ/AVI monotherapy) vs 30.5% (CAZ/AVI combination) vs 41.0% (other regimens) 30-day all-cause mortality: 20.6% (CAZ/AVI monotherapy) vs 27.5% (CAZ/AVI combination) vs 44.1% (other regimens) ($p = 0.03$)	Large Italian endemic KPC-Kp BSI cohort. CAZ/AVI independently associated with improved survival. No survival benefit demonstrated for CAZ/AVI + polymyxin. Rapid diagnostics improved treatment patterns but not mortality
Balandin et al. [140]	2018–2019	Multicentre retrospective observational cohort	68	CCI: mean 4.9 ± 2.7 SOFA: mean 10.6 ± 4.0 – SOFA 1: 7.6 ± 4.0 – SOFA 3: 7.1 ± 4.2 – SOFA 7: 5.8 ± 4.5 APACHE II: 19.5 ± 4.5 Septic shock: 38.8% Mechanical ventilation: 80.3%	<i>Enterobacteriaceae</i> (79.4%) – <i>Resistella spp.</i> (66.7%) – <i>Bertranda spp.</i> (13.0%) – <i>E. coli</i> (7.4%) – <i>Citrobacter spp.</i> (5.6%) – <i>Enterobacter spp.</i> (3.6%) – <i>Proteus spp.</i> (1.9%) <i>P. aeruginosa</i> (19.1%) <i>Burkholderia cepacia</i> (1.5%)	RTI: 76.5% BSI: 22.4% IAI: 22.1% SST: 8.8% UTI: 10.3% Other: tracheobronchitis, mediastinitis, biliary infections	Monotherapy: 50.0% Combination therapy: 50.0% Combination with: – AGs, COL, TGC	Clinical success (30d): 73.5% Microbiological success (30d): 36.8% eradication Recurrence: 0% Mortality: 30d: 32.4% 90d: NR	High illness severity ICU cohort. Ventilation, bacteremia, RTI, corticosteroid use, and higher SOFA scores associated with mortality. No outcome difference between mono- and combination therapy.
Gu et al. [141]	2019–2020	Retrospective observational cohort	90 total infections CAZ/AVI group: 42	(CAZ/AVI vs OAA) CCI: 3 (2–5) vs 3 (2–4) SOFA (infection onset): 6 (4–8) vs 5 (3–8.5) Septic shock: 47.6% vs 50.0% Mechanical ventilation: 66.7% vs 47.9% RRT: 21.4% vs 12.5%	<i>K. pneumoniae</i> (100%, CR)	(CAZ/AVI vs OAA) RTI: 78.6% vs 70.8% Bacteremia: 40.5% vs 58.3% UTI: 9.5% vs 4.2% IAI: 2.4% vs 2.1% SST: 2.4% vs 6.3% Other (CNS): 2.4% vs 8.4%	Monotherapy: 38.1% Combination therapy: 61.9% Combination with: – COL – TGC – FOS – AG	Clinical success (30d): NR Microbiological success (30d): NR Recurrence: NR Mortality: 30d: 19.0% vs 45.8% 90d: NR	Predominantly critically ill cohort, with high rates of septic shock, mechanical ventilation, and organ failure at infection onset.
Castón et al. [142]	2014–2018	Single-center retrospective observational cohort	47	CCI: median 4 (IQR 2–6) SOFA: median 3 (IQR 2–6) APACHE II: median 14 (IQR 9–19) Septic shock: 53.2% Mechanical ventilation (prior month): 23.4% INCREMENT-CPE > 7 : 57.4%	<i>K. pneumoniae</i> (100%, KPC-producing)	IAI: 38.3% RTI: 29.8% UTI: 14.9% SST: 8.4% CLABSI: 4.2% Surgical wound: 4.2%	Monotherapy: 59.6% Combination therapy: 27.7% Combination with: – Gentamicin – TGC – COL – Fosfomycin	Clinical success (30d): 78.7% Microbiological success (30d): 59.6% Mortality: (30d): 23.4% Development of resistance: 12.7%	Cohort included a high proportion of critically ill patients, with frequent septic shock, bacteremia, and elevated INCREMENT-CPE scores. RTI and INCREMENT-CPE > 7 were independently associated with clinical failure. Emergence of CAZ/AVI resistance observed (12.7%), mainly in prolonged IAI.
Castón et al. [92]	2012–2016	Multicentre retrospective observational cohort (CAZ/AVI vs other treatments)	31 total CAZ/AVI: 8 Other: 23	CCI: mean ≈ 2 Pitt index mean ≈ 3 MSSC score: 100% high risk Neutropenia: 77.4% Severe neutropenia (grade IV): 95.8% Septic shock: 38.7% Severe sepsis: 12.9% Septic shock: 41.9% Critical care admission: 12.5%	CPE <i>K. pneumoniae</i> : 80.6% <i>Serratia marcescens</i> : 6.4% <i>Klebsiella oxytoca</i> : 6.4% <i>Enterobacter cloacae</i> : 3.2% <i>E. coli</i> : 3.2% Carbapenemases: OXA-48 (61.3%), KPC (38.7%)	Primary BSI: 45.2% CLABSI: 19.4% RTI: 19.4% IAI: 6.5% UTI: 3.2% Other: 6.5%	CAZ/AVI used in 25.8% as targeted therapy Combination therapy: frequent (mainly AGs, fosfomycin, TGC, COL)	Clinical success (14 d): CAZ/AVI 85.7% vs others 34.8% ($p = 0.03$) Microbiological success: NR Mortality: 30 d: CAZ/AVI 25% vs others 52.2% 90 d: NR	Critically ill, profoundly immunocompromised patients with hematologic malignancies and high baseline mortality. CAZ/AVI associated with significantly higher early clinical cure but not statistically significant mortality reduction
Zhang et al. [143]	2019–2023	Retrospective, single-center, observational	81 KT recipients	SOFA (median, IQR): 5 (5–6) APACHE II (median, IQR): 10 (9–13) CHRT: 50.6%	CRKP: 75.3% (61/81) CRPA: 19.8% (16/81) CRAB: 4.9% (4/81)	Surgical site infections: 44.4% BSI: 43.2% RTI: 39.5% UTI: 35.8% Multiple sites: 49.4%	Monotherapy: 49.4% Combination therapy: 50.6% Combination with: – MER 43.9% – Imipenem-clastatin 29.3% – TGC 17.1% – Polymyxin 7.3% – Amikacin 2.4% Salvage therapy: 39.5%	Clinical success (14 d): 72.8% Microbiological success: 66.7% Recurrence (90 d): 4.9% Mortality: 30 d: 22.2%	Critically ill kidney transplant recipients with high rates of CRIT use and multistate infections; early CAZ/AVI initiation associated with higher clinical cure, while higher APACHE II scores predicted mortality

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Table 2. (Continued).

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with CAZ-AVI	Outcomes	Comments
Falcone et al. [144]	2015–2018	Multicenter retrospective observational ICU study	102 ICU patients	CCI: median 2 (IQR 1–3) SOFA: median 5 (IQR 3–9.5); higher in non-survivors (7.5 vs 4) APACHE II: median 15 (IQR 11–21); higher in non-survivors (19 vs 13.5) Septic shock: 39.2% Mechanical ventilation: 39.2%	<i>K. pneumoniae</i> (KPC-producing): 100%	KPC-Kp BSI: 100% CLABSI: 12.7% Primary BSI: 13.7% IAI: 23.5% UTI: 20.6% SSTI: 17.6% RTI: 10.8%	Monotherapy / combination regimens reported CAZ/AVI ± fosfomycin or AGs 12.7% COL-containing regimens: 59.8% Other regimens: 16.7%	Clinical success (30 d): NR Microbiological success (30 d): NR Mortality: 7 d: 20.6% 14 d: 32.4% 30 d: 45% Early appropriate therapy (<24 h): 29.1% vs 63.8% mortality Composite endpoint (30 d mortality or nephrotoxicity): reduced with CAZ/AVI vs COL (HR 0.231)	Critically ill ICU population with high severity and mortality. Early (<24 h) appropriate therapy strongly associated with survival. CAZ/AVI did not significantly reduce 30-day mortality, but was associated with lower composite endpoint vs COL, supporting a safer profile in severe KPC-Kp BSI. Recurrence NR.
Mayo Oliveira et al. [145]	2020–2021	Observational, single-center, cohort study	89 ICU patients (COVID-19: 49; non-COVID-19: 40)	CCI: NR SOFA: NR Septic shock: NR Ventilated: ICU population (ventilation not quantified)	Colonization (MDR): <i>K. pneumoniae</i> (66.6% of colonized patients; majority VIM-producing) Bacteremia pathogens (10.1%): <i>K. pneumoniae</i> (n = 4) <i>P. aeruginosa</i> (n = 3) <i>E. faecium</i> (n = 1) <i>Enterobacter asburiae</i> (n = 1) <i>K. pneumoniae</i> (CRKP) Predominantly ST258 (73%) Carbapenemases: KPC-2 (47%), KPC-3 (50%), OXA-232 (6%)	Colonization surveillance cultures Blood cultures (for bacteremia)	Empirical CAZ/AVI: 41.6% overall SARS-CoV-2+: 4.3% SARS-CoV-2-: 40% Combination therapy: CAZ/AVI + AZT in 52.8%	Clinical success (30 d): NR Microbiological success (30 d): NR Mortality: 41.6% overall 42.9% SARS-CoV-2+ vs 40% SARS-CoV-2 Deaths ≤ 28 d: 81%	Exclusively critically ill ICU population; no difference in outcomes by SARS-CoV-2 status
Lutembach et al. [146]	2011–2016	Prospective, multicenter, observational real-world cohort with translational PK/PD and machine-learning modeling	49 patients	Pitt bacteremia score: median 4 (IQR 2–4) CCI: median 3 (IQR 2–5) Mechanical ventilation: 53% Hypotension: 67%	<i>K. pneumoniae</i> (CRKP) Predominantly ST258 (73%) Carbapenemases: KPC-2 (47%), KPC-3 (50%), OXA-232 (6%)	BSI only	Monotherapy: CAZ/AVI alone: 22% (11/49) Combination therapy: CAZ/AVI + COL: 18% (9/49)	Mortality: ~33% 30-day mortality overall: COL monotherapy: 52% mortality (15/29) CAZ/AVI monotherapy: 9% mortality (1/11) CAZ/AVI + COL: 0% mortality (0/9) Mortality (30 d): 52% overall; (alone or with AZT) independently associated with survival in CR-GNB BSI	Critically ill population with high disease severity. Real-world CAZ/AVI use in CRE bacteremia. Combination therapy showed synergistic killing and lowest mortality. Study integrates clinical, bacterial, and PK/PD variables using machine learning; not designed to assess clinical cure or microbiological eradication.
Barbueno et al. [147]	2020–2022	Prospective, observational, multicenter	466 total CR-GNB BSI patients	INCREMENT-CPE score: median 10 (IQR 6–12); 75% critically ill (ICU)	<i>K. pneumoniae</i> (53%) <i>A. baumannii</i> (25%) Carbapenemases among Enterobacteriales: KPC 50%, MBL 48%, OXA 6%, mixed 5%	BSI only	Monotherapy and combination therapy: CAZ/AVI alone or CAZ/AVI + AZT	Mortality (30 d): 52% overall; (alone or with AZT) independently associated with survival in CR-GNB BSI	High-risk, predominantly ICU population; CAZ/AVI (alone or with AZT) independently associated with survival in CR-GNB BSI
Riccobene et al. [148]	2018–2022	Retrospective, multicenter, observational real-world cohort	ENT: 229/320 PSA: 36/027	ICU admission: ENT: 27.9% PSA: 41.5%	Enterobacteriales: <i>E. coli</i> , <i>Enterobacter spp.</i> , <i>Serratia spp.</i> , <i>Chrobacter spp.</i> , <i>Proteus spp.</i> , <i>Morganella spp.</i> <i>P. aeruginosa</i> <i>K. pneumoniae</i> : 95.6% <i>E. coli</i> : 4.4% OXA-48: 93.9% KPC: 6.1%	UTI (ENT 73.6%; PSA 47.0%) RTI (ENT 8.2%; PSA 38.0%) Blood (ENT 12.9%; PSA 8.1%) Other	Subset analysis for CAZ/AVI	Clinical success: NR Microbiological success: NR Mortality (hospital): ENT overall: 5.1% PSA overall: 10.5%	Large real-world evidence study in predominantly hospitalized and ICU patients. Demonstrates that timely initiation of CAZ/AVI is associated with lower mortality and shorter LOS, especially in carbapenem-non-susceptible infections
Asian et al. [149]	2019–2023	Retrospective, multicenter, 1:1 matched cohort	180 (CAZ/AVI = 90; OAT = 90)	ICU: 63.9%; Septic shock: 35.6%; Mechanical ventilation: 41.1%; INCREMENT-CPE ≥ 8: 51.1%; SOFA score: mean 7.7 ± 5.6; Pitt score: mean 3.7 ± 3.2	<i>K. pneumoniae</i> : 95.6% <i>E. coli</i> : 4.4% OXA-48: 93.9% KPC: 6.1%	RTI: 41.1% IAI: 20.0% UTI: 13.3% Primary BSI: 12.2% BII: 6.7% CLABSI: 5.6% CNS: 1.1% BSI: 100%	CAZ/AVI monotherapy: 54.4% (49/90) CAZ/AVI combination therapy: 45.6% (41/90) Combination agents: AGs, polymyxins (COL), TGC, fosfomycin (≥48 h) Monotherapy: CAZ/AVI as definitive backbone in 13% (22/170) Combination therapy: 34% (58/170)	30-d mortality: CAZ/AVI 35.6% vs OAT 56.7% (aOR 0.37) 21-d clinical response: CAZ/AVI 50.0% vs OAT 26.7% Relapse: CAZ/AVI 5.6% vs OAT 11.1% Clinical success (30 d): NR Microbiological success (30 d): NR Mortality: 30 d: 27.6% (47/170) 90 d: NR	Patients were predominantly critically ill (63.9% ICU); 51.1% INCREMENT-CPE ≥ 8. Mortality and clinical response benefits with CAZ/AVI were observed without significant differences between CAZ/AVI monotherapy and combination therapy
Bavaro et al. [150]	2021–2022	Retrospective, multicenter cohort	170	CCI: NR SOFA: NR APACHE: NR Septic shock: 32% (54/170)	<i>P. aeruginosa</i>	BSI: 100%	Monotherapy: 55% (33/60) Combination therapy: 45% (27/60) Combination with: – COL: 26% (17/72) – GC: 22% (16/72) – AGs: 40% (11/27)	Clinical success (30 d): 65% (39/60) Microbiological success (30 d): 53% (32/60) Mortality: 30 d in-hospital: 32% (19/60) 90 d: NR	CAZ/AVI used as part of antipseudomonal cephalosporins, which were independently associated with reduced 30-day mortality. Combination therapy beneficial only in septic shock
King et al. [151]	2015–2016	Retrospective, multicenter	60	CCI: median 4.5 (IQR 3–7) SOFA: NR APACHE: NR Septic shock: 21% (vasopressors 14/60) Pitt bacteremia score: median 2 (IQR 0–5) ICU admission: 59% (35/60)	<i>K. pneumoniae</i> 83% (50/60) <i>E. coli</i> 8% (5/60) Enterobacter spp. 7% (4/60) Other Enterobacteriales ≤ 2% each	RTI: 27% (16/60) Bacteremia: 36% (23/60) IAI: 7% (4/60) SSTI: 13% (8/60) UTI: 28% (17/60) Other: BII 5% (2/60)	Monotherapy: 55% (33/60) Combination therapy: 45% (27/60) Combination with: – COL: 26% (17/72) – GC: 22% (16/72) – AGs: 40% (11/27)	Clinical success (30 d): 65% (39/60) Microbiological success (30 d): 53% (32/60) Mortality: 30 d in-hospital: 32% (19/60) 90 d: NR	Critically ill real-world CRE cohort: 59% ICU, 38% mechanically ventilated, 21% on vasopressors. Mortality higher in ICU (46% vs 12% non-ICU).

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Table 2. (Continued).

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with CAZ-AVI	Outcomes	Comments
Rempenault et al. [152]	2016–2019	Retrospective, observational	15	CCI (median, range): – CAZ/AVI: 5 (0–10) – C/T: 2 (1–7) Septic shock: NR Mechanical ventilation: NR	Enterobacteriaceae: 53.3% (8/15) <i>P. aeruginosa</i> : 60.0% (9/15) MDR organisms: 86.7% (13/15) ESBL producers: 40.0% (6/15) CPE (NDM): 6.7% (1/15)	BLIs only: – Femoral head/neck resection chamber: 40.0% (6/15) – Osteosynthesis infection: 20.0% (3/15) – PJI: 13.3% (2/15) – Septic arthritis: 13.3% (2/15) – Spondylodiscitis: 6.7% (1/15) – Ankle BJI: 6.7% (1/15)	CAZ/AVI regimens (n = 9): – Monotherapy: 11.1% (1/9) – Combination therapy: 88.9% (8/9) Combination with: – AZT (NDM case) – Other active agents (variable, not standardized)	Clinical success: – CAZ/AVI: 77.8% (7/9) – C/T: 60.0% (3/5) Mortality: 30 d: 0% (0/15) 90 d: 0% (0/15)	Complex chronic BLIs, predominantly MDR and polymicrobial, managed with extensive surgery. CAZ/AVI patients had higher comorbidity burden but better outcomes than C/T. No deaths despite prolonged therapy. Represents true real-world salvage use of CAZ/AVI in severe orthopedic infections.
Qian et al. [153]	2019–2021	Retrospective, single-center, observational; propensity score matched	363 total (49 CAZ/AVI; 314 control); matched cohort: 140 (40 CAZ/AVI; 100 control)	ICU admission: 52.6% overall; 79.6% CAZ/AVI (unmatched), 80.0% CAZ/AVI (matched)	<i>P. aeruginosa</i> (100% MDRPA). Co-infection: <i>A. baumannii</i> 10.7%, <i>K. pneumoniae</i> 9.9%	RTI: 91.7% UTI: 18 cases IAI: 7 cases BSI: 3 cases Mixed sources: 13 cases	Monotherapy: 33/49 (67.3%). Combination therapy: 16/49 (32.7%). agents: polymyxins, quinolones (exact proportions NR)	Clinical success: CAZ/AVI overall: 61.2% Monotherapy: 57.6% (19/33) Combination therapy: 68.8% (11/16) Microbiological success: Monotherapy: 45.5% (15/33) Combination therapy: 68.8% (11/16)	Severe MDRPA infections with very high ICU and airway support rates. CAZ/AVI group had higher baseline severity pre-matching. CAZ/AVI associated with lower clinical failure vs comparators after PSM (OR 0.381; <i>p</i> = 0.012)
Satin Et al. [154]	2016–2018	Multicenter observational cohort	137	CCI: median 5 (IQR 3–7) APACHE II: median 20 (IQR 15–25) Pitt bacteremia: median 3 (IQR 1–5) ICU at onset: 23% (31/137) Mechanical ventilation: 35% (48/137)	BSI only Sources: IAI 33% (45/137) Vascular catheter 13% (18/137) RTI 13% (18/137) UTI12% (17/137) Other/unknown 29%	CAZ/AVI monotherapy: 21 / 112 = 18.8% Combination therapy (≥2 active agents): 23 / 112 = 20.5%	Overall mortality: 14-day: 29% (40/137) 30-day: 38% (52/137) CAZ/AVI monotherapy: 14-day mortality 0% (0/21) 30-day mortality 10% (2/21) Polymyxin monotherapy: 14-day 19% 30-day 31% Combination therapy: 14-day 17% 30-day 43%	CAZ/AVI showed numerically lower mortality than polymyxins	
Almangour et al. [155]	2017–2022	Retrospective, multicenter, observational cohort	200	CCI: median 5 (IQR 3–8) overall APACHE II: median 20 (IQR 13–25) mono vs 19 (12–30) combo ICU at onset: 112/200 (56%) Mechanical ventilation: 96/200 (48%) Septic shock: 74/200 (37%)	<i>P. aeruginosa</i> (MDR, susceptible to CAZ/AVI or C/T) HAP: 56/200 (28%) VAP: 42/200 (21%) Wound: 47/200 (24%) UTI: 20/200 (10%) IAI: 16/200 (8%) CLABSI: 7/200 (4%) Other: 12/200 (6%) BSI: 37/200 (19%)	Monotherapy: CAZ/AVI or C/T alone (118 pts) Combination therapy: CAZ/AVI or C/T + ≥1 agent (82 pts) Combination agents included: – IV COL 44% – AZT 20% – Inhaled COL 17% – Fluoroquinolone 16% – AGS 15% – Carbapenem 11%	Clinical cure: 127/200 (64%) – Monotherapy: 80/118 (68%) – Combination: 47/82 (57%) In-hospital mortality: 81/200 (41%) – Monotherapy: 44/118 (37%) – Combination therapy: 37/82 (45%) 30-day mortality: 50/200 (25%) – Monotherapy: 28/118 (24%) – Combination therapy: 22/82 (27%) Microbiologic eradication: – Monotherapy: 56/89 (63%) – Combination therapy: 33/60 (55%)	Severe real-world MDR <i>P. aeruginosa</i> population with high ICU (56%), ventilation (48%), and shock (37%) rates. Combination therapy did not improve mortality or clinical cure compared with monotherapy, but was associated with higher AKI (32% vs 12%). Represents true real-world comparative use of CAZ/AVI/ C/T in critically ill patients	
Sousa et al. [156]	2016–2017	Retrospective, observational, single-center	57	CCI: median 3 (IQR 0–13) APACHE II: median 24 (IQR 8–45) INCREMENT-CPE: median 6 (IQR 2–13); >7 ICU at onset: 22/57 (38%) Sepsis/septic shock: 31/57 (54%) Vasopressors: 20/57 (35%) Mechanical ventilation: 17/57 (30%)	Enterobacteriales: <i>K. pneumoniae</i> (OXA-48): 54/57 (95%) <i>E. coli</i> : 2/57 (3%) Enterobacter cloacae: 1/57 (2%) BSI: 26/57 (46%)	Monotherapy: CAZ/AVI alone (46 pts) Combination therapy: CAZ/AVI + active agent (11 pts) Combination agents: – IV COL – Inhaled COL – TGC – Amikacin – Imipenem	Clinical cure: 44/57 (77%) – Monotherapy: 37/46 (80%) – Combination therapy: 7/11 (64%) Microbiological cure: 37/57 (65%) – Monotherapy: 31/46 (67%) – Combination therapy: 6/11 (54%) 14-day mortality: 8/57 (14%) – Monotherapy: 7/46 (15%) – Combination therapy: 1/11 (9%) 30-day mortality: 13/57 (22%) – Monotherapy: 10/46 (22%) – Combination therapy: 3/11 (27%) 90-day recurrence: 6/57 (10%)	High-risk outbreak setting with OXA-48 <i>K. pneumoniae</i> , high INCREMENT-CPE scores and frequent bacteremia. CAZ/AVI used mainly as salvage therapy after failure or toxicity of COL/carbapenems	

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Table 2. (Continued).

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with CAZ-AVI	Outcomes	Comments
Shi et al. [157]	2020–2023	Retrospective, single-center observational study	75	SOFA: median 13 (IQR 11–16) ICU admission: 72.0% (54/75) Mechanical ventilation: 56.0% (42/75) CRRT: 20.0% (15/75) Septic shock: NR	<i>K. pneumoniae</i> 47.9% <i>K. pneumoniae</i> 28.2% <i>S. maltophilia</i> 39.4% CRKP + other pathogens: 5.3% (4/75)	RTI: 49.3% BSI: 17.3% UTI: 4.0% IAI: 1.3% SSTI: 1.3% CNS: 1.3% RTI + BSI: 9.3% RTI + UTI: 4.0% RTI + SSTI: 2.7% RTI + IAI: 1.3% BSI + UTI: 1.3% BSI + IAI: 2.7% RTI + BSI + UTI: 1.3% RTI + BSI + IAI: 1.3% LRTI	Monotherapy: 61.3% (46/75) Combination therapy: 38.7% (29/75) With 1 agent: 33.3% With 2 agents: 5.3% (Combination agents: TGC, carbapenems, AG)	Clinical success: 70.7% (53/75) Mortality: 14.4% (8/55) (6/75) 28 d: 18.7% (14/75) Microbiological clearance: 71.2% (47/66 evaluable)	Critically ill CRKP cohort in China with very high SOFA scores and ICU burden
Pan et al. [158]	2022–2024	Single-center retrospective study	71	APACHE II: 24.2 ± 6.3 Septic shock: 38.0% Mechanical Ventilation: 93.0% ICU stay: 19.4 ± 13.6 d	<i>P. aeruginosa</i> 47.9% <i>K. pneumoniae</i> 28.2% <i>S. maltophilia</i> 39.4% mixed MDR-GNB 21.1%	RTI: 91.2% BSI: 14.7% IAI: 10.0% UTI: 10.0% CNS: 4.1% SSTI: 2.4% Multi-site infection: 25.9%	Monotherapy: 74.6% (53/71) Combination: 25.4% (18/71) (Combination with: Polymyxin B 11.3%, TGC 9.9%)	Mortality: 28 d 43.7% (31/71) Survival: 56.3% AKI: 26.8%	Critically ill ICU LRTI population with very high baseline severity. All isolates susceptible to CAZ/AVI (100%). Mortality driven by APACHE II score, Aspergillus infection, and shorter CAZ/AVI duration; combination therapy not independently protective
Long et al. [159]	2021–2023	Multicenter retrospective real-world cohort; PSM analysis	170 PSM cohort: 82 (41 vs 41)	APACHE II: median 23 (IQR 20–25) ICU admission: 72.4% Mechanical ventilation: 77.6% Vasoactive drugs: 61.2% Sepsis/septic shock: 38.8% CRRT/RTT: 14.1%	CRPA: 100% • DTR-PA: 72.9% • Polymicrobial CRE ICU admission: 72.4% Mechanical ventilation: 77.6% Vasoactive drugs: 61.2% Sepsis/septic shock: 38.8% CRRT/RTT: 14.1%	RTI: 91.2% BSI: 14.7% IAI: 10.0% UTI: 10.0% CNS: 4.1% SSTI: 2.4% Multi-site infection: 25.9%	CAZ/AVI monotherapy: 50.6% CAZ/AVI combination therapy: 49.4% Combination with carbapenems, other anti-carbapenems, β -lactams, quinolones, or AGs	Clinical success: 54.5% Microbiological clearance (overall): 59.7% 7-day microbiological clearance: 36.4% AKI: 24.7% 30-day mortality: 13.0% 90-day mortality: NR	Critically ill ICU-predominant CRPA population with high rates of DTR-PA and polymicrobial infection. CAZ/AVI achieved significantly higher microbiological clearance than polymyxin B, while clinical success, AKI, and 30-day mortality were similar after PSM
Soriano et al. [160]	2018–2022	Multinational, multicenter, retrospective real-world study	516	CCI: NR SOFA: NR APACHE II: NR Septic shock: NR ICU admission: 50% (276/516) Direct ICU admission: 23% (116/516) Immunocompromised: 47% (243/516) Severe kidney disease: 22% (113/516)	<i>K. pneumoniae</i> : 60% (306/516) <i>P. aeruginosa</i> : 14% (69/516) <i>Klebsiella spp.</i> : 10% (50/516) MDR organisms: ~69% of isolates	RTI: 22% (114/516) BSI / other: 41% (209/516) UTI: 20% (103/516) IAI: 17% (90/516)	Monotherapy: 31% (158/516) Combination therapy: 69% (358/516) Combination with: – AZT – Vancomycin – Meropenidazole – Amikacin	Clinical success (overall): 77% (399/516) Microbiological success: NR Mortality: 23% (119/516) In-hospital mortality: 23% (119/516) 30-day mortality: NR 90-day mortality: NR	Large multinational real-world cohort including high-complexity and immunocompromised patients, with 50% ICU admission and predominance of MDR Gram-negative infections. CAZ/AVI was mainly used as salvage or second-line therapy
Liu et al. [161]	2017–2024	Single-center retrospective real-world study	45	CCI: 6.7 ± 3.9 APACHE II score: 22.8 ± 9.8 Pitt bacteremia score: 3.2 ± 2.6 INCREMENT-CPE score: 7.4 ± 3.9 Septic shock: 35.6% (16/45) ICU acquisition: 42.2% (19/45) Mechanical ventilation initiation: 13.3% (6/45) RTT: 8.9% (4/45)	<i>K. pneumoniae</i> (OXA-48) 93.3% OXA-181 6.7%	RTI 29%; primary BSI 22%; IAI 20%; UTI 18%; Catheter-related 9%	CAZ/AVI in 40%; other active therapy 60%; combination 9%	Clinical success Overall: 49% CAZ/AVI 50% Other therapy 48% Mortality 30-day: 28.9% (CAZ/AVI 22.2% vs other 33.3%) In-hospital: 48.9%	Real-world single-center study focused exclusively on OXA-48-producing CRKP bacteremia. Patients were elderly with high comorbidity burden (CCI) and significant disease severity (APACHE II, Pitt bacteremia, INCREMENT-CPE)

Abbreviations: A. *baumannii*; Acinetobacter baumannii; AG: Aminoglycoside; AKI: Acute kidney injury; ALL: Acute Lymphoblastic Leukemia; APACHE II: Acute Physiology and Chronic Health Evaluation II; AZT: Aztreonam; BAT: Best available therapy; BJI: Bone and joint infection; BSI: Bloodstream infection; CAZ-AVI: Ceftazidime-avibactam; CARB: Carbapenem-based therapy; CCI: Charlson comorbidity index; CLABSI: Central line-associated bloodstream infection; COL: Colistin (polymyxin E); CPKP: Carbapenemase-producing *Klebsiella pneumoniae*; CRE: Carbapenem-resistant Enterobacteriales; CR-GNB: Carbapenem-resistant Gram-negative bacteria; CRKP: Carbapenem-resistant *Klebsiella pneumoniae*; CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*; CRRT: Continuous renal replacement therapy; CVWH: Continuous venovenous hemofiltration; CVC: Central venous catheter; CIAI: Complicated intra-abdominal infection; CMITT: Clinically modified intention-to-treat population; CUTI: Complicated urinary tract infection; DTR: Difficult-to-treat resistance; ECOG: Eastern Cooperative Oncology Group performance status; EOT: End of treatment; ESBL: Extended-spectrum β -lactamase; FUI: Fever of unknown origin; HAP: Hospital-acquired pneumonia; HSC: Hematopoietic stem cell transplantation; IAI: Intra-abdominal infection; ICU: Intensive care unit; IHD: Intermittent hemodialysis; INCREMENT-CPE: INCREMENT score for carbapenemase-producing Enterobacteriales; INCREMENT-SOT-CPE: INCREMENT score for solid organ transplant recipients with CPE; IPW: Inverse probability weighting; IQR: Interquartiles; IV: Intravenous; KPC: *Klebsiella pneumoniae* carbapenemase; LRTI: Lower respiratory tract infection; MASCC: Multinational Association for Supportive Care in Cancer score; MBL: Metallo- β -lactamase; MER: Meropenem; MIC: Minimum inhibitory concentration; MMITT: Microbiologically modified intention-to-treat population; MDR: Multidrug-resistant; MDRPA: Multidrug-resistant *Pseudomonas aeruginosa*; MM: Multiple myeloma; NDM: New Delhi metallo- β -lactamase; NR: Not reported; OAAT/OAAS: Other active antimicrobial therapy/agents; OXA-48: Oxacillinase-48 carbapenemase; PK/PD: Pharmacokinetics/pharmacodynamics; PSM: Propensity score matching; qSOFA: Quick Sequential Organ Failure Assessment; RRT: Renal replacement therapy; SD: Standard deviation; SOT: Solid organ transplant; SOFA: Sequential Organ Failure Assessment; SSTI: Skin and soft tissue infection; *S. maltophilia*: *Stenotrophomonas maltophilia*; TGC: Tigecycline; TMP-SMX: Trimethoprim-sulfamethoxazole; TOC: Test of cure; UTI: Urinary tract infection; VAP: Ventilator-associated pneumonia; vHAP: Ventilated hospital-acquired pneumonia.

In recent years, real-world evidence has provided valuable insights into the clinical performance of MER-VAB [171–178], as summarized in Table 3. Study populations were predominantly composed of critically ill patients with CRE infections [171,172,174], with KPC-producing strains accounting for approximately 77–90% of isolates in two cohorts [171,172], while others enrolled more heterogeneous CRE populations [173], exclusively KPC-Kp infections [175,177,178], or ESBL-producing Enterobacterales alongside CR-Kp [177]. Across observational studies, clinical success rates ranged from 60% to 77% [171–174,176], increasing to 81.9% in infections caused by KPC-Kp [176,177]. In addition to low to moderate recurrence rates (4.8–13.1%) [171–173,175,176], emergent resistance during MER-VAB therapy was uncommon, with reported rates of 0–1.7% [172,173,175,177], and a higher estimate of 5% reported only in a small study [171]. Overall, 30-day mortality remained below 20% in most of the cohorts [171–173,176] but reached 31.6% in KPC-Kp infections [175–178]. It is noteworthy that, in the study by Tumbarello and colleagues [177], mortality was substantially higher than that reported in other studies enrolling exclusively KPC-Kp cases [175,176,178], where it ranged from 15.4% to 24.3% [175,176,178]. The divergence likely reflects the greater baseline severity of illness, since nearly half of patients had an INCREMENT score ≥ 8 or required ICU admission at infection onset, as well as the high prevalence of COVID-19 in this cohort. Mortality was higher among COVID-19 patients (43.1% vs 28.5%), and, in turn, COVID-19 was associated with reduced survival in patients experiencing LRTIs (45.6%) and cUTIs (50%) [177].

So far, few studies have compared the clinical efficacy of MER-VAB and CAZ-AVI [172,178–180]. A recent meta-analysis of retrospective studies encompassing 3,280 patients with MDR Gram-negative infections (GNIs) demonstrated no significant differences between the two agents regarding all-cause mortality, clinical cure, or microbiological recurrence [181]. Nevertheless, detailed examination of the principal contributing studies suggests the presence of subtle yet potentially clinically meaningful differences. In a multicenter retrospective study of 131 patients with CRE infections, approximately 40% presented with bacteremia, and respiratory infections represented the most common non-bacteremic source. *K. pneumoniae* was the predominant pathogen, followed by *Enterobacter* species, with KPC production detected in 71.9% and 76.9% of tested isolates in the CAZ-AVI and MER-VAB groups, respectively. Combination therapy was more frequently administered with CAZ-AVI (61% vs 15.4%, $p < 0.01$). Although the overall clinical outcomes were comparable, MER-VAB was accompanied by numerically higher clinical success (69.2% vs 61.9%), shorter ICU LOS (median 12.0 vs 15.0 days), and lower 30-day/90-day mortality (11.5% vs 19.1%/26.9 vs 28.6%). Recurrence rates were similar between groups (11.5% vs 14.3%); however, resistance emerged more often during CAZ-AVI monotherapy, whereas MER-VAB resistance was not reported [172]. Similar findings were reported by Marino and colleagues among critically ill patients with KPC-Kp infections, in whom early clinical response at 72 h was more than twice as likely with MER-VAB (OR 2.19, 95% CI 1.35–3.55) [178]. Lastly, in a large U.S.-based retrospective cohort derived from the PREMIER Healthcare Database, 2,775 adult patients with serious infections (e.g. sepsis,

cUTIs, cAIs, pneumonia) were treated with MER-VAB ($n = 455$) or CAZ-AVI ($n = 2,320$) over a 2-year period. Both agents were initiated on average 5–6 days after infection onset, suggesting limited empirical use and probable administration following microbiological confirmation. In adjusted analyses, MER-VAB was linked to lower in-hospital mortality (16.5% vs 20.6%, $p = 0.021$) and a shorter post-infection onset ICU LOS (19.6 vs 22.4, $p = 0.042$). A trend toward reduced ICU admissions (40.2% vs 43.9%), and incidence of *C. difficile* infection (11.5% vs 14.2%) was also observed [179]. Consistently, a recent propensity-score-weighted cohort study demonstrated similar 30-day mortality between CAZ-AVI and MER-VAB; however, emergence of resistance occurred more frequently with CAZ-AVI (12% vs 0%), despite comparable recurrence rates, highlighting a potential advantage of MER-VAB in preventing resistance selection [180].

MER-VAB resistance remains relatively uncommon, with reported rates generally around 2–5%, but is increasingly described in KPC-producing *K. pneumoniae* [112]. It is primarily driven by porin alterations (OmpK35/36 loss or mutations) combined with increased *bla*_{KPC} expression or gene copy number, rather than inhibitor failure, and may be further facilitated by co-production of additional carbapenemases [9,21,112].

Collectively, the available evidence points toward specific clinical aspects favoring MER-VAB use. First, in KPC-Kp infections, MER-VAB efficacy appears to be preserved even in the presence of documented CAZ-AVI resistance [175–177]. In addition, given that both meropenem and vaborbactam achieve epithelial lining fluid penetration of approximately 65% and 79% of their respective unbound plasma concentrations [182], respectively, MER-VAB represents a promising therapeutic option for LRTIs, consistent with available clinical data [176]. Considering the importance of treatment timing in severe CRE infections [183], early use of MER-VAB seems to improve clinical outcomes [173,175,184]. For instance, MER-VAB initiation within 48 h showed a trend toward fewer adverse outcomes in suspected or confirmed MDR GNIs (aOR 0.277, 95% CI 0.081–0.941) [173]. Conversely, mortality was higher when MER-VAB was administered as second line in KPC-Kp infections, including cases involving CAZ-AVI-resistant isolates [177]. Moreover, MER-VAB is characterized by a low propensity for resistance development during therapy, with emergence primarily driven by porin mutations rather than KPC enzyme variants [162–165]. Finally, MER-VAB exhibits a favorable safety profile, with an overall incidence of AEs of 3% [185], fewer renal-related AEs, and a comparable risk of treatment discontinuation due to AEs relative to comparators [186]. Since it is mainly administered as monotherapy, the risk of combination therapy-related toxicity, such as colistin- or aminoglycoside-associated nephrotoxicity, is further reduced.

In summary, MER-VAB provides high clinical cure rates, low mortality, and reduced risk of resistance and nephrotoxicity in KPC-producing CRE infections and is slightly favored over other agents by IDSA [53]. In contrast, ESCMID adopts a more neutral stance, suggesting MER-VAB or CAZ-AVI for severe CRE infections when *in vitro* activity is demonstrated (conditional recommendation; moderate to low certainty of evidence) [110].

Table 3. Real-world evidence on meropenem–vaborbactam in severe Gram-negative infections.

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with meropenem–vaborbactam	Outcomes	Comments
Shields et al. [171]	2019	Single-center prospective observational study of patients with CRE infections treated with MVB for >48 h	N = 20	CCI: 4 (0–11) SOFA: 5 (1–14) APACHE II score: 20 (7–40) Septic shock: N/A	<i>K. pneumoniae</i> (70%), <i>K. oxytoca</i> (10%), <i>E. coli</i> (10%), <i>E. cloacae</i> (5%), <i>C. freundii</i> (5%) KPC was detected in 90% of isolates; all <i>K. pneumoniae</i> isolates harbored mutant <i>ompK35</i> and wild-type <i>ompK36</i> at baseline	Bacteremia: 40% Respiratory: 40% SST: 10% UTI: 5% Intra-abdominal: 5%	MVB monotherapy: 80% MVB combination therapy with: – inh Gentamicin 10% – iv and inh Gentamicin 5% – Ciprofloxacin 5%	Clinical success: 65% Recurrence: 10% Microbiological failure (90d): 35% Infection relapse: 15% Emergent resistance: 5% 30-day mortality: 10% 90-day mortality: 20%	One recurrent infection with MVB-nonsusceptible <i>ompK36</i> mutant <i>K. pneumoniae</i> reported
Ackley et al. [172]	2020	Multicenter retrospective cohort study of patients with CRE infections treated with CAZ/AVI or MVB for ≥72 h (U.S.A.)	N = 131; CAZ/AVI: 80.2%, MVB: 19.8%	CCI: CAZ/AVI: 5.0 (3.0–6.0); MVB: 5.0 (3.0–8.0); p = 0.65 SOFA: N/A APACHE II score: CAZ/AVI: 26.0 (22.0–30.0); MVB: 27.0 (24.0–34.0); p = 0.19 Septic shock: N/A	<i>Klebsiella spp</i> CAZ/AVI: 72.4% MVB: 57.7%; p = 0.15 <i>Enterobacter spp</i> CAZ/AVI: 19.1% MVB: 30.8%; p = 0.19 <i>E. coli</i> CAZ/AVI: 8.6% MVB: 11.5%; p = 0.7 <i>Citrobacter spp</i> CAZ/AVI: 1.9% MVB: 7.7%; p = 0.18 <i>Serratia spp</i> CAZ/AVI: 0 MVB: 3.9%; p = 0.2 KPC was detected in 71.9% & 76.9% of tested isolates in the CAZ/AVI and MVB groups, respectively	Bacteraemia CAZ/AVI: 6.7%, MVB: 3.8%; p = 0.75 Nonbacteremic infections: CAZ/AVI: 58.1%, MVB: 65.4%; p = 0.75) – Respiratory: CAZ/AVI: 49.2%, MVB: 58.8% – SST: CAZ/AVI: 29.5%, MVB: 11.8% – Intra-abdominal: CAZ/AVI: 19.7%, MVB: 29.4% – Other: CAZ/AVI: 1.6%, MVB: 0 Polymicrobial infections CAZ/AVI: 59.1% MVB: 57.7%; p = 0.9	Combination therapy CAZ/AVI: 61%, MVB: 15.4%; p < 0.01 CAZ/AVI combination therapy with: – Colistin 19.1% – Tigecycline 17.1% – Aminoglycoside: 14.3% – Polymyxin B 9.5% – Fluoroquinolone 7.6% – TMP-SMX 3.8% MVB combination therapy with: – Colistin 7.7% – Tigecycline 3.9% – Polymyxin B 3.9%	Clinical success: CAZ/AVI 61.9%, MVB 69.2%; p = 0.49 30-day mortality: CAZ/AVI 19.1%, MVB 11.5%; p = 0.57 90-day mortality CAZ/AVI 28.6%, MVB 26.9%; p = 0.48 Recurrence: CAZ/AVI 14.3%, MVB 11.5%; p = 1.0 Emergent resistance: CAZ/AVI 20%, MVB 0%	Combination therapy was used more frequently in the CAZ/AVI group; resistance developed more often during CAZ/AVI monotherapy
* Alosaimy et al. [173]	2021	Multicenter, retrospective, cohort study of patients with suspected or confirmed MDR GNIs treated with MBV for ≥72 h (U.S.A.)	N = 126	CCI: 4.0 (2.0–6.0) SOFA: 7 (4–10) APACHE II score: 18.0 (12.0–26.0) Septic shock: N/A	CRE pathogen: 78.6%; <i>K. pneumoniae</i> (53.5%), <i>E. coli</i> (25.3%), <i>Enterobacter spp.</i> (24.2%), <i>C. freundii</i> (4%),	Respiratory: 38.1% Intra-abdominal: 19% UTI: 13.5% SST: 10.3% Bacteremia: 9.5% Other: 7.9% Unknown: 1.6% Polymicrobial infections: 11.9%	MVB monotherapy: 65.9% MVB combination therapy with: – Amikacin 7.1% – Aztreonam 4.8% – Ciprofloxacin 0.8% – Colistin 4% Gentamicin 0.6% – levofloxacin 5.6% – Minocycline 4.8% – Polymyxin B 4% – Tigecycline 1.6% – TMP-SMX 4% – Tobramycin 4.8% – Others: 3.2%	CRE subgroup Clinical success: 74.7% 30-day mortality: 19.2% 90-day mortality: 34.3% 30-day recurrence: 13.1% MVB resistance: 0%	Trend toward reduced adverse clinical outcomes with MVB initiation within 48 h (aOR 0.27; 95% CI, 0.081–0.941).

(Continued)



Table 3. (Continued).

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with meropenem–vaborbactam	Outcomes	Comments
Zhang et al. [174]	2021	Single-center retrospective case series of patients receiving MVB for ≥48 h with an MVB-susceptible CRE culture within 14 days prior to initiation (U.S.A.)	N = 15	CCI: 6 (0–10) ** SOFA 7 (2–13) ** Septic shock: 22.9% APACHE II score: N/A	<i>K. pneumoniae</i> (66.7%), <i>E. coli</i> (20%), <i>K. aerogenes</i> (6.7%), <i>C. koseri</i> (6.7%) Polymicrobial index cultures: 46.7%	Bone and joint infections: 33.3% Bacteremia: 20% Respiratory: 13.3% Intra-abdominal: 13.3% UTI: 13.3% SST: 6.7%	MVB combination therapy: 60%	Positive clinical response: 60% Negative clinical response: 33.3% Uncertain clinical response: 6.7%	– Of five non-responders, one died of related and one of unrelated causes; three (60%) had inadequate source control
Tumbarello et al. [175]	2022	Multicenter retrospective observational cohort study of patients with KPC-Kp infections treated with MVB for ≥72 h	N = 37	CCI ≥ 4: 51.3% SOFA score: N/A INCREMENT score ≥ 8: 51.3% APACHE II score: N/A Septic shock: 18.9%	KPC-producing <i>K. pneumoniae</i> producing; CAZ/AVI resistant 59.5%	Bacteremia: 62.2% Respiratory: 27% Intra-abdominal: 2.7% UTI: 5.4% SST: 2.7%	MVB monotherapy: 37.8% MVB combination therapy with: – 1 other active antimicrobial: 45.9% – ≥2 active antimicrobials: 16.2%	Clinical cure: 75.6% microbiologically confirmed: 89.3% In-hospital infection recurrence: 8.1% (3/37); preserved MVB susceptibility In-hospital mortality: 24.3%	No association was observed between clinical outcomes and CAZ/AVI susceptibility status of the isolates
Tiseo et al. [176]	2024	Single-center prospective observational study of patients with ESBL-producing Enterobacterales and CR-Kp treated with MVB for ≥48 h (Italy)	N = 104	CCI: N/A SOFA: N/A APACHE II score: N/A Septic shock: 15.4% <i>KPC-Kp subgroup:</i> CCI :5 (3–8) SOFA: 3 (2–6) Septic shock: 13.1%	ESBL-producing non-hv <i>Enterobacterales</i> : 23.1% ESBL-producing hv <i>K. pneumoniae</i> : 16.3% CRE: 60.6% –KPC-producing <i>K. pneumoniae</i> 96.8%; CAZ/AVI resistant isolates 6.5%; –NDM-producing: <i>K. pneumoniae</i> : 3.2%	BSI: 39.4% UTI: 20.2% Respiratory: 19.2% Intra-abdominal: 13.5% Other: 9.6% KPC-producing Kp subgroup BSI: 68.9% Respiratory: 27.9% UTIs: 16.4% Intra-abdominal: 11.5% Other: 14.8%	MVB monotherapy: 86.5% MVB combination therapy with: – Tigecycline 5.8% – Fosfomycin 5.8% – Aztreonam 1.9%	Clinical success: 77% 30-day mortality: 15.4% (16/104) Relapse: 4.8% ESBL-producing non hvKp subgroup analysis clinical success 66.7%; 30-day mortality 20.8% ESBL-producing hvKp subgroup analysis clinical success 76.5%; 30-day mortality 17.6% KPC-Kp subgroup analysis clinical success 81.9%; 30-day mortality: 11.5%	– Therapeutic option for selected ESBL-producing or hvKp infections resistant to piperacillin/tazobactam, ceftolozane/tazobactam, and ertapenem – Promising outcomes in HAP/VAP from KPC-producing <i>K. pneumoniae</i> – Multivariable analysis showed SOFA score as an independent risk factor for failure, and source control as a protective factor

(Continued)

Table 3. (Continued).

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with meropenem–vaborbactam	Outcomes	Comments
Tumbarello et al. [177]	2024	Multicenter retrospective observational study of patients with KPC-Kp infections treated with MVB for ≥24 h (Italy)	N = 342	CCI ≥ 3: 79.5 SOFA: N/A APACHE II score: N/A Septic shock: 14.9% Nearly half of KPC-Kp infections were classified as high-mortality risk by the INCREMENT score	KPC-producing <i>K. pneumoniae</i> ; CAZ/AVI resistant isolates 24.8%	BSIs: 50.3% Respiratory: 31.3% UT: 8.8% -Other: 9.6%	MVB monotherapy: 62.3% MVB combination therapy with: -plus 1 other active antimicrobial 28.6% - ≥2 active antimicrobials 9.4%	Clinical success: N/A 30-day mortality: overall 31.6%; MBV monotherapy 30.9%; MVB combination therapy 32.6%; MVB as second-line therapy 43.3% CAZ/AVI-resistant isolates: 30-day mortality 24.2% with first-line MVB vs 36.5% with second-line MVB In-hospital recurrence: 9.6% Emergent resistance: 1.7%	- Early MVB initiation (≤48 h) was linked to lower mortality (20.9%; 31/148) and was an independent negative predictor of death; however, this association was not sustained after adjusting for propensity scores related to combination therapy - Mortality was higher with underlying COVID-19 (43.1% vs 28.5%), and COVID-19 significantly reduced survival in cases of LRTIs (45.6%) and cUTIs (50%) - Relapse rates were comparable between MVB monotherapy and combination therapy, and combination regimens conferred no additional survival benefit
Marino et al. [178]	2025	Multicenter retrospective observational cohort study of ICU patients with KPC-Kp infections treated with CAZ/AZI or MVB for ≥48 h (Italy)	N = 177 Post-PSM analysis: n = 88 (CAZ/AVI 59.1%; MVB 40.9%)	Post-matched cohort CCI: N/A SOFA: N/A APACHE II score: CAZ/AVI: 18.00 (13.50, 23.00); MVB: 17.00 (16.50, 17.00); p = 0.141 Septic shock: CAZ/AVI: 59.6%; MVB: 63.9%; p: 0.865	KPC-producing <i>K. pneumoniae</i>	Post-matched cohort BSI: CAZ/AVI: 50%; MVB: 61.1% Pneumonia: CAZ/AVI: 11.5%; MVB: 19.4% BSI plus pneumonia: CAZ/AVI: 38.5%; MVB: 19.4% Polymicrobial infections (20.5%) CAZ/AVI 21.2%; MVB: 19.4%	Post-matched cohort CAZ/AVI combination therapy with: (55.8%) - Fosfomycin 28.8% - Aztreonam 7.7% - Aminoglycoside 7.7% - Tigecycline 7.7% MVB combination therapy with: 16.7% - Fosfomycin 8.3% - Colistin 5.6% - Tigecycline 2.8%	Post-matched cohort 30-day mortality CAZ/AVI: 26.9%; MVB: 19.4% aHR of MVB on mortality: 0.65 (95% CI 0.55–1.68)	Early clinical response at 72 h improved with MVB (post-PSM: OR 2.19, 95% CI: 1.35–3.55)

aHR: adjusted hazard ratio; aOR: adjusted odds ratio; APACHE: Acute physiology and chronic health evaluation; BSI: Bloodstream infection; CAZ/AVI: Ceftazidime–Avibactam; CCI: Charlson's comorbidity index; CI: Confidence interval; CRE: Carbapenem-resistant Enterobacterales; EOT: End of treatment; ESBL: Extended spectrum beta-lactamase; GNI: Gram-negative infections; HAP: hospital-acquired pneumonia; hv: hypervirulent; IQR: interquartile range; Kp: *Klebsiella pneumoniae*; KPC: *Klebsiella pneumoniae* Carbapenemase; MIC: Minimum inhibitory concentration; MVB: Meropenem–Vaborbactam; N/A: Not applicable; NDM: New Delhi metallo-β-lactamase; OR: Odds ratio; PSM: Propensity score matching; SOFA: Sequential organ failure assessment; SST: Soft and skin tissue; TMP-SMX: Trimethoprim–sulfamethoxazole; U.S.A.: United States of America; UT: Urinary tract; VAP: Ventilator-associated pneumonia.

*Severity scores and treatment regimens apply to the entire study population and not solely to the CRE subgroup.

**Severity scores apply only to patients in the ICU at the time of MVB initiation and not to the entire study cohort.

***Lower respiratory tract source includes patients with pneumonia without bacteremia and those with BSI secondary to a lower respiratory tract infection.

•Continuous variables are presented as median (IQR).

9. Imipenem–cilastatin–relebactam

IMI-REL is a combination of a carbapenem with cilastatin sodium, a renal dehydropeptidase inhibitor, and relebactam, which is a beta-lactamase inhibitor [187]. Cilastatin limits the renal metabolism of imipenem and does not have antibacterial activity. The bactericidal activity of imipenem results from inhibition of PBP-2 and PBP-1B in Enterobacterales and *P. aeruginosa* leading to the disruption of bacterial cell wall synthesis. Relebactam has no antibacterial activity per se but inhibits imipenem degradation by serine beta lactamases such as SHV, TEM, CTX-M, and KPC [187]. Evidence from serial data coming from the Study for Monitoring Antimicrobial Resistance Trends (SMART) underlines a high activity of this combination against non-Morganellaceae and non-Proteaceae Enterobacterales and *P. aeruginosa* across Europe, U.S.A., and China [55,188,189]. The drug is active against KPC and AmpC-producing *K. pneumoniae* but has no activity against MBL-, GES-, and OXA-48-producing *K. pneumoniae* nor CRAB [190,191]. Relebactam does not enhance the activity of imipenem against *Bacteroides* spp; activity of the combination is equal to imipenem alone [192]. IMI-REL is active against MDR and XDR *Burkholderia* as well as *Mycobacterium abscessus*; in two studies *in vitro* synergy with other antimycobacterial drugs (amoxicillin, rifabutin, moxifloxacin) has been shown [193–195].

Recent data on consecutively collected isolates from 72 United States medical centers in 2020–2022, estimate the susceptibility rate over 72% for CRE and over 97% for *P. aeruginosa* isolates [196]. Karlowisky et al. reported that in isolates from Italy and Greece, two countries with high AMR burden, IMI-REL inhibited 98–99% of KPC-positive non-Morganellaceae Enterobacterales in both countries and inhibition of *P. aeruginosa* isolates ranged from 84% in Greece to 91–92% in Italy [197].

Imipenem–cilastatin–relebactam has been approved in 2020 in Europe for the treatment of HAP and VAP, bacteremia associated with HAP/VAP, as well as infections by Gram-negative aerobic pathogens with limited treatment options [187]. In the registrational trials RESTORE-IMI-1 and –2, IMI-REL was compared to colistin for treating imipenem-non-susceptible infections or to piperacillin–tazobactam for HAP/VAP providing promising results [198,199]. In a recent meta-analysis of six RCTs including 1606 patients, IMI-REL was non-inferior to comparators in clinical and microbiological response rate as well as 30-day all-cause mortality irrespective of site of infection and drug dosage [200]. Chaftari et al. conducted an RCT in 100 cancer patients with febrile neutropenia comparing IMI-REL with standard-of-care antibiotics (cefepime, piperacillin–tazobactam or meropenem). Patients treated with IMI-REL had a favorable clinical response at end-of-treatment visit with similar success rates at test-of-cure visit. Microbiological eradication was also similar in both arms in this vulnerable population [201].

Real-world data on the use of IMI-REL are still sparse; published literature is presented in detail in Table 4 [202–210]. Real-world retrospective studies on IMI-REL report heterogeneous results with clinical success rates ranging from 56% to 100% and 30-day mortality from 11% to 43% due to variations in

resistance rates of causative pathogens (MDR or DTR). Shields et al. treated 160 patients mainly with pneumonia by *P. aeruginosa* resulting in almost 22% 30-day mortality. The drug in this study was in the majority of cases given as second-line treatment after failure of other antimicrobials [208]. In a recent study of 195 patients from Greece with 77.5% carbapenem-non-susceptible pathogens, clinical success was as high as 72.8% and only 34.4% of patients received a combination treatment mainly with colistin or tigecycline [202].

Adverse effects of IMI-REL are in general similar to imipenem with predominant gastrointestinal disorders [211]. Seizures, eosinophilia, and *C. difficile* infection have been reported [204,209,210]. The drug has a more favorable renal safety profile than colistin-based regimens, but there is a definite need for post-marketing studies to better characterize renal safety [212]. Although cost for IMI-REL drug acquisition is high, cost-effectiveness studies suggest that favorable clinical outcomes may be cost-saving by reduced nephrotoxicity-related cost [213]. Caution should be also paid to a potentially moderate-to-high sodium load of 1.5 up to 3 g/day [214]. Emergence of resistance under treatment has been reported in five patients treated for nosocomial pneumonia due to mutations in MexAB-OprM and/or MexEF-OprN efflux operons that arose independently in each patient [215]. Although the risk for development of resistance under treatment is considered lower than other antipseudomonal drugs (e.g. CAZ-AVI), Wangchinda et al. reported a rate as high as 39% within 30-days of treatment for MDR *P. aeruginosa* [203].

IMI-REL is the newest BLBLI and data are insufficient, so that ESCMID guidelines on infections by MDR do not prioritize this combination neither in patients with CRE nor carbapenem-non-susceptible *P. aeruginosa* [110]. In contrast, IDSA guidelines recommend IMI-REL as the preferred treatment option for infections outside of the urinary tract caused by KPC-producing CRE, equally placed to CAZ-AVI and MER-VAB [53]. Published evidence on the empirical use of IMI-REL in critically ill patients is currently lacking. Several important knowledge gaps warrant urgent investigation in this population, including PK/PD information in particular situations (e.g. renal replacement therapy [RRT], ARC, extracorporeal membrane oxygenation [ECMO]), the benefit of combination therapy for the most severe infections especially those involving *P. aeruginosa*, and the impact of IMI-REL on the gut microbiota [216]. After considering all the above, the French Intensive Care Society underlined that there is insufficient evidence to prioritize IMI-REL vs the other new antibiotics when strains are susceptible, and that there is insufficient evidence to recommend combining IMI-REL with any other antibiotics [217], although expert opinion is considering monotherapy an acceptable option for serious infections by *P. aeruginosa* [218]. Especially in *P. aeruginosa* infections, IMI-REL may retain susceptibility when there is resistance to ceftolozane–tazobactam and CAZ-AVI [53,219,220]. However, there are no head-to-head comparative studies to support a preference for one over the other [221]. IMI-REL should probably not be used empirically in critically ill patients but reserved in patients with septic shock and known colonization by carbapenemase-producing

Table 4. Real-world evidence on imipenem–cilastatin–relebactam in severe Gram-negative infections.

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with Imipenem – cilastatin–relebactam	Outcomes	Comments
Petrakis et al. [202]	2025	Retrospective, single-center	195	Charlson Index: 4 SOFA: NR Apache: 14 Septic shock: NR	<i>P. aeruginosa</i> 63.1% <i>K. pneumoniae</i> 24.6% Carbapenem-nonsusceptible 77.5%	Pneumonia: 45.6% IAI: 13.8% SST: 10.8% UTI: 33.3%	Combination therapy: 34.4% Combination with: – COL 9.7% – TGC 8.7%	Clinical success: (30d) 72.82% Microbiological success: (30d) 87.7% Mortality: 30d: 11.3% 90d: NR	AE in 4.1%, discontinuation in 2 cases
Wangchinda et al. [203]	2025	Retrospective, multicenter	63	Charlson Index: 5 SOFA: 7 Apache: NR Septic shock: 48%	MDR <i>P. aeruginosa</i>	Pneumonia: 87% Bacteremia: 13%	Combination therapy: 25% Combination with: – Inhaled antibiotics 69% – IV antibiotics 19% – Both inhaled and IV 12%	Clinical success: (30d) 56% Microbiological success: (30d) NR Mortality: 30d: 18% 90d: 29%	Development of resistance within 30 days 39% AE in 1 patient interstitial nephritis
Marino et al. [204]	2025	Retrospective-prospective observational, multicenter	29	Charlson Index: 4 SOFA: NR Apache: NR Septic shock: 55.2%	<i>P. aeruginosa</i> 10.3% <i>K. pneumoniae</i> 62.1%	Pneumonia: 33.3% Bacteremia: 22.2% IAI: 22.2% SST: 7.4% UTI: 11.1%	Combination therapy: 48.3% Combination with: NR	Clinical success: (30d) 75.9% Microbiological success: (30d) 100% Mortality: 30d: 18% 90d: 29%	CDI 3.5%
Caniff et al. [205]	2025	Retrospective, multicenter	151	Charlson Index: 4 SOFA: NR Apache: 15 Septic shock: NR	<i>P. aeruginosa</i> 72.2% <i>K. pneumoniae</i> 12.6% Carbapenem-nonsusceptible 85.4%	Pneumonia: 52.3% Bacteremia: 19.2% IAI: 11.3% SST: 10.6% UTI: 9.3%	Combination therapy: 24.5% Combination with: – AMG 6.6% – COL 0.7% – TGC 0.7% – COL inhaled 9.9%	Clinical success: (30d) 70.2% Microbiological success: (30d) 85.4% Mortality: 30d: 18.5% 90d: NR	AE 6% Mainly gastrointestinal discontinuation in 2 cases
Machuca et al. [206]	2025	Retrospective, multicenter	14	Charlson Index: 3 SOFA: NR Apache: NR Septic shock: 64.3%	DTR <i>P. aeruginosa</i>	Pneumonia: 28.6% IAI: 7.1% SST: 57%	Monotherapy 100%	Clinical and microbiological success: (30d) 64.3% Mortality: 30d: 42.9% 90d: NR	AE (nausea) in 1 patient
Leanza et al. [207]	2024	Retrospective, single-center	10	Charlson Index: 3 SOFA: NR Apache: NR Septic shock: 64.3%	DTR <i>P. aeruginosa</i> 50% KPC <i>K. pneumoniae</i> 50%	Pneumonia: 40% Bacteremia: 20% SST: 20% UTI: 10%	Monotherapy 90% Combination therapy: 10% Combination with: – FOF 10%	Clinical success: (30d) 100% Microbiological success: (30d) NR Mortality: 30d: 0% 90d: NR	No AE

(Continued)



Table 4. (Continued).

Reference	Year	Study design	Number of patients	Severity score	Pathogens	Source of isolates	Treatment options with Imipenem – clastatin-relebactam	Outcomes	Comments
Shields et al. [208]	2024	Retrospective, multicenter	160	Charlson Index: 5 SOFA: NR Apache: NR Septic shock: 19%	<i>P. aeruginosa</i> 89.2% <i>K. pneumoniae</i> 18.9% <i>E. cloacae</i> 10.8% <i>E. coli</i> 10.8%	Pneumonia: 53.8% Bacteremia: 3.1% IAI: 1.9% UTI: 16.9%	Monotherapy NR Combination therapy: NR	Clinical success: (30d) NR Microbiological success: (30d) NR Mortality: 30d: 21.3% 90d: NR	IMI/REL generally used as second-line
Larcher et al. [209]	2022	Case series	3	Charlson Index: 0 SOFA: NR Apache: NR Septic shock: NR	DTR <i>P. aeruginosa</i>	Pneumonia: 2 patients Bone/joint infection: 1 patient	Combination therapy: 2 out of 3 patients – FOF 1 patient – COL 1 patient	Clinical success: (30d) 100% Microbiological success: (30d) 100% Mortality: 30d: 0% 90d: NR	eosinophilia in 1 patient
Rebold et al. [210]	2022	Case series	21	Charlson Index: 4 SOFA: NR Apache: 21 Septic shock: NR	<i>P. aeruginosa</i> 76% of which 95% MDR	Pneumonia: 52.4% Bacteremia: 3.1% IAI: 4.8% SST: 4.8% UTI: 14.2%	Monotherapy NR Combination therapy: NR	Clinical success: (30d) 61.9% Microbiological success: (30d) NR Mortality: 30d: 33.3% 90d: NR	AE in 1 patient gastrointestinal and 1 patient seizures

AE adverse event; AMG aminoglycoside; CDI *Clostridioides difficile* colitis; COL colistin; DTR difficult-to-treat resistant; FOF fosfomycin; IAI intra-abdominal infection; IMI/REL imipenem/relebactam; IV intravenous; MDR multidrug resistant; NR not reported; SOFA sequential organ failure assessment score, SST skin soft tissue; TGC tigecycline; UTI urinary tract infection.

Enterobacterales or DTR *P. aeruginosa* without MBL-risk [217,222]. In cases of MBL, *in vitro* data support the synergy of IMI-REL with aztreonam, but clinical data are lacking [223,224].

10. Aztreonam–avibactam

Aztreonam–avibactam (ATM-AVI) represents a therapeutic option to the global emergence of MBL-producing Gram-negative pathogens, which have rapidly become a dominant driver of carbapenem resistance in Enterobacterales and non-fermenting organisms [28]. MBL enzymes such as NDM, VIM, and IMP hydrolyze nearly all β -lactams, including carbapenems, while remaining unaffected by available β -lactamase inhibitors, leaving extremely limited therapeutic options. Although ATM is intrinsically stable to MBL hydrolysis, its clinical activity is frequently compromised by co-production of ESBLs, AmpC enzymes, and selected class D oxacillinases that inactivate monobactam in contemporary clinical isolates. Avibactam, a non- β -lactam inhibitor with potent activity against class A, class C, and selected class D β -lactamases, restores aztreonam activity by protecting it from these accompanying resistance mechanisms while preserving its MBL stability, forming the conceptual basis of the aztreonam–avibactam combination [12,28]. Importantly, ATM-AVI is particularly well suited for the treatment of infections caused not only by isolated MBL-producing organisms but also by Enterobacterales harboring dual carbapenemase or mixed resistance mechanisms, as well as *Stenotrophomonas maltophilia*. Clinical isolates frequently co-produce MBLs such as NDM or VIM together with serine β -lactamases including KPC, OXA-48-like enzymes, ESBLs, or AmpC cephalosporinases [225], a scenario that is increasingly encountered in endemic regions allowing effective single-agent therapy with ATM-AVI for these infections [226,227].

Large global surveillance programs consistently demonstrate potent *in vitro* activity of ATM-AVI against MBL-producing Enterobacterales. In a multinational collection of 1,610 MBL-positive isolates obtained between 2019 and 2021 from 27 countries across Asia-Pacific, Europe, and Latin America, the combination inhibited 98.8% of isolates at ≤ 8 mg/L, with an MIC₉₀ of 2 mg/L, including 100% of VIM- and IMP-producing strains and 98.7% of NDM producers [228]. Comparable large-scale surveillance of CRE confirmed activity against 99.6% of isolates, including those harboring multiple carbapenemases and strains resistant to CAZ-AVI, colistin, and tigecycline [229]. Aztreonam–avibactam also exhibits exceptional activity against *S. maltophilia*, inhibiting 99.6% of 1,400 contemporary clinical isolates, including strains resistant to trimethoprim-sulfamethoxazole, fluoroquinolones, and minocycline [230]. In contrast, activity against MBL-producing *P. aeruginosa* strains remains inconsistent and generally poor. Systematic *in vitro* analyses demonstrate susceptibility in only a small minority of MBL-positive *Pseudomonas* isolates (6% only), largely due to dominant non-enzymatic resistance mechanisms, porin loss, efflux overexpression, and co-production of additional β -lactamases that limit

effective aztreonam exposure despite avibactam protection [231].

The marketed formulation delivers a fixed-dose combination of ATM and avibactam in a 3:1 mass ratio. PK/PD modeling demonstrated that prolonged infusions administered every 6 h achieve high joint probability of target attainment for both components across renal function groups, forming the basis of the approved dosing strategy [45,232].

Aztreonam–avibactam has received approval by the EMA for cIAI, HAP, VAP, cUTI including pyelonephritis, and for treatment of aerobic Gram-negative infections with limited therapeutic options [233], while the FDA has approved the agent for cIAI [234]. Clinical validation was primarily provided by the Phase III REVISIT trial, a prospective, multinational, randomized descriptive study enrolling 422 hospitalized adults with cIAI or HAP/VAP [235]. Patients received ATM-AVI as prolonged infusions with optional metronidazole or comparator therapy consisting of meropenem with or without colistin. Enterobacterales accounted for approximately 93% of baseline pathogens, and ATM-AVI exhibited an MIC₉₀ of 0.25 mg/L among baseline isolates. Carbapenemase-producing organisms were identified in 24% of isolates, including confirmed MBL producers in approximately 12%. Clinical cure was achieved in 68.4% of ATM-AVI recipients compared with 65.7% in the comparator arm, while 28-day mortality was numerically lower in the ATM-AVI group, with favorable tolerability and low rates of treatment-related adverse events [235].

To specifically address infections caused by MBL-producing pathogens, the ASSEMBLE study was designed as a Phase III prospective comparative investigation enrolling patients with documented MBL-positive Gram-negative infections, including cIAI, HAP, cUTI, and BSI [236]. Although enrollment was necessarily limited due to the rarity of confirmed MBL disease, only 15 patients were randomized in the trial. All baseline Enterobacterales isolates in the ATM-AVI arm demonstrated susceptibility within the approved breakpoint range, with only a single NDM-5-producing *E. coli* isolate showing reduced susceptibility. Despite extreme resistance profiles, clinical cure at test-of-cure occurred in 42% of patients treated with ATM-AVI, whereas no clinical cures were observed with the best available therapy (BAT); 28-day mortality was also lower (8% vs 33%). These encouraging outcomes support the biological and therapeutic relevance of ATM-AVI for true MBL-driven infections [236].

Prior to the availability of ATM-AVI as a fixed formulation, clinicians relied on off-label co-administration of CAZ-AVI plus ATM to overcome MBL-mediated resistance [237]. Although microbiologically logical, this strategy lacks regulatory approval, is supported largely by observational and anecdotal data, requires complex dual infusions with higher aztreonam exposures, and is associated with suboptimal joint pharmacodynamic target attainment and absence of validated susceptibility breakpoints [238,239]. ATM-AVI resolves these limitations by delivering optimized inhibitor exposure within a single coordinated regimen and achieving superior joint pharmacodynamic performance.

Resistance to ATM-AVI remains uncommon but is increasingly reported, particularly among NDM-producing Enterobacterales, most notably *Escherichia coli*. The primary mechanisms involve alterations in PBP3 (e.g. insertions or point mutations) combined with production or structural modification of additional β -lactamases such as CMY variants, which together reduce aztreonam binding and compromise avibactam-mediated inhibition [9,21,112]. Importantly, resistance may emerge during therapy with ATM plus CAZ-AVI, highlighting the role of selective pressure in driving these mutations [112]. Furthermore, these mechanisms are frequently associated with cross-resistance to cefiderocol and other PBP3-targeting agents, significantly narrowing available treatment options in extensively drug-resistant isolates [21,112].

From a stewardship and economic perspective, ATM-AVI also offers potential advantages over colistin-containing regimens historically used for MBL infections. Colistin is associated with substantial nephrotoxicity, prolonged hospitalization, and increased downstream healthcare costs. Emerging cost-effectiveness analyses suggest that ATM-AVI may represent an economically favorable alternative in settings where colistin-based therapy would otherwise be required [240]. In summary, ATM-AVI constitutes a major advance in the therapeutic armamentarium against MBL-producing Gram-negative pathogens. Figure 1 provides a concise comparative review of approved BLBLI combinations, outlining differences in antimicrobial coverage, approved clinical indications, epithelial lining fluid penetration, and key practical considerations for each agent [5–9,28,29,53,110].

10.1. Ceftazidime–avibactam plus aztreonam

Before the availability of fixed ATM-AVI formulations, the combination CAZ-AVI with ATM emerged as a pragmatic salvage strategy to address infections caused by MBL-producing Gram-negative pathogens [237]. Although CAZ-AVI revolutionized treatment of serine carbapenemase-producing Enterobacterales, its lack of intrinsic MBL activity necessitated combination approaches. The addition of ATM, protected from co-produced serine β -lactamases by avibactam, provided a mechanistically rational solution where no licensed MBL-active agents were available [53].

Early evidence consisted largely of compassionate-use reports and small series in critically ill patients with bloodstream infections and deep-seated disease due mainly to NDM- and VIM-producing Enterobacterales. These consistently demonstrated rapid microbiological clearance and clinical improvement, often following failure of polymyxin-based regimens [241–245]. Clinical success was also reported in high-risk populations including transplant recipients [241,243], neutropenic patients [244], and pediatric cohorts [242].

More robust evidence emerged from prospective studies by Falcone and colleagues, where CAZ-AVI plus ATM was associated with significantly lower 30-day mortality and clinical failure compared with alternative regimens dominated by polymyxins and tigecycline [98]. These findings were reinforced in a larger cohort of 343 patients, in which the combination independently reduced mortality and outperformed colistin-containing therapies, while cefiderocol regimens

Comparative Activity and Clinical Use of approved Novel β -lactam/ β -lactamase Inhibitors combinations

Ceftazidime-Avibactam	Meropenem-Vaborbactam	Imipenem-Cilastatin-Relebactam	Aztreonam-Avibactam
Mechanism of action Diazabicyclooctane non β -lactam- β -lactamase inhibitor	Mechanism of action Cyclic boronic acid inhibitor	Mechanism of action Diazabicyclooctane non β -lactam- β -lactamase inhibitor	Mechanism of action Diazabicyclooctane non β -lactam- β -lactamase inhibitor
Spectrum ✓ ESBL, AmpC, KPC, OXA-48 (Enterobacterales) ✓ DTR <i>P. aeruginosa</i> X No MBL X No <i>Acinetobacter</i> , anaerobes	Spectrum ✓ ESBL, AmpC, KPC (Enterobacterales) X No OXA-48, MBL ✓ As active as meropenem alone against <i>P. aeruginosa</i> , <i>Acinetobacter</i> spp	Spectrum ✓ ESBL, AmpC, KPC, porin mutation (Enterobacterales) ✓ DTR <i>P. aeruginosa</i> X No OXA-48, MBL, <i>A. baumannii</i> X No <i>Proteus</i> spp, <i>Providencia</i> spp	Spectrum ✓ ESBL, AmpC, KPC, OXA-48 (Enterobacterales) ✓ MBL (VIM, NDM, IMP) ✓ <i>S. maltophilia</i> (Including MBL) ✓ As active as aztreonam against <i>P. aeruginosa</i> and <i>A. baumannii</i>
Clinical Indications ► cUTI, cIAI, HAP/VAP± bacteremia ► Infections with Gram-negative with limited treatment options	Clinical Indications ► cUTI, cIAI, HAP/VAP± bacteremia ► Infections with Gram-negative with limited treatment options	Clinical Indications ► HAP/VAP ± bacteremia ► Infections with Gram-negative limited treatment options	Clinical Indications ► cUTI, cIAI, HAP/VAP ► Infections with Gram-negative limited treatment options
ELF Penetration Ceftazidime: 30%/Avibactam:35%	ELF Penetration Meropenem:65%/Vaborbactam:79%	ELF Penetration Imipenem: 55%/Relebactam: 54%	ELF Penetration Aztreonam:20–60%/Avibactam:35%
Key Points ► Preferred in penicillin allergy ► Paediatric patients from birth	Key Points ► Suitable for LRTI ► High sodium load	Key Points ► Suitable for DTR <i>P. aeruginosa</i> ► Neurologic side effect i.e., seizure	Key Points ► Only agent active against MBL ► Dual carbapenemase production

Figure 1. Comparative activity and clinical use of novel β -lactam/ β -lactamase inhibitor (BLBLI) combinations.

Abbreviations: AmpC, AmpC β -lactamase; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; DTR, difficult-to-treat resistance; ELF, epithelial lining fluid; ESBL, extended-spectrum β -lactamase; KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo- β -lactamase; OXA-48, oxacillinase-48 carbapenemase; VAP, ventilator associated pneumonia.

showed no clear survival benefit [246]. Additional ICU cohorts further supported improved eradication and survival with synergy-guided therapy [247,248].

These data led to incorporation of CAZ-AVI plus ATM into IDSA guidance for severe MBL-producing Enterobacterales infections, with additional consideration for *S. maltophilia* [53]. Exploratory combinations pairing aztreonam with other BLBLIs, including MER-VAB and IMI-REL, have shown promising synergy *in vitro* and limited clinical rescue success, though evidence remains preliminary [224,249–252].

Overall, CAZ-AVI plus ATM served as a crucial therapeutic bridge in the MBL era, establishing proof of concept for inhibitor-protected aztreonam strategies and significantly improving outcomes in otherwise untreatable infections.

11. Sulbactam–durlobactam

Carbapenem-resistant *A. baumannii* (CRAB) represents one of the most critical antimicrobial resistance threats worldwide, associated with limited therapeutic options and mortality frequently exceeding 40% in severe infections [4,253]. The rapid global dissemination of OXA-type carbapenemases has rendered traditional β -lactams, carbapenems, and even high-dose ampicillin–sulbactam largely ineffective in many settings [254]. Historically, treatment strategies have relied on toxic and suboptimal agents such as colistin, tigecycline, and combination regimens supported primarily by low-quality observational data [53,255,256]. The urgent need for targeted, mechanism-based therapies has driven the development of sulbactam–durlobactam (SUL-DUR), a novel BLBLI combination specifically optimized for CRAB infections [13,257].

Sulbactam possesses intrinsic bactericidal activity against *A. baumannii* through inhibition of PBP1 and PBP3; however, its activity is compromised by degradation from class A, C, and particularly class D β -lactamases prevalent in CRAB. Durlobactam, a diazabicyclooctane inhibitor, restores sulbactam activity by effectively inhibiting these enzymes, including OXA-type carbapenemases [256]. Large contemporary surveillance studies have confirmed the potent *in vitro* activity of SUL-DUR against *A. baumannii*, with susceptibility rates approaching 95–97% among carbapenem-resistant isolates and MIC₉₀ values typically ≤ 4 μ g/mL, supporting current pharmacodynamic breakpoints for clinical efficacy [258,259]. In a recent U.S. multicentre surveillance study including isolates collected across 17 states (January 2023–May 2025), carbapenem resistance was observed in approximately 70% of isolates. Notably, SUL-DUR retained high activity, with 96.9% susceptibility, and demonstrated markedly greater efficacy compared with sulbactam alone (37.9% susceptible), highlighting the critical role of durlobactam in restoring sulbactam activity [260]. Importantly, very low MICs have also been reported in NDM-producing *E. coli*, suggesting an expanded spectrum driven by durlobactam's PBP2 binding, including cefiderocol and AZT-ATM-resistant isolates [261].

On the basis of robust preclinical and clinical evidence, SUL-DUR received FDA approval in 2023 for the treatment of HAP and VAP caused by susceptible strains of *A. baumannii*. This approval marked the first pathogen-specific β -lactam

therapy developed explicitly for CRAB infections and represented a major milestone in antimicrobial drug development [262].

The clinical foundation for SUL-DUR was established by the landmark ATTACK phase 3 randomized controlled trial, which compared SUL-DUR plus imipenem–cilastatin to colistin-based therapy in patients with severe CRAB infections, predominantly pneumonia and bacteremia [263]. SUL-DUR demonstrated non-inferior 28-day mortality with a numerically lower death rate (19% vs 32%) and, critically, a markedly reduced incidence of nephrotoxicity (13% vs 38%), addressing one of the most significant limitations of polymyxin therapy. These results provided high-quality evidence supporting both efficacy and improved safety [263].

Importantly, mechanistic investigations following the ATTACK trial have clarified that imipenem functioned not merely as background coverage but as a synergistic partner enhancing antibacterial efficacy. Structural and time-kill analyses revealed complementary PBP targeting, with sulbactam preferentially inhibiting PBP1 and PBP3, while imipenem binds with high affinity to PBP2 and PBP1a [264]. In the presence of durlobactam, which protects both agents from OXA-mediated hydrolysis, this combination produces simultaneous inactivation of multiple essential PBPs through target redundancy, resulting in rapid bactericidal activity and suppression of regrowth even in isolates harboring PBP mutations associated with reduced sulbactam susceptibility [40,264].

Reflecting this paradigm shift, the IDSA recommends SUL-DUR, in combination with a carbapenem, as the preferred front-line therapy for CRAB infections, positioning it ahead of cefiderocol and colistin-based regimens due to concerns regarding emerging resistance and inferior outcomes with older agents. This guidance underscores the role of SUL-DUR as a targeted, pathogen-specific solution rather than a salvage therapy [53].

Beyond clinical trials, accumulating real-world evidence further supports the translational impact of SUL-DUR. Published case reports consistently demonstrate clinical effectiveness in severe and refractory CRAB infections across multiple organ systems. Successful treatment has been described in liver transplant recipients with OXA-23-producing CRAB pneumonia and septicemia who failed polymyxin-based regimens, showing rapid clinical improvement, microbiological eradication, and recovery of renal function following SUL-DUR therapy [265]. Central nervous system efficacy has also been documented in refractory CRAB meningitis and ventriculitis, with persistent culture positivity resolving after initiation of SUL-DUR [266], supported by pharmacokinetic data demonstrating therapeutic cerebrospinal fluid penetration of both sulbactam and durlobactam [267]. In critically ill populations, SUL-DUR has proven effective as salvage therapy in burn patients with CRAB strains resistant to both colistin and cefiderocol, achieving complete microbiologic clearance despite complex resistance mechanisms including bla_{OXA-23} and siderophore pathway mutations [268]. Similarly, successful resolution of chronic wound and osteomyelitis-associated CRAB infections following the emergence of cefiderocol resistance highlights the robustness of SUL-DUR activity in multidrug-resistant settings [269].

More recent real-world reports further expand this evidence base. A 2026 multicenter case series of critically ill patients with CRAB bloodstream infections demonstrated that initiation of SUL-DUR was associated with rapid clinical stabilization and consistent microbiological clearance, supporting its role as both first-line and salvage therapy in high-mortality settings [270]. In addition, successful use of SUL-DUR in complex, multi-site XDR *A. baumannii* infections complicating severe acute pancreatitis has been reported, where the agent achieved clearance across abdominal, biliary, and respiratory compartments after failure of multiple last-line regimens [271].

Despite this favorable profile, resistance to SUL-DUR remains relatively uncommon but is increasingly reported and mechanistically well defined. Large *in vitro* datasets show low resistance rates in *A. baumannii* populations (~1–5%), including carbapenem-resistant isolates, although higher rates are observed in selected or high-risk cohorts [272]. More recent real-world genomic studies demonstrate emerging resistance even in treatment-naïve CRAB isolates, with rates up to 12.7% and high-level MICs (>64 mg/L) [273]. The primary mechanism involves mutations in PBP3, especially PBP3 (e.g. N392T, A515V) and PBP1b (P112S, G137R), which reduce sulbactam-binding affinity [273]. In addition, resistance is strongly associated with co-production of metallo- β -lactamases (e.g. NDM-1), which are not inhibited by durlobactam, as well as the presence of OXA-type carbapenemases [273]. Clonal dissemination of resistant lineages (e.g. ST231, ST837) further contributes to spread [273]. Secondary mechanisms, including efflux pump overexpression and permeability defects, may also play a role [272].

Together, robust *in vitro* susceptibility data, pharmacodynamic breakpoint alignment, high-quality randomized trial outcomes, and expanding clinical experience position SUL-DUR as a cornerstone therapy for CRAB [40,53,259,263]. Its mechanism-driven design directly addresses the dominant resistance pathways of *A. baumannii*, offering a safer and more effective alternative to legacy agents [256]. SUL-DUR represents a major advancement in the frontline management of one of the most formidable multidrug-resistant pathogens in modern medicine.

12. Emerging BLBLI combinations

BLBLI combinations have transformed the treatment of infections caused by resistant Gram-negative pathogens, providing effective options for DTR infections. Nevertheless, the continued emergence of antimicrobial resistance, the co-existence of multiple resistance mechanisms, and limited therapeutic options, particularly MBL producers and CRAB, underscore the need for ongoing antimicrobial innovation and robust clinical trials [6,7]. Recently developed BLBLI regimens have shown promising *in vitro* and clinical activity against ESBL-producing Enterobacterales and carbapenem-resistant organisms [13]. In this section, we summarize emerging BLBLI combinations currently undergoing or having completed Phase 3 clinical evaluation, organized by β -lactamase inhibitor class illustrated in Table 5 [14,32,33,83–87,274–282].

12.1. Completed phase 3 studies

12.1.1. Boronic acid-based BLBLIs

Taniborbactam, a bicyclic boronate β -lactamase inhibitor with activity against Ambler class A, C, and D enzymes, as well as metallo- β -lactamases (Ambler class B), demonstrates *in vitro* activity against the majority of carbapenem-resistant Enterobacterales, MDR *P. aeruginosa*, as well as isolates resistant to both ceftolozane–tazobactam and ceftazidime–avibactam when combined with cefepime [274,275]. Results from a Phase 3 clinical trial in adult patients with cUTIs demonstrated the superiority of this combination over meropenem in achieving both microbiologic and clinical success [274]. However, despite these promising data, cefepime–taniborbactam has not received U.S. Food and Drug Administration approval, primarily due to manufacturing-related concerns rather than issues of efficacy or safety. Importantly, the sponsoring company has ceased operations, introducing substantial uncertainty regarding the future development and availability of this agent. Consequently, although taniborbactam remains a scientifically important advance with broad-spectrum inhibitory activity, its role in the near-term clinical landscape is currently uncertain [276].

12.2. Ongoing or pending results phase 3 studies

12.2.1. Diazabicyclooctanes-based BLBLIs

A novel bicyclo-acyl hydrazide non- β -lactam inhibitor, zidebactam, exhibits activity against several class A and C β -lactamases while also functioning as a β -lactam enhancer through high-affinity binding to PBP2. In combination with cefepime, cefepime–zidebactam recently completed evaluation in the Phase 3 ENHANCE trial, which assessed its efficacy, safety, and tolerability versus meropenem for the treatment of hospitalized adults with cUTIs or acute pyelonephritis. The favorable results of this pivotal study led to FDA approval of cefepime–zidebactam (ZAYNICH®) for the treatment of adults with cUTIs, including pyelonephritis, caused by susceptible microorganisms [277,278]. Importantly, published case reports have demonstrated encouraging clinical outcomes in infections caused by multidrug-resistant Gram-negative pathogens, including metallo- β -lactamase-producing Enterobacterales and *Pseudomonas aeruginosa*, highlighting the potential therapeutic value of this combination beyond urinary tract infections [279,280].

Funobactam, another DBO compound, having activity against Ambler class A, C, and D enzymes (serine- β -lactamase inhibitor, including OXA-23 and OXA-24 enzymes), is under Phase 3 clinical evaluation for cUTIs and HAP/VAP (Clinicaltrial.gov identifier: NCT05204368, NCT05204563). Combined with imipenem, it has activity against carbapenem-resistant Enterobacterales, *A. baumannii* and *P. aeruginosa* [14].

Pralurbactam, a BLI with a DBO structure, is *in vitro* active against Ambler class A, C, and D enzymes and is currently under investigation in combination with meropenem for infections caused by carbapenem-resistant pathogens [279]. Based on the results of Huang et al., this combination regimen might be a potential treatment for KPC- and/or OXA-48-producing Enterobacterales infections [281]. It is currently being

Table 5. Summary of Phase 3 clinical trials evaluating novel β -Lactam/ β -Lactamase inhibitor combinations. Trial characteristics and antibacterial spectrum of investigated drug.

Combination regimen	Trial ID	Status ⁶	Comparator regimen	Indication	Spectrum of activity
Cefepime + Enmetazobactam	NCT03687255	Completed FDA/EMA approval	Piperacillin/tazobactam	cUTI, HAP, VAP, BSI	ESBLs, AmpC, KPC-with mutated omega loop, OXA-1
Cefepime + Taniborbactam	NCT03840148	Completed	Meropenem	cUTI/AP	class A; class B (but not IMP-1); class C; class D, OXA-48; <i>P. aeruginosa</i> , cefepime and carbapenem R
Cefepime + Taniborbactam	NCT06168734	Withdrawn	Meropenem	HAP/VAP	class A; class B (but not IMP-1); class C; class D, OXA-48; <i>P. aeruginosa</i> , cefepime and carbapenem R
Cefepime + Zidebactam	NCT04979806	Completed	Meropenem	cUTI/AP	class A; class B, (IMP, VIM, NDM); class C; class D, (OXA-48); highly active against <i>P. aeruginosa</i> , including carbapenem R and MBL-producing; probably limited activity against <i>Acinetobacter spp.</i>
Imipenem/Cilastatin + Funobactam	NCT05204368	Ongoing	Meropenem	cUTI / AP	class A; class C; class D, (especially including those produced by <i>A. baumannii</i> , such as OXA-24/40-like)
Imipenem/Cilastatin + Funobactam	NCT05204563	Completed	IMI/CIL/REL	HAP/VAP	class A; class C; class D, (especially including those produced by <i>A. baumannii</i> , such as OXA-24/40-like)
Meropenem + Pralurbactam	NCT07089186	Ongoing	BAT	cUTI, HAP, VABP, cIAI, BSI	class A; class C; class D, OXA-48
Meropenem + Pralurbactam	NCT06633718	Ongoing (not yet recruiting)	CAZ/AVI + Metronidazole	cIAI	class A; class C; class D, OXA-48
Cefepime + Nacubactam	NCT05887908	Completed	IMI/CIL	cUTI/AP	class A; class C; class D, (OXA-48)
Aztreonam + Nacubactam	NCT05887908	Completed	IMI/CIL	cUTI/AP	class A; class B; class C; class D, (OXA-48); MBL <i>P. aeruginosa</i>
Cefepime + Nacubactam	NCT05905055	Completed	BAT	cUTI, AP, HAP, VABP, and cIAI	class A; class C; class D, (OXA-48)
Aztreonam + Nacubactam	NCT05905055	Completed	BAT	cUTI, AP, HAP, VABP, and cIAI	class A; class B; class C; class D, (OXA-48); MBL <i>P. aeruginosa</i>

AP, acute pyelonephritis; BAT, best alternative therapy; BSI, bloodstream infection; CAZ/AVI, ceftazidime-avibactam; EMA, European Medicine Agency; cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections; ESBL, extended-spectrum β -lactamase; FDA, Food and Drug Administration; HAP, hospital-acquired pneumonia; IMI/CIL/REL, imipenem-cilastatin-relebactam; IMP, imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo- β -lactamases; NDM, New Delhi metallo- β -lactamase; OXA, oxacillinase; VAP, ventilator-associated pneumonia; VIM, Verona Integron-borne metallo- β -lactamase.

evaluated in two Phase 3 clinical trials for the treatment of carbapenem-resistant Enterobacterales infections (Clinicaltrial.gov identifier: NCT07089186, NCT06633718).

Finally, nacubactam combinations with cefepime or aztreonam are now under clinical evaluation in Phase 3 studies for the treatment of cUTI, HAP/VAP, and cIAI (Clinicaltrial.gov identifier: NCT05905055, NCT05887908). Nacubactam is a DBO-type BLI with activity against Class A and C β -lactamases and some class D enzymes, while it has also intrinsic antibiotic activity against serine β -lactamases producing *Enterobacterales* through inhibition of PBP-2 [282]. A significant advantage of the combination of nacubactam with aztreonam is the activity against MBL-producing *Enterobacterales* and *P. aeruginosa* [283].

As evidenced by the investigational regimens described above, cefepime has emerged as a frequently selected β -lactam backbone in contemporary BLBI development and cefepime-containing regimens represent one of the promising therapeutic strategies currently being investigated. This fourth-generation cephalosporin remains stable to hydrolysis by class C AmpC and class D OXA-48 enzymes, exhibiting a broad spectrum bactericidal activity against Gram-negative

pathogens and demonstrates an enhanced activity through its rapid penetration of outer membrane porin channels [284]. Figure 2 summarizes the differential spectrum of current and emerging BLBI agents across clinically relevant resistance mechanisms [5–9,14,32].

12.3. Promising BLIs in phase 1 studies

Xeruborbactam (formerly QPX7728) is a novel cyclic boronate β -lactamase inhibitor with a broad spectrum of activity, encompassing both serine β -lactamases and MBLs [34]. In contrast to earlier β -lactamase inhibitors, xeruborbactam demonstrates potent inhibitory activity across Ambler classes A, B, C, and D, including clinically significant carbapenemases such as KPC, OXA-type enzymes, and MBLs of the NDM and IMP families [34]. This 'pan- β -lactamase' inhibition profile is mediated by the ability of cyclic boronates to form reversible covalent interactions with both serine- and zinc-dependent active sites, representing a key structural and mechanistic advance over previous inhibitor generations [34]. Beyond β -lactamase inhibition, xeruborbactam has been shown to exhibit intrinsic antibacterial activity against selected Gram-

BLBLI Combination	AmpC	KPC	MBL	DTR <i>P. aeruginosa</i>	<i>A. baumannii</i> (CRAB)
Ceftazidime–avibactam	●	●	●	● ¹	●
Meropenem–vaborbactam	●	●	●	●	●
Imipenem–relebactam ²	●	●	●	● ¹	●
Sulbactam–durlobactam	●	●	●	●	●
Aztreonam–avibactam	●	●	●	● ¹	●
Cefepime–enmetazobactam	●	●	●	●	●
Cefepime–taniborbactam	●	●	●	● ³	●
Cefepime–zidebactam	●	●	●	●	●
Imipenem–cilastatin– funobactam	●	●	●	● ¹	●
Cefepime–nacubactam	●	●	●	●	●
Meropenem–nacubactam	●	●	●	●	●
Aztreonam–nacubactam	●	●	●	●	●
Meropenem–Pralubactam	●	●	●	●	●

¹ Susceptibility rates may vary according to the resistance mechanism and geographical region
² Imipenem–relebactam exhibits no activity against *Proteus* spp., *Providencia* spp., and *Morganella* spp
³ In vitro activity against MBL producing Gram-negative with the exception of IMP

● Strong activity (≥80% susceptible)
● Partial / variable activity (50–79%)
● Poor or minimal activity (<50%)

Figure 2. Antimicrobial activity of approved and investigational β -lactam/ β -lactamase inhibitor (BLBLI) combinations against major resistance mechanisms in Gram-negative pathogens.

negative pathogens, including Enterobacterales and *A. baumannii*, likely mediated through secondary interactions with PBPs [1]. This dual mechanism may contribute to enhanced antibacterial efficacy and reduced dependence on partner β -lactams. Notably, xeruborbactam restores the activity of meropenem against CRAB, including isolates producing OXA-23 carbapenemase, highlighting its potential utility against highly resistant non-fermenting pathogens [285]. Preclinical studies have consistently demonstrated potent *in vitro* activity of xeruborbactam-based combinations against MDR and extensively XDR Gram-negative organisms, including CRE and DTR *P. aeruginosa* [14]. Importantly, its activity against MBL-producing organisms distinguishes xeruborbactam from currently approved β -lactamase inhibitors, which generally lack clinically meaningful inhibition of class B enzymes. Xeruborbactam is currently undergoing phase I clinical development exclusively in combination with β -lactam antibiotics. Intravenous regimens include combinations with cefiderocol (e.g. ClinicalTrials.gov identifiers NCT06547554 and NCT07104162) and additionally oral development programs are evaluating a prodrug formulation of xeruborbactam in combination with ceftibuten (e.g. NCT06079775 and NCT06157242), representing a potentially transformative approach toward oral therapy for infections caused by MDR Gram-negative pathogens. Collectively, xeruborbactam represents one of the most advanced next-generation boronate β -lactamase inhibitors, with a unique combination of pan-enzyme inhibition, intrinsic antibacterial activity, and flexible pairing with both intravenous and oral β -lactams. While clinical efficacy data are not yet available, its pharmacological profile positions it as a highly promising candidate for the management of DTR Gram-negative infections, particularly those involving MBL-producing organisms for which current therapeutic options remain limited.

13. Expert opinion

The emergence of BLBLI combinations represents the most clinically transformative antimicrobial advance of the past decade for infections caused by KPC-producing CRE. Prior to their availability, therapy relied largely on toxic and pharmacodynamically suboptimal agents such as polymyxins and tigecycline, consistently associated with high mortality and treatment failure. Accumulating real-world evidence now demonstrates substantial survival benefit and improved microbiological eradication with CAZ-AVI, MER-VAB, IMI-REL, effectively converting a previously near-untreatable phenotype into one routinely manageable in modern clinical practice.

These agents have reestablished β -lactams as the backbone of therapy for severe CRE infections, enabling simplified regimens, reduced toxicity, and earlier effective treatment. Their incorporation into international guidelines reflects not only superior efficacy but also improved safety and downstream economic benefits through reduced nephrotoxicity, shorter hospitalization, and decreased ICU utilization. Implementation across healthcare systems, however, depends heavily on access to rapid diagnostics and structured antimicrobial stewardship programs. It is of great significant to mention that delayed identification of resistance mechanisms remains a major barrier to optimal use.

Although comparative data suggest broadly similar clinical effectiveness among BLBLIs for KPC-producing organisms, mechanistic distinctions retain clinical relevance. Vaborbactam provides particularly potent KPC inhibition and appears to confer a higher genetic barrier to resistance. Avibactam uniquely retains activity against OXA-48-like carbapenemases, expanding epidemiological applicability, while relebactam reliably inhibits KPC and AmpC enzymes and improves activity against DTR *P. aeruginosa*. These differences

support mechanism-guided therapeutic selection rather than empirical interchangeability, particularly in regions with heterogeneous carbapenemase epidemiology. Infectious site wise, MER-VAB shows advantageous pharmacokinetics in the lung compared to CAZ-AVI, whereas for IMI-REL evidence is more limited.

Similarly, a paradigm-shifting development is the introduction of SUL-DUR for CRAB. Unlike earlier regimens reliant on polymyxins or combination salvage therapy, this agent restores the clinical utility of sulbactam through potent inhibition of class D β -lactamases, directly targeting one of the most therapeutically challenging pathogens in modern infectious diseases. Early clinical data demonstrate comparable or improved efficacy with significantly reduced nephrotoxicity, marking a decisive transition away from polymyxin-based therapy in CRAB infections. This reinforces a broader conceptual shift and pathogen-specific BLBLI design can overcome even historically 'untreatable' resistance phenotypes when aligned with mechanistic insight.

In parallel, agents such as C-T and FEP-ETZ occupy a complementary but distinct niche. Ceftolozane-tazobactam remains a cornerstone for DTR *P. aeruginosa*, driven by enhanced stability against AmpC and favorable PK/PD properties in pulmonary infections, though its lack of activity against carbapenemases limits its role in CRE. Cefepime-enmetazobactam, by contrast, provides expanded activity against ESBL-producing strains representing an important carbapenem-sparing option; however, its clinical positioning remains more limited compared with established BLBLIs, and real-world data in severe infections are still emerging. Collectively, these agents highlight the increasing specialization of β -lactam therapy, where spectrum, resistance mechanism, and infection site must all inform optimal selection.

Despite these advances, the principal vulnerability of the current BLBLI era is the lack of activity against MBL-producing organisms. The rapid expansion of NDM, VIM, and IMP producers represents the dominant emerging threat to modern β -lactam therapy. Aztreonam-avibactam provides a rational pharmacologic strategy by protecting aztreonam from co-produced serine β -lactamases, but its role remains constrained by dosing complexity and limited post-marketing experience. In endemic settings, increasing MBL prevalence may progressively erode the clinical impact of existing BLBLIs unless next-generation inhibitors capable of dual serine and metallo- β -lactamase inhibition become widely available.

Stewardship will be decisive in shaping the durability of these advancements. Resistance mediated by KPC structural mutations, porin alterations, and permeability changes has already been described, particularly with avibactam-based regimens. Appropriate use therefore requires integration of rapid molecular diagnostics, PK/PD-optimized dosing, therapeutic drug monitoring where feasible, and early de-escalation. Importantly, shortening treatment duration also contributes to resistance containment with accumulating evidence supporting 7-day therapy for BSI, reducing antibiotic exposure and selective pressure, thereby lowering the risk of resistance emergence without compromising clinical outcomes.

Future research should prioritize ultrabroad-spectrum inhibitors capable of neutralizing both serine and metallo- β -

lactamases within a single therapeutic platform, alongside improved pharmacokinetic strategies for critically ill patients. Real-world surveillance and better understanding of resistance development during therapy will be essential to preserve therapeutic longevity.

Over the next decade, management of carbapenem-resistant infections will likely shift toward mechanism-specific BLBLI therapy guided by rapid genomic diagnostics. Polymyxin-based regimens may largely disappear, while treatment success will increasingly depend on precision antimicrobial therapy combined with rigorous stewardship and real-time epidemiological monitoring.

14. Conclusion

Modern BLBLI combinations have reshaped the management of carbapenem-resistant Gram-negative infections by restoring β -lactam activity and improving outcomes compared with legacy therapies. Accumulating clinical and real-world evidence demonstrates superior survival, microbiological eradication, and safety for agents such as ceftazidime-avibactam, meropenem-aborbactam, and imipenem-relebactam in KPC- and OXA-48-producing Enterobacterales, as well as for ceftolozane-tazobactam in difficult-to-treat *P. aeruginosa*. The inclusion of cefepime-enmetazobactam further expands carbapenem-sparing options for ESBL-producing pathogens, while sulbactam-durlobactam represents a major advance for carbapenem-resistant *Acinetobacter baumannii*, addressing a longstanding therapeutic gap. In parallel, aztreonam-avibactam provides a targeted strategy against metallo- β -lactamase-producing organisms.

Despite these advances, the durability of BLBLI therapy remains challenged by the ongoing evolution of resistance, including enzyme diversification, permeability defects, and selection under treatment pressure. These limitations underscore the need for next-generation inhibitors with broader activity against both serine and metallo- β -lactamases. Sustained clinical effectiveness will depend on optimized PK/PD-driven dosing strategies, integration of rapid diagnostics, and implementation of robust antimicrobial stewardship programs.

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