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Review Article

Beta-lactam antibiotic and beta-lactamase inhibitor combinations versus carbapenem antibiotics in the treatment of infections caused by extended-spectrum beta-lactamase and carbapenem-resistant Enterobacterales

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Abstract:

The growing threat of antimicrobial resistance, particularly involving extended-spectrum beta-lactamase (ESBL)-producing and carbapenem-resistant Enterobacterales (CRE), has significantly challenged existing treatment options. While carbapenems have traditionally served as the gold standard for severe infections caused by ESBL-E, their widespread use has contributed to resistance and the emergence of CRE. In response, β-lactam/β-lactamase inhibitor (BL/BLI) combinations, such as ceftazidime–avibactam and piperacillin–tazobactam, have gained interest as carbapenem-sparing alternatives. Observational studies and meta-analyses suggest that BL/BLI combinations can achieve outcomes similar to carbapenems in selected, low-risk infections, particularly when guided by susceptibility testing and MIC-based dosing; however, the MERINO randomised trial found piperacillin–tazobactam to be inferior to meropenem for ESBL-producing bloodstream infections. Newer agents have shown expanded activity against KPC, OXA-48, and even metallo-β-lactamase-producing pathogens. This review highlights the evolving role of BL/BLI therapies, the need for individualised treatment strategies, and the importance of antimicrobial stewardship in curbing resistance.

Keywords: Extended-spectrum β-lactamase; carbapenem-resistant Enterobacterales; β-lactam/β-lactamase inhibitors; carbapenems; antimicrobial resistance; antimicrobial stewardship

Introduction

In recent years, the effectiveness of antibiotic treatments in managing bacterial infections has significantly diminished due to the increasing prevalence of antimicrobial resistance (AMR). According to Aslam et al. [1], AMR occurs when microorganisms such as bacteria, viruses, fungi and parasites develop resistance to the agents used to treat them. The emergence of AMR is driven by the overuse and misuse of antibiotics [2]. AMR poses a serious threat to global health [3]. Antibiotic-resistant infections are estimated to cause at least 700,000 deaths annually worldwide, with projections of 10 million deaths per year by 2050 if no action is taken [4]. Members of the order Enterobacterales, especially *Escherichia coli* and *Klebsiella pneumoniae*, are widely recognised as significant pathogens, playing a major role in various infections acquired both in healthcare facilities and within the community [5]. Enterobacterales are a large group of Gram-negative bacilli that normally reside in the human gastrointestinal tract, but they are also a common cause of nosocomial infections (NIs) because they spread easily between patients in healthcare settings [6]. Extended-spectrum β-lactamases (ESBLs) are enzymes made by certain bacteria that can break down and destroy a group of antibiotics called β-lactams [7]. Gram-negative bacteria mainly rely on producing these enzymes to resist the effects of β-lactam antibiotics [8]. The

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key phenotypic property of ESBL enzymes is their ability to hydrolyse third-generation cephalosporins [9]. The global rise in ESBL-related infections has led to a parallel increase in the use of carbapenem antibiotics. However, frequent use of carbapenems creates selective pressure that promotes the development of carbapenem-resistant bacteria [10]. One of the major risk factors for acquiring infections caused by carbapenem-resistant bacteria is prior treatment with carbapenems. Even short-term exposure to these antibiotics, especially in intensive care patients, can increase the risk of colonisation with Gram-negative bacteria resistant to imipenem. This has given rise to a new challenge, the rapid spread of carbapenem resistance, largely driven by the efficient transmission of carbapenemase genes among carbapenemase-producing Enterobacterales (CPE) [11].

The threat of CPE is substantial as carbapenems have traditionally been used in the treatment of infections caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E) and are still considered a last line of defence against Enterobacterales to date. Few antibiotics retain activity against CPE due to the ability of carbapenemases to hydrolyse most other β-lactam antibiotics as well as the frequent coexistence in CPE isolates of additional mechanisms of resistance against other antibiotic classes such as fluoroquinolones and aminoglycosides [12]. Most carbapenem resistance is caused by three enzyme groups which are Klebsiella pneumoniae carbapenemase (Ambler class A), metallo-β-lactamases (Ambler class B), and oxacillinase-48 (Ambler class D) [11].

Carbapenems, such as meropenem and imipenem, have long been considered the last-resort antibiotics for treating severe infections caused by ESBL-E. Their broad-spectrum activity and stability against most beta-lactamases make them highly effective in managing complicated infections. However, the widespread and sometimes inappropriate use of carbapenems, particularly as empirical therapy, has significantly contributed to the emergence and global spread of carbapenem-resistant Enterobacterales (CRE). These resistant strains pose a serious threat to public health due to limited treatment options and high mortality rates. The global epidemiology of CRE reflects a growing crisis that demands urgent attention in antimicrobial stewardship and infection control practices to preserve the efficacy of these vital agents [12].

In response to this crisis, beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations, including the established agent piperacillin–tazobactam and newer agents such as ceftazidime–avibactam, have provided options for treating infections caused by ESBL-producing organisms and some CRE. These combinations help restore the activity of beta-lactam antibiotics and are considered useful carbapenem-sparing alternatives, potentially reducing resistance pressure from overuse of carbapenems [13].

There is a growing concern over the rise of multidrug-resistant Gram-negative bacteria, particularly ESBL-producing Enterobacterales and CRE. While carbapenems have long been the mainstay for treating such infections, their overuse has contributed to increasing resistance. As BL/BLI combinations emerge as potential alternatives, there is an urgent need to evaluate and compare their clinical efficacy, resistance patterns, and impact on mortality against carbapenems. Such comparisons are essential to support antibiotic stewardship efforts and ensure the selection of the most appropriate and sustainable treatment strategies.

Methodology

Study Design

This article is a narrative comparative review of the published evidence on beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations and carbapenems for the treatment of infections caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E) and carbapenem-resistant Enterobacterales (CRE). The review focuses on clinical efficacy, mortality, safety, resistance and pharmacokinetic/pharmacodynamic considerations, together with their implications for antimicrobial stewardship.

Literature Search Strategy

Relevant literature was identified through PubMed/MEDLINE, ScienceDirect and Google Scholar. The search terms were combined with Boolean operators as follows: ("extended-spectrum beta-lactamase" OR "ESBL" OR "carbapenem-resistant Enterobacterales" OR "CRE") AND ("beta-lactam/beta-lactamase inhibitor" OR "piperacillin-tazobactam" OR "ceftazidime-avibactam" OR "meropenem-vaborbactam" OR "ceftolozane-tazobactam") AND ("carbapenem" OR "meropenem"). The reference lists of key reviews, trials and meta-analyses were hand-searched for further studies. Reports and guidance documents were obtained from the World Health Organization, the US Centers for Disease Control and Prevention and the Infectious Diseases Society of America (IDSA). The search was last updated in May 2025.

Eligibility Criteria

Full-text articles published in English were eligible, mainly those published between 2012 and 2025. Randomised controlled trials, observational cohort studies, systematic reviews and meta-analyses, genomic surveillance studies and treatment guidelines were included when they compared BL/BLI combinations with carbapenems, or reported on the efficacy, safety, resistance mechanisms or pharmacokinetics/pharmacodynamics of either class in ESBL-E or CRE infections. Older landmark publications were retained for background. Conference abstracts without full text, non-English articles and duplicate reports were excluded.

Study Selection and Data Synthesis

Titles and abstracts were screened for relevance, and the full texts of potentially eligible articles were reviewed by the authors. Information was extracted on study design, setting, population, infection site, pathogen, antibiotic regimen, treatment context (empirical or definitive), 30-day or 28-day mortality, clinical and microbiological outcomes and adverse events. Because the included studies differed widely in design and outcome definitions, no meta-analysis was performed. The evidence was synthesised narratively by antibiotic class and infection type and then discussed in relation to antimicrobial stewardship. Outcome data from a representative study are presented in Table 1.

Extended-Spectrum β-Lactamase and Carbapenem-Resistant Enterobacterales

One of the most important issues facing the management of infectious diseases today is the global increase in antibiotic resistance in Gram-negative bacteria. ESBL-E and CRE exhibit two of the most concerning resistance mechanisms; they are linked to higher mortality, longer hospital stays, and fewer treatment options [14,15]. While CRE infections show resistance to carbapenems, which are frequently the antibiotics used as a last resort, ESBLs are enzymes that can hydrolyse penicillin and third-generation cephalosporins [16]. Resistance genes such as blaCTX-M, blaKPC and blaNDM are commonly carried on mobile genetic elements in these organisms, promoting resistance evolution and quick horizontal transmission [16,17]. Although carbapenems have been considered the standard of care for severe ESBL infections, their extensive use has greatly aided in the development and spread of CRE [15]. As a result, for low-risk infections, β-lactam/β-lactamase inhibitor (BL/BLI) combinations such as piperacillin–tazobactam, ceftazidime–avibactam, and cefepime–enmetazobactam have drawn interest as potential carbapenem-sparing alternatives [18,19]. The purpose of this literature review is to evaluate the clinical effectiveness, safety, and resistance outcomes of carbapenem monotherapy and BL/BLI combinations in the management of infections linked to ESBL and CRE.

The escalating threat of antimicrobial resistance at the local level is exemplified by a genomic surveillance study from Central Texas conducted by Parker et al. [20], which explored the genetic and phenotypic relationships between ESBL-E and CRE. Out of 132 clinical isolates analysed between 2018 and 2020, the majority (116) were identified as ESBL producers, while 16 were classified as CRE. The most frequently isolated species were *Klebsiella pneumoniae* and *Escherichia coli*. Interestingly, more than half (54%) of the CRE isolates did not produce carbapenemase enzymes (non-CP-CRE), suggesting that resistance in these strains likely arose through alternative mechanisms, including porin loss (for instance, mutations in OmpK36) and increased efflux activity. A significant finding was the clonal distribution of the high-risk *K. pneumoniae* sequence type ST307, present across both ESBL and non-CP-CRE isolates, all of which harboured the CTX-M-15 β-lactamase gene, one of the most widespread ESBL genes globally. These strains also exhibited mutations associated with fluoroquinolone resistance, such as GyrA S83I, pointing to a progressive evolutionary pathway from ESBL production to carbapenem resistance. Furthermore, three CRE isolates were found to carry colicinogenic plasmids, which may contribute to enhanced bacterial competitiveness and persistence in healthcare environments. Most concerning, the incidence of CRE in Travis County rose by 850% between 2014 and 2020, with *K. pneumoniae* accounting for over half of all CRE infections. These findings underscore the evolutionary potential of ESBL-producing organisms to develop carbapenem resistance in the absence of carbapenemase genes and reinforce the importance of genomic surveillance in tracking resistance mechanisms and controlling the spread of high-risk clones like ST307.

BL/BLI Combinations

Sargianou et al. [17] reviewed the emerging role of novel BL/BLIs aimed at overcoming existing limitations. The review emphasised agents including cefepime–enmetazobactam, aztreonam–avibactam, and sulbactam–durlobactam. Cefepime–enmetazobactam exhibited superiority over piperacillin–tazobactam (PTZ) in the ALLIUM trial for the treatment of complicated urinary tract infections, whereas aztreonam–avibactam displayed significant efficacy against metallo-β-lactamase (MBL)-producing pathogens, which are typically resistant to both carbapenems and conventional BL/BLI combinations. Sulbactam–durlobactam, although not active against Enterobacterales, demonstrated non-inferiority to colistin in the treatment of *Acinetobacter baumannii* pneumonia, while exhibiting superior renal safety. These novel agents present considerable promise as carbapenem-sparing therapies, thereby broadening the treatment options for multidrug-resistant infections.

Wilson et al. [21] conducted a systematic review and meta-analysis of 25 studies to evaluate newer BL/BLIs, specifically ceftazidime–avibactam, ceftolozane–tazobactam, imipenem–relebactam, and meropenem–vaborbactam. The pooled analysis of clinical success did not demonstrate a statistically significant benefit of newer BL/BLIs compared to older standard therapies (OR 1.21; 95% CI, 0.96–1.51). However, a notable difference was identified in patients infected with CRE or multidrug-resistant (MDR) *Pseudomonas aeruginosa*. In this subgroup, newer BL/BLIs demonstrated a significant association with increased clinical success (pooled OR 2.20; 95% CI 1.60–3.57) and a reduction in 28–30-day mortality (OR 0.50; 95% CI 0.33–0.75). By infection site, the newer agents were associated with higher clinical success in complicated urinary tract infections (cUTIs), but not in hospital- or ventilator-associated pneumonia [21]. Adverse events were not assessed in this meta-analysis; however, these agents avoid the nephrotoxicity associated with polymyxins and aminoglycosides.

Carbapenem Antibiotics

Carbapenems are broad-spectrum β-lactam antibiotics essential for treating severe infections caused by multidrug-resistant Gram-negative bacteria [22]. They exert bactericidal activity by binding to penicillin-binding proteins (PBPs) and inhibiting cell wall

synthesis, and differences in PBP affinity among agents contribute to variations in spectrum. For example, meropenem and doripenem exhibit higher affinities for PBP2 and PBP3 in *Pseudomonas aeruginosa*, enhancing their antipseudomonal activity compared to imipenem. While imipenem shows stronger activity against *Enterococcus faecalis*, ertapenem notably lacks efficacy against *P. aeruginosa* and *Acinetobacter baumannii*, limiting its use in nosocomial settings [23]. The rising prevalence of carbapenem-resistant organisms represents a substantial threat to global health. Resistance mechanisms involve the production of carbapenemases, including Klebsiella pneumoniae carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), and oxacillinase (OXA) enzymes, alongside reduced outer membrane permeability and the overexpression of efflux pumps [24]. These mechanisms collectively reduce the effectiveness of carbapenems, even against pathogens that are typically susceptible. Carbapenems show low to moderate protein binding, are eliminated predominantly by the kidneys and are distributed mainly in extracellular fluids [25]. Their antibacterial activity is time-dependent, with clinical efficacy closely linked to sustaining drug concentrations above the minimum inhibitory concentration (ƒT > MIC) for an adequate duration. Optimised dosing regimens, especially prolonged or continuous infusions, are recommended to improve therapeutic outcomes in critically ill patients [26].

BL/BLI Combinations Versus Carbapenem Antibiotics

Beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations have become known as viable options to carbapenems for treating infections caused by ESBL-E and CRE. Despite increasing concerns about the overuse of carbapenems and the resultant development of carbapenem-resistant pathogens, particularly *Klebsiella pneumoniae* and P*seudomonas aeruginosa*, several studies have attempted to investigate whether BL/BLIs might provide equivalent therapeutic results with fewer ecological drawbacks. Recent work reveals results that differ according to infection severity, pathogen type, and treatment context (empirical vs definitive), thereby offering significant insights into the complex function of BL/BLIs.

A meta-analysis conducted by Sfeir et al. [27] examined the mortality outcomes associated with BL/BLIs compared to carbapenems in bloodstream infections (BSIs) caused by ESBL-E. The analysis, which encompassed 25 observational studies and 3,842 patients, revealed no statistically significant difference in 30-day mortality between the two groups. This was consistent for both empirical (OR 1.13; 95% CI 0.87–1.48) and definitive therapies (OR 0.96; 95% CI 0.59–1.86), indicating that PTZ and other BL/BLIs could serve as effective carbapenem-sparing alternatives based upon susceptibility data. Mortality outcomes were stratified by PTZ MIC, revealing a trend towards improved survival in patients with MIC ≤0.5 μg/mL, underscoring the significance of pharmacodynamic targets in BL/BLI therapy. The study highlighted that PTZ was the most used BL/BLI and exhibited a favourable safety profile, although specific adverse events were not consistently reported across the studies.

In contrast, the MERINO trial by Harris et al. [28], the only large randomised controlled trial in this setting, compared piperacillin–tazobactam with meropenem as definitive therapy for bloodstream infections caused by ceftriaxone-non-susceptible E. coli or K. pneumoniae. Among 379 patients, 30-day mortality was 12.3% with piperacillin–tazobactam versus 3.7% with meropenem, and non-inferiority was not shown. Although later analyses suggested that factors such as piperacillin–tazobactam MIC testing and co-carriage of OXA-1 may have contributed, MERINO remains the principal reason why current guidelines do not recommend piperacillin–tazobactam for serious ESBL-E infections [29].

The ASPECT-NP trial conducted by Kollef et al. [30] provides a comprehensive assessment of ceftolozane–tazobactam for treating nosocomial pneumonia, specifically ventilator-associated pneumonia (VAP) and ventilated hospital-acquired pneumonia (vHAP). This study was a randomised, double-blind, phase 3 non-inferiority trial involving 726 critically ill, mechanically ventilated patients, comparing high-dose ceftolozane–tazobactam (3 g every 8 hours) with standard-dose meropenem (1 g every 8 hours). The primary endpoint of 28-day all-cause mortality was achieved, showing mortality rates of 24.0% in the ceftolozane–tazobactam group and 25.3% in the meropenem group, indicating non-inferiority (difference: 1.1%, 95% CI: −5.1 to 7.4). Clinical cure rates at the test-of-cure visit were

similar between groups (54.4% vs. 53.3%, respectively), with no significant differences noted across key subgroups, including patients infected with ESBL-E or multidrug-resistant *Pseudomonas aeruginosa*. Adverse events were common in both treatment groups, as anticipated in a critically ill population; however, the safety profiles were largely similar. Treatment-related adverse events were observed in 11% of patients administered ceftolozane–tazobactam and in 8% of those treated with meropenem. The most frequently reported adverse events included gastrointestinal symptoms, abnormal liver function tests, and *C. difficile* colitis; however, no deaths were considered related to the administration of the study drug. Serious treatment-related adverse events were observed in 2% of patients treated with ceftolozane–tazobactam and 1% in the meropenem group, with no instances of neurotoxicity or seizures reported, even at the elevated cephalosporin dosage.

Zhang et al. [31] conducted a meta-analysis that included one randomised controlled trial (RCT) and 25 cohort studies, encompassing a total of 2,786 patients with BSI caused by ESBL. The findings confirmed that BL/BLIs demonstrated non-inferiority to carbapenems regarding therapeutic response (OR 1.19, P = 0.45) and mortality (OR 1.06, P = 0.68). Zhang et al. provided a significant insight regarding the comparative advantage of BL/BLIs in definitive therapy. Their findings show that targeted use based on susceptibility testing led to a numerically higher treatment response (OR 1.42) and a slightly lower mortality rate (OR 0.85), in contrast to their application in empirical therapy (OR 0.89 and OR 1.14, respectively). This differentiation highlights the essential function of rapid diagnostics and MIC-informed dosing in improving BL/BLI efficacy.

A single-centre retrospective study by Muharam et al. [32] provides additional evidence for the non-inferiority of BL/BLIs, especially PTZ, in the treatment of urinary tract infections (UTIs) caused by ESBL-E. In this Southeast Asian cohort, clinical success rates were similar between the BL/BLI and carbapenem groups (81.3% compared to 76.6%), and mortality rates were also similar (15.6% versus 17.0%). Upon adjusting for confounding variables, clinical failure was more closely associated with factors such as severe sepsis, catheter presence, and co-infection than with antibiotic selection, indicating that BL/BLIs represent a safe and effective option for non-severe ESBL-E UTIs.

When treating CRE infections, especially those that make KPC enzymes, newer BL/BLI combinations are recommended. These include ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–cilastatin–relebactam. These agents are more effective and safer than older regimens such as colistin-based therapy. In the TANGO II trial, patients treated with meropenem–vaborbactam had lower 28-day mortality than those receiving best available therapy (15.6% vs 33.3%), and a lower incidence of nephrotoxicity (4.0% vs 24.0%) [33].

For CRE that make metallo-β-lactamases (MBLs) like the NDM enzyme, carbapenems and conventional BL/BLI combinations are inactive. In these cases, the Infectious Diseases Society of America (IDSA) recommends either ceftazidime–avibactam combined with aztreonam, or the newer drug cefiderocol, both of which have been shown to be effective [15].

With regard to pharmacokinetics and pharmacodynamics, the effectiveness of PTZ depends on its pharmacodynamic target, the proportion of the dosing interval during which free plasma concentrations remain above the MIC (ƒT > MIC). Sfeir et al. [27] indicated that PTZ demonstrated optimal effectiveness at MICs of ≤0.5 μg/mL, suggesting that insufficient drug exposure may have led to diminished efficacy in infections with higher MICs. None of the included studies reported the use of therapeutic drug monitoring, although prolonged or continuous infusion was proposed as a strategy to improve PTZ's time-dependent bactericidal activity. The ASPECT-NP trial reinforced pharmacokinetic and pharmacodynamic principles through a 3 g q8h dosing regimen of ceftolozane–tazobactam, specifically selected to achieve 100% ƒT > MIC in critically ill pneumonia patients [30]. The findings underscore the significance of personalised dosing strategies and pharmacokinetic/pharmacodynamic optimisation to achieve therapeutic success, especially in critically ill patients exhibiting altered pharmacokinetic profiles.

Discussion

The increasing prevalence of infections due to extended-spectrum β-lactamase-producing and carbapenem-resistant Enterobacterales presents a significant global challenge, primarily because of limited options for treatment and increased mortality rates [34]. Carbapenems have traditionally been used as the primary treatment for extended-spectrum β-lactamase-related infections due to their broad-spectrum efficacy and structural resilience against various β-lactamases, including extended-spectrum β-lactamases and AmpC enzymes [29]. However, their excessive use, particularly in empirical treatment contexts, has resulted in significant selective pressure, facilitating the emergence and spread of carbapenem-resistant Enterobacterales. Resistant pathogens commonly emerge in high-risk clinical settings, including intensive care units and long-term care facilities, especially in patients subjected to prolonged hospitalisations, invasive interventions, and broad-spectrum antibiotic treatments [35]. In the United States alone, carbapenem-resistant Enterobacterales account for more than 13,000 infections and 1,100 deaths each year [14]. Carbapenemase-producing strains have also been detected outside human healthcare, for example in companion animals hospitalised in Switzerland [36].

Carbapenem-resistant Enterobacterales develop resistance via various mechanisms, primarily through the production of carbapenemases, including KPC, NDM, and OXA-48, which hydrolyse carbapenems, rendering them ineffective. Other mechanisms involve mutations in porin channels that decrease drug uptake and the overexpression of efflux pumps that remove antibiotics from the bacterial cell [37]. These genetic elements are frequently encoded on mobile plasmids, which enable horizontal gene transfer among bacterial species in healthcare environments, communities, and the food supply chain [38]. The ongoing misuse of carbapenems reduces their clinical effectiveness and promotes the dissemination of resistance mechanisms, resulting in outbreaks of challenging infections. This underscores the necessity for surveillance, infection control, and antibiotic stewardship initiatives.

In the context of increasing carbapenem resistance, β-lactam/β-lactamase inhibitor combinations are receiving renewed attention as viable carbapenem-sparing alternatives. These agents integrate a β-lactam antibiotic with an inhibitor that obstructs β-lactamase enzymes, thus reinstating antibacterial efficacy [39]. Traditional combinations such as piperacillin–tazobactam maintain their efficacy against numerous extended-spectrum β-lactamase-producing organisms in low-risk infections. However, their effectiveness is constrained in high-inoculum or carbapenem-resistant Enterobacterales-related infections. Recent β-lactam/β-lactamase inhibitor agents, including ceftazidime–avibactam, meropenem–vaborbactam, and aztreonam–avibactam, provide enhanced enzyme coverage, demonstrating efficacy against KPC, OXA-48, and MBL producers. These agents facilitate targeted therapy informed by susceptibility patterns and pharmacodynamic factors, thereby diminishing the selection pressure linked to carbapenem usage. Consequently, they serve as a vital tool in combating resistance while preserving clinical efficacy, particularly in non-critical infections where narrower-spectrum, mechanism-based strategies are favoured [40].

Numerous clinical studies have investigated the comparative efficacy of β-lactam/β-lactamase inhibitor combinations and carbapenems in treating extended-spectrum β-lactamase-producing infections. Multiple studies have demonstrated that β-lactam/β-lactamase inhibitors are non-inferior to carbapenems in terms of mortality and clinical response when used appropriately. For instance, a meta-analysis by Muhammed et al. [18] reported no significant difference (RR 1.05; 95% CI 0.83–1.37; I^2 = 20.7%; P = 0.241), with no evidence of small-study effects, in mortality between patients receiving empirical carbapenems and those receiving β-lactam/β-lactamase inhibitors in bloodstream infections (BSIs) caused by ESBL-producing Enterobacterales. Similarly, Rodríguez-Baño et al. [41] found comparable outcomes between PTZ and carbapenems in treating extended-spectrum β-lactamase-producing *E. coli* bacteraemia, especially in urinary tract infections with low minimum inhibitory concentrations (MICs). These findings are echoed in Sfeir et al. [27] and Zhang et al. [31], whose meta-analyses confirmed the non-inferiority of β-lactam/β-

lactamase inhibitors in both empirical and definitive therapies. Notably, Zhang et al. [31] highlighted a trend toward better performance of β-lactam/β-lactamase inhibitors in definitive therapy settings, reinforcing the value of rapid diagnostics and MIC-guided treatment. However, these largely observational data contrast with the MERINO randomised trial, in which piperacillin–tazobactam failed to show non-inferiority to meropenem for ceftriaxone-resistant E. coli and K. pneumoniae bloodstream infections (30-day mortality 12.3% vs 3.7%) [28]. Accordingly, current IDSA guidance recommends a carbapenem for ESBL-E infections outside the urinary tract and advises against piperacillin–tazobactam in this setting, even when the isolate tests susceptible [29].

Despite notable pharmacological and spectrum-related differences between β-lactam/β-lactamase inhibitor combinations and carbapenems, many studies report no statistically significant difference in mortality outcomes between the two. This paradox can be elucidated through the meticulous selection of patients and the types of infections for which β-lactam/β-lactamase inhibitors are administered [42]. Most studies indicate that β-lactam/β-lactamase inhibitors are utilised for stable patients presenting with lower-risk infections, especially those attributed to Escherichia coli exhibiting low minimum inhibitory concentrations (MICs), as well as infections originating from urinary or bloodstream sources. These situations are associated with reduced bacterial burden and improved source control, thereby enhancing the effectiveness of β-lactam/β-lactamase inhibitors [43].

Furthermore, when BL/BLIs are used as definitive therapy once susceptibility results are available, clinicians can adjust antibiotic choice based on MICs, maximising pharmacokinetic and pharmacodynamic factors such as via prolonged or continuous infusions [44]. These strategies significantly improve the effectiveness of β-lactam/β-lactamase inhibitors, rendering them similar to carbapenems in relevant clinical scenarios. The mortality rates seem comparable not due to the pharmacological equivalence of the medications, but because BL/BLIs are used strategically in contexts where they are most likely to be effective. This substantiates the justification for using β-lactam/β-lactamase inhibitors as carbapenem-sparing alternatives in appropriately chosen patients without jeopardising clinical results [41].

Emerging non-carbapenem β-lactam/β-lactamase inhibitor combinations have further potential in addressing infections associated with extended-spectrum beta-lactamases and carbapenem-resistant Enterobacterales. Agents such as cefepime–enmetazobactam, aztreonam–avibactam, and sulbactam–durlobactam exhibit improved action against resistant infections that are not well covered by typical β-lactam/β-lactamase inhibitors. The ALLIUM trial showed that cefepime–enmetazobactam outperformed PTZ in complicated urinary tract infections [45], whereas aztreonam–avibactam had significant efficacy against metallo-β-lactamase-producing pathogens. Moreover, sulbactam–durlobactam demonstrated non-inferiority to colistin in treating Acinetobacter baumannii pneumonia and had a better renal safety profile. These data show that the treatment landscape is growing, giving new options to clinicians attempting to minimise carbapenem dependency.

From an antimicrobial stewardship perspective, β-lactam/β-lactamase inhibitor combinations provide a compelling alternative to carbapenems, especially for treating lower-risk infections caused by extended-spectrum β-lactamase-producing organisms [43]. Their use aligns with the basic principles of stewardship, which seek to minimise unnecessary broad-spectrum antibiotic exposure and mitigate the development of resistance. By reserving carbapenems for critically ill patients or those with infections caused by multidrug-resistant organisms, healthcare systems may alleviate the selection pressure that promotes the growth of carbapenem-resistant Enterobacterales [46].

The study by Muharam et al. [32] (Table 1) illustrates this approach in practice. In an area with elevated extended-spectrum β-lactamase frequency, the research revealed that piperacillin–tazobactam (PTZ) had similar clinical success and mortality rates as carbapenems in the treatment of urinary tract infections. These results support the use of β-lactam/β-lactamase inhibitors in non-severe urinary tract infections and endorse their incorporation into empirical treatment methods where local susceptibility patterns allow. The strategic use of β-lactam/β-lactamase inhibitors may maintain the clinical efficacy of

carbapenems, prolong the viability of existing antimicrobial medicines, and diminish healthcare expenses related to resistant infections [31]. This highlights the crucial importance of β-lactam/β-lactamase inhibitors in stewardship frameworks, particularly in resource-constrained environments where resistance monitoring and infection management may pose greater challenges.

Table 1. Clinical and microbiological outcomes of β-lactam/β-lactamase inhibitor combinations versus carbapenems (definitive therapy) for ESBL-E urinary tract infections. Data from Muharam et al. [32].

Outcome	BL/BLI (n = 32)	Carbapenem (n = 47)	P value
Clinical outcome			
Success	26 (81.3)	36 (76.6)	0.621
Failure	6 (18.8)	11 (23.4)	
Mortality	5 (15.6)	8 (17.0)	0.869
Microbiological outcome			
Success	21 (65.6)	23 (48.9)	0.143
Failure	2 (6.3)	4 (8.5)	1.000
Breakthrough infection	2 (6.3)	5 (10.6)	0.695
No repeat culture	7 (21.9)	15 (31.9)	0.328

Values are n (%). Definitive therapy groups. BL/BLI, β-lactam/β-lactamase inhibitors.

The pharmacokinetic and pharmacodynamic characteristics are essential in assessing the clinical efficacy of β-lactam/β-lactamase inhibitor combinations and carbapenems, especially against bacteria that produce extended-spectrum β-lactamase and carbapenem-resistant Enterobacterales. Both medication classes demonstrate time-dependent lethality, indicating that their effectiveness is maximised when plasma levels remain above the minimum inhibitory concentration (MIC) of the target pathogen for an extended period [47]. Nevertheless, beta-lactam/beta-lactamase inhibitor combinations, such as piperacillin–tazobactam, exhibit increased vulnerability to pharmacodynamic constraints in high-inoculum infections owing to the "inoculum effect," whereby elevated bacterial loads diminish medication efficacy despite in vitro susceptibility [29]. Consequently, prolonged or continuous infusions are often used to sustain sufficient drug concentrations and surpass MIC thresholds, particularly when addressing extended-spectrum β-lactamase producers with marginal susceptibility.

In contrast, carbapenems often exhibit more dependable pharmacokinetic/pharmacodynamic profiles in critically ill patients and sustain their effectiveness throughout a wider spectrum of infection severities and bacterial loads. They have enhanced stability against β-lactamases and are less influenced by inoculum size, making them more reliable in severe or systemic infections [48]. However, new β-lactam/β-lactamase inhibitor agents such as ceftazidime–avibactam and meropenem–vaborbactam have been pharmacologically refined to improve stability and attain effective concentrations in difficult clinical situations, thereby enhancing their pharmacokinetic and pharmacodynamic predictability and broadening their application in the treatment of carbapenem-resistant Enterobacterales [49]. Consequently, while carbapenems have pharmacodynamic superiority in some contexts, beta-lactam/beta-lactamase inhibitor combinations, especially newer formulations, may attain similar performance when correctly dosed and aligned with the infection profile.

Notwithstanding the encouraging findings from observational studies and meta-analyses, several limitations remain in the existing data comparing β-lactam/β-lactamase inhibitor combinations with carbapenems [27]. The WHO Global Research Agenda for Antimicrobial Resistance in Human Health identifies a significant lack of data in children [50], whose pharmacokinetics, antibiotic tolerability, and infection dynamics may markedly vary from those in adults. Furthermore, there is an absence of comprehensive data about long-term clinical outcomes, including recurrence rates, the development of resistance over time, and post-treatment sequelae. Contemporary research seldom examines the efficiency and

safety of combination therapies that include β-lactam/β-lactamase inhibitors or carbapenems with other drugs (e.g., aminoglycosides, colistin), which are often used in clinical settings for severe or resistant infections. These exclusions limit the generalisability of results and impede the formulation of complete treatment recommendations for various patient populations and illness types [31].

Furthermore, the majority of existing studies are retrospective or observational, often exhibiting considerable variation in patient demographics, illness severity, and dosage regimens. There is a distinct need for meticulously planned, prospective, head-to-head randomised controlled trials (RCTs) that directly compare β-lactam/β-lactamase inhibitors with carbapenems in both empirical and definitive therapeutic contexts [18]. These studies should include pharmacodynamic goals and categorise outcomes according to MIC values and infection locations [31]. Furthermore, real-world efficacy studies are crucial for corroborating trial results across diverse patient demographics and healthcare environments. These investigations may provide insights regarding medication efficacy outside the regulated settings of clinical trials, including adherence, adverse events, and resistance patterns. Addressing these evidence deficiencies is essential for enhancing treatment regimens and directing worldwide antimicrobial stewardship initiatives.

Conclusion

In conclusion, carbapenems remain the treatment of choice for serious ESBL-E infections, particularly bloodstream infections, whereas piperacillin–tazobactam is a reasonable carbapenem-sparing option only for selected, lower-risk infections such as ESBL-E urinary tract infections. For CRE, newer BL/BLI combinations such as ceftazidime–avibactam, meropenem–vaborbactam and imipenem–relebactam are now preferred over older regimens for KPC producers, while ceftazidime–avibactam plus aztreonam or cefiderocol are recommended for metallo-β-lactamase producers. These agents serve as important carbapenem-sparing alternatives that support antimicrobial stewardship by reducing selective pressure and preserving last-line therapies. However, current evidence is largely based on observational studies, with limited data on long-term outcomes, paediatric populations, and combination therapies. Therefore, future research should prioritise robust, prospective randomised controlled trials to better define the clinical role of BL/BLI combinations and optimise treatment strategies for resistant Gram-negative infections.

Conflict of interest

The authors declare no conflict of interest

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