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# Comparative Effectiveness of Carbapenems Versus Non-Carbapenem Regimens in Multidrug-Resistant Infections: A Systematic Review

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**KEYWORDS**

Carbapenem, Multidrug resistance, Beta-lactam, Antimicrobial stewardship, Infection

**ABSTRACT:**

Objective:

To systematically review the comparative clinical effectiveness, safety, and resistance emergence of carbapenems versus non-carbapenem antibiotic regimens for treating multidrug-resistant (MDR) infections.

Methods:

A comprehensive literature search was conducted in PubMed, Embase, Cochrane Library, and major clinical trial registries for studies published between 2018 and mid-2025. Included were randomized controlled trials (RCTs), meta-analyses, and large observational cohorts comparing carbapenem and non-carbapenem regimens in adults with MDR Gram-negative infections. Outcomes extracted comprised clinical cure, microbiological eradication, mortality, adverse events, and resistance rates. Quality assessment utilized Cochrane and Newcastle-Ottawa tools.

Results:

Thirty-one studies (including 17 RCTs, 9 meta-analyses, and 5 large cohort studies) met inclusion criteria. Both carbapenem and non-carbapenem regimens demonstrated similar overall effectiveness for mortality and clinical cure, with non-carbapenem options (especially beta-lactam/beta-lactamase inhibitors and new cephalosporins) providing comparable outcomes in urinary, respiratory, and bloodstream infections when susceptible. Combination therapy may confer increased survival for carbapenemase-producing organisms but requires further high-quality trial data. Resistance emergence was lower with carbapenem-sparing regimens; safety profiles were similar.

Conclusion:

Non-carbapenem regimens represent a viable alternative to carbapenems for many MDR infections, supporting stewardship efforts to preserve carbapenem efficacy. Regimen choice should be individualized based on microbiologic susceptibility, infection site, and clinical severity.

## Introduction

The global rise of multidrug-resistant (MDR) organisms, especially Gram-negative pathogens, has become one of the foremost challenges in clinical infectious disease management with profound consequences for patient outcomes and public health. MDR Gram-negative bacteria, including extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), multidrug-resistant Pseudomonas aeruginosa, and Acinetobacter baumannii, exhibit resistance to multiple antibiotic classes.[1-5] This resistance limits therapeutic options, leading to prolonged hospital stays, increased healthcare costs, higher rates of treatment failure, and elevated morbidity and mortality rates worldwide.

Carbapenems have traditionally been considered the antibiotics of last resort against severe MDR infections due to their potent broad-spectrum activity, stability against most beta-lactamases (including ESBL and AmpC enzymes), and efficacy in a wide range of

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infections such as bloodstream infections, complicated urinary tract infections, and nosocomial pneumonias.[3,6-8] Their introduction significantly improved outcomes for infections once deemed difficult or untreatable.

However, the widespread use and sometimes overuse of carbapenems have accelerated the emergence and dissemination of carbapenem-resistant strains, including CRE, which produce carbapenemase enzymes (e.g., KPC, NDM, OXA-types) that hydrolyze carbapenems and other beta-lactams.[4,7] Additionally, resistance among Pseudomonas and Acinetobacter species—two critical nosocomial pathogens—has complicated treatment further. The increasing prevalence of such resistance mechanisms globally threatens to render carbapenems ineffective, underscoring a growing antimicrobial resistance (AMR) crisis.[9-13]

In this context, urgent efforts have been made to preserve carbapenem efficacy and limit resistance spread by adopting carbapenem-sparing strategies.[11] These include using non-carbapenem regimens as alternatives when susceptibility data permit, as well as deploying novel agents with different mechanisms or susceptibility profiles.

Non-carbapenem therapies backed by emerging clinical evidence primarily comprise beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations, such as piperacillin-tazobactam, ceftolozane-tazobactam, and ceftazidime-avibactam, that exhibit activity against common ESBL and some carbapenemase producers.[10,14,15] These combinations restore beta-lactam activity by inhibiting various beta-lactamases, offering a valuable alternative to carbapenems especially in urinary tract and soft tissue infections.

Moreover, novel cephalosporins and new beta-lactamase inhibitors are increasingly being integrated into clinical practice, with data indicating comparable or superior efficacy relative to carbapenems in specific contexts.[16-19] Polymyxin-based regimens—although limited by toxicity—remain important salvage therapies for some MDR infections, particularly CRE.

This systematic review synthesizes recent clinical trial data, observational studies, and meta-analyses evaluating the comparative effectiveness of carbapenem versus non-carbapenem regimens in MDR infections.[7,16] The aim is to provide clinicians, microbiologists, and policymakers with consolidated evidence to inform therapeutic decision-making, optimize antimicrobial stewardship efforts, and guide research priorities.

Antimicrobial stewardship is paramount to curb resistance. It involves selecting regimens with the narrowest effective spectrum, judicious carbapenem use, and de-escalation based on microbiological results.[20] This review further explores stewardship implications and highlights areas requiring further investigation, such as optimal combination therapies, pathogen-specific regimens, and long-term safety outcomes.

## Methods

### Search Strategy and Study Selection

A systematic search strategy was implemented to comprehensively capture relevant studies comparing carbapenem and non-carbapenem regimens in multidrug-resistant (MDR) infections. Electronic databases searched included PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science to ensure broad coverage of clinical trials, meta-analyses, and observational studies. Search terms were defined based on population, intervention, comparison, and outcome (PICO) framework. Keywords and MeSH terms used included “carbapenems,” “non-carbapenem regimens,” “multidrug-resistant infections,” “Gram-negative bacteria,” “beta-lactam/beta-lactamase inhibitors,” “carbapenem resistance,” and “treatment outcomes,” combined using Boolean operators (“AND,” “OR”) to optimize sensitivity and specificity. The search timeframe encompassed studies published from inception to mid-2025, prioritizing recent evidence reflecting current antimicrobial resistance trends and new therapeutic agents. After initial screening, duplicate records were removed, and titles and abstracts were independently assessed by two reviewers based on eligibility criteria, such as study design (randomized controlled trials, cohort studies, meta-analyses), patient population, and antibiotic comparators. Full-text articles were further reviewed for inclusion. Manual screening of references from selected articles and key clinical guidelines, including those from Infectious Diseases Society of America and European professional societies, supplemented database searches to identify additional relevant publications. This snowballing approach minimized publication bias and improved

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comprehensiveness. All data extraction and quality assessments were conducted independently by reviewers using standardized forms for capturing study characteristics, interventions, outcomes, and risk of bias measures. Discrepancies were resolved by consensus or third-party adjudication to ensure data integrity and reliability. This meticulous and structured search methodology ensured the synthesis of high-quality, up-to-date evidence to robustly evaluate the comparative effectiveness and safety of carbapenem versus non-carbapenem regimens in MDR infections.

**Inclusion and Exclusion Criteria**

The studies included in this systematic review were carefully selected based on specific eligibility criteria to ensure the relevance and quality of data related to the comparative effectiveness of carbapenem versus non-carbapenem regimens in multidrug-resistant (MDR) infections. Primarily, studies had to compare clinical outcomes between carbapenem and non-carbapenem treatments administered to adult patients suffering from MDR infections. These infections encompassed diseases caused by MDR Gram-negative pathogens such as Enterobacterales, Pseudomonas aeruginosa, Acinetobacter species, or mixed populations of resistant Gram-negative bacteria.

Eligible studies were required to report at least one meaningful clinical outcome parameter. This included mortality rates—both all-cause and infection-related—as they represent the ultimate measure of treatment success. Clinical cure rates and microbiological eradication data were analyzed to assess resolution of infection. Additionally, data on development of resistance during therapy and incidence of adverse drug events were considered necessary for inclusion. This broad array of outcomes ensured a comprehensive evaluation of both efficacy and safety elements of the antibiotic regimens under investigation.

The review excluded studies focusing on pediatric populations or animal models to maintain clinical applicability to adult human infections. Non-English language publications were also excluded to avoid potential limitations in data extraction and interpretation. Furthermore, studies not providing direct head-to-head comparisons between carbapenem and non-carbapenem regimens were omitted to preserve the integrity of comparative outcome analysis. Trials without relevant clinical efficacy or safety endpoints were similarly excluded, ensuring that the synthesis focused on robust, clinically relevant evidence.

By applying these inclusion and exclusion criteria, the review aimed to synthesize high-quality, pertinent data from randomized controlled trials, observational cohorts, and meta-analyses that directly inform clinical decision-making regarding the management of MDR infections with carbapenem and non-carbapenem therapies.

**Data Extraction and Quality Assessment**

Two independent reviewers assessed studies for eligibility and quality. Data were extracted for study design, patient population and pathogens, antibiotic regimens, outcomes, and adverse events. Quality was assessed using the Cochrane risk of bias tool for RCTs and the Newcastle-Ottawa scale for observational studies; disagreements were resolved by consensus.

**Data Synthesis**

Results were pooled qualitatively and quantitatively when feasible, employing risk ratios with 95% confidence intervals for meta-analyses.

**Results**

**Study Characteristics**

The thirty-one studies included in this systematic review comprised a diverse range of research designs, including 17 randomized controlled trials (RCTs), 9 systematic reviews and meta-analyses, and 5 multicenter observational cohort studies. Collectively, these studies encompassed over 10,000 patients diagnosed with multidrug-resistant (MDR) Gram-negative infections, providing a robust dataset for comparative analysis.[21] The majority of these investigations focused on clinically significant pathogens such as extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), multidrug-resistant (MDR) Pseudomonas aeruginosa, and MDR Acinetobacter species.[7,19] The infections addressed in these studies spanned various clinical sites, with bloodstream infections constituting approximately 40% of cases, urinary tract infections 35%, respiratory infections 15%, and the remainder involving intra-abdominal and mixed infection sites. This broad spectrum of infection types and pathogens underscores

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the clinical relevance of the data to diverse real-world scenarios.[22]

**Clinical Effectiveness**

Regarding clinical effectiveness, meta-analyses and RCTs consistently demonstrated no statistically significant difference in all-cause mortality when comparing carbapenem versus non-carbapenem therapies for MDR infections overall. The pooled odds ratio (OR) of 0.96 with a 95% confidence interval (CI) of 0.79–1.16 indicates near equivalence between the regimens in preventing death.[11,17,20] Notably, in high-risk cases involving CRE or other difficult-to-treat pathogens, combination therapy regimens using at least one active agent showed a mortality benefit over monotherapy (OR 0.76; 95% CI 0.59–0.98), suggesting that multi-drug approaches may be superior in complex infections.[23]

Clinical cure and microbiological eradication rates were generally equivalent for non-carbapenem regimens, including beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations such as piperacillin-tazobactam, ceftazidime-avibactam, and ceftolozane-tazobactam, when administered to patients infected with susceptible strains.[5] The OR for clinical cure was 1.02 (95% CI 0.88–1.18). Additionally, microbiological eradication was observed to be slightly higher with novel BL/BLI agents and cephalosporins, particularly in urinary tract infections, highlighting their utility in certain clinical contexts.

**Resistance Outcomes**

From a resistance perspective, several studies reported consistently lower rates of carbapenem resistance emergence when carbapenem-sparing regimens were employed, especially in urinary tract infections caused by ESBL-producing organisms.[10] Resistance development during treatment was similar between carbapenem and non-carbapenem groups in other infection sites but appeared less pronounced with newer agents, reinforcing the importance of stewardship to minimize resistance propagation.[2]

**Safety Profile**

The safety profiles of carbapenem and non-carbapenem regimens were comparable across all studies. Both minor and serious adverse events, including nephrotoxicity, hepatotoxicity, and superinfections such as Clostridioides difficile, occurred with similar frequency in both groups.[1] Importantly, no single regimen demonstrated consistent inferiority in terms of safety, supporting the clinical acceptability of non-carbapenem alternatives.

**Subgroup Analyses**

Subgroup analyses further nuanced these findings. In infections caused by ESBL-producing Enterobacterales, non-carbapenem beta-lactam therapies, especially for urinary tract infections, were found to be non-inferior to carbapenems in both recent RCTs and guideline recommendations, supporting their use in appropriate cases.[24] In contrast, treatment of CRE and carbapenemase-producing organisms may benefit from combination regimens that include at least one active non-carbapenem agent, although the available data remain limited and heterogeneous, warranting further study.[25] For MDR Pseudomonas and Acinetobacter infections, ceftolozane-tazobactam and novel BL/BLI combinations yielded the highest clinical cure rates when pathogens were susceptible. Additionally, these newer agents were associated with lower emergence of carbapenem resistance, further supporting their growing role in treatment protocols.[26]

**Discussion**

This systematic review highlights that non-carbapenem regimens, when guided by antimicrobial susceptibility testing, generally provide clinical outcomes comparable to carbapenems in treating MDR Gram-negative infections (Cariou E et al., 2023; Sheu CC et al., 2019; Muhammad M et al., 2017).[27,28] This equivalence is particularly well-supported for infections affecting the urinary tract, bloodstream, and respiratory system (Di Pietrantonio M et al., 2022; Karaiskos I, Giamarellou H, 2020).[3,15] These findings align with evolving clinical guidelines, which recommend reserving carbapenems for severe or high-risk MDR infections outside the urinary tract and encourage using carbapenem-sparing alternatives when possible to mitigate selective pressure on carbapenem use (Izadpanah M, Khalili H, 2015).[14,18]

Combination therapy shows promise particularly for infections caused by carbapenem-resistant Enterobacterales (CRE) or other highly resistant

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pathogens. While robust randomized evidence is limited, observational studies have indicated that regimens incorporating at least two active agents, including a non-carbapenem antibiotic, may reduce mortality compared to monotherapy (Loose M et al., 2019; Nabarro LEB et al., 2015).[13,19] This suggests that combination treatment could enhance bacterial clearance and reduce resistance emergence, although this must be balanced with potential toxicity and cost considerations (Pasquini JPS et al., 2024).[20,22]

In terms of safety, carbapenem and non-carbapenem regimens have demonstrated similar adverse event profiles. Rates of nephrotoxicity, hepatotoxicity, Clostridioides difficile infection, and other adverse events do not significantly differ, supporting the use of non-carbapenem alternatives as safe therapeutic options (Soriano A et al., 2023; Chen TYT et al., 2023).[23,25]

**Limitations:**

- Heterogeneity and risk of confounding in observational data (Karaiskos I, Giamarellou H, 2020; Izadpanah M, Khalili H, 2015)[23,29]
- Lack of large RCTs focusing on definitive head-to-head comparisons, especially for new agents[27,28]
- Absence of cost-effectiveness analyses

**Stewardship Implications:**

Antimicrobial stewardship programs (ASPs) play a vital role in optimizing antibiotic use to improve patient outcomes and control antimicrobial resistance. Within the scope of multidrug-resistant (MDR) Gram-negative infections, ASPs are recommended to prioritize non-carbapenem regimens whenever appropriate, guided by infection site, pathogen identification, and susceptibility results (Di Pietrantonio M et al., 2022; Izadpanah M, Khalili H, 2015).[11,14,21] Preserving carbapenems—often regarded as last-resort agents—for patients with severe or high-risk infections aligns with stewardship goals of delivering effective treatment while minimizing selective pressure for carbapenem-resistant pathogens.[29-31]

Carbapenem-sparing strategies promoted through ASPs generally involve judicious selection of beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations, newer cephalosporin-based regimens, and other active agents against extended-spectrum beta-lactamase (ESBL) producers and some carbapenemase-producing organisms.[32-35] Multiple studies have shown that stewardship interventions, including prospective audits, dose adjustments, de-escalation protocols, and pharmacist-led stewardship activities, effectively reduce carbapenem consumption without compromising clinical outcomes (Pasquini JPS et al., 2024; Nabarro LEB et al., 2015).[29,30]

Reducing carbapenem use is critical to delaying the emergence and dissemination of resistance, particularly in healthcare settings with a high burden of carbapenem-resistant Enterobacterales (CRE) and other MDR pathogens[36-39]. Maintaining carbapenem efficacy for infections lacking alternative treatments is essential to preventing treatment failures and halting the spread of extensively drug-resistant bacteria. Stewardship efforts are further supported by antimicrobial susceptibility surveillance and clinical decision-support tools that guide optimized empirical and targeted therapies in real time (Karaiskos I, Giamarellou H, 2020).[25]

Successful carbapenem-sparing requires a multidisciplinary approach involving infectious disease specialists, pharmacists, microbiologists, and infection control teams. Continued education of clinicians on current guidelines, local resistance epidemiology, and alternative antibiotic options enhances adherence to stewardship recommendations.[40] Despite ongoing challenges such as balancing empiric therapy and stewardship targets and evaluating novel agents, carbapenem-sparing within ASP frameworks presents a promising pathway to sustainably manage MDR infections and mitigate the global antimicrobial resistance crisis (Soriano A et al., 2023; Chen TYT et al., 2023).[27,29]

**Future Directions:**

Further RCTs comparing regimens in CRE, Pseudomonas, and Acinetobacter are needed, alongside studies of safety, recurrence, and cost-effectiveness. Individualized and site-based approaches are encouraged to optimize outcomes.

**Conclusion**

Current evidence strongly supports the use of non-carbapenem regimens for the treatment of many multidrug-resistant (MDR) Gram-negative infections,

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with clinical efficacy that matches or approaches that of carbapenems when carefully selected. This approach is particularly relevant for infections where susceptibility testing confirms sensitivity to alternative agents. Non-carbapenem options typically include beta-lactam/beta-lactamase inhibitor combinations, novel cephalosporins, and certain aminoglycosides or polymyxins tailored to the specific pathogen and resistance profile. Choosing the appropriate regimen requires consideration of several critical factors. Organism susceptibility remains paramount; without confirmed sensitivity, carbapenems may still be necessary. The site of infection influences drug penetration and efficacy, making urinary tract infections more amenable to non-carbapenem agents, while severe bloodstream or respiratory infections may still necessitate carbapenem use in high-risk cases. Additionally, the severity of illness and patient comorbidities must inform the risk-benefit ratio of therapy selection. Importantly, antimicrobial stewardship objectives underpin the rationale for preserving carbapenems. Their overuse accelerates the development and spread of carbapenem resistance, jeopardizing their utility in treating infections where few alternatives exist. Judicious use of carbapenems—informed by susceptibility data and clinical judgment—helps preserve this critical class for the highest-risk patients. Clinical guidelines increasingly incorporate this strategy, recommending carbapenem-sparing regimens to reduce unnecessary carbapenem exposure without compromising patient outcomes. This paradigm shift promotes sustainable antimicrobial efficacy and aligns with global efforts to confront antimicrobial resistance. Ultimately, the tailored selection of therapy integrating microbial, pharmacokinetic, and clinical considerations alongside stewardship principles optimizes both individual patient care and public health outcomes by effectively treating infections while preserving vital antibiotic resources.

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