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# Meropenem in the Management of Severe Multidrug-Resistant Bacterial Infections

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**Abstract**

**Background:** The multidrug-resistant (MDR) Gram-negative bacterial infections are a significant health problem worldwide, with high morbidity and mortality. Meropenem has long been a first-line treatment in the treatment of serious infections, but its presence in the treatment has changed as a result of the expanding resistance to antimicrobials and the development of new therapeutic agents. **Objective:** To critically analyse the modern role of meropenem in the treatment of severe cases of MDR bacterial infections, focusing on clinical effectiveness, pharmacokinetic/pharmacodynamic (PK/PD) optimization, pathogen-specific use, and the development of new methods of treatment. **Methods**: The literature review was carried out in PubMed, Scopus, and Web of Science databases to find out the studies published since 2018 and up to 2025. Included were eligible studies randomized controlled trials, observational studies, systematic reviews, and clinical guidelines that covered the use of meropenem in MDR Gram-negative infections. **Results:** Meropenem is also very effective in severe infections by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*,

with good clinical evidence. Nevertheless, its effectiveness is much lower in carbapenem-resistant organisms, especially carbapenem-resistant *Enterobacterales* (CRE) and *Acinetobacter baumannii* where other agents show better results. In multidrug-resistant *Pseudomonas aeruginosa*, it becomes variable and relies on the susceptibility and dosing. Optimization of PK/PD, such as high-level resistance, may improve clinical outcome in critically ill patients but not overcome high-level resistance, including prolonged infusion and therapeutic drug monitoring. The development of new 2-lactam/2-lactamase combinations of inhibitors has further changed the paradigm of treatment towards the targeted therapy. **Conclusion:** Meropenem is also a useful but less selective therapeutic agent in MDR infections. To be utilized optimally, pathogen-specific susceptibility, resistance mechanisms, and PK/PD principles should be integrated. To optimize the clinical outcome and reduce the development of antimicrobial resistance, strategic implementation within a precision-based treatment framework is needed.

## Introduction

AMR has become one of the most significant global health crises and poses a threat to the efficacy of contemporary medical interventions. Multidrug-resistant (MDR) bacterial infections are linked to high morbidity, mortality, and economic cost, especially in critically ill patients (Salam *et al*., 2023). According to recent estimates in the world, AMR by bacteria is directly linked to more than one million deaths each year, and the number of deaths that are linked to resistant infections are significantly higher (Antimicrobial Resistance Collaborators. (2022). The pressure is particularly strong in low- and middle-income countries, where the lack of access to newer antimicrobial agents and diagnostic constraints make it harder to deal with it (Sulis *et al*., 2022).

The most significant contributors to MDR infections are gram-negative bacteria. *Escherichia coli, Klebsiella pneumoniae, P. aeruginosa*, and *A. baumannii* are common pathogens that are often involved in severe infections, including sepsis, hospital-acquired pneumonia, ventilator-associated pneumonia, bloodstream infections, and intra-abdominal infections (Morris *et al*., 2020). These organisms have varied and flexible resistance mechanisms, which enable them to resist various classes of antibiotics and continue to stay in healthcare settings.

One of the key contributors to this challenge is the rising incidence of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* and carbapenem-resistant bacteria. ESBL-producing strains have become common in community and hospital environments, diminishing the efficacy of third generation cephalosporins (Husna *et al*., 2023). More alarming is the emergence of carbapenem-resistant *Enterobacterales* (CRE) and carbapenem-resistant *P. aeruginosa* and *A. baumannii*, which the World Health Organization has declared critical priority pathogens (Antochevis *et al*., 2025). These organisms are linked to high mortality rates especially in critically ill patients where the treatment is in many cases, very limited.

Gram-negative multidrug-resistant infections are predicted to have especially poor clinical outcomes, with mortality rates varying widely based on the pathogen and severity of the infection (Macesic *et al*., 2025). Carbapenem-resistant *Enterobacterales* (CRE)-induced infections have been reported to have a mortality rate of about 30-50 %, and carbapenem-resistant *A. baumannii* (CRAB)-induced infections have been linked with even greater mortality, ranging between 40 and 60 % in critically ill patients (Sannathimmappa *et al*., 2023). MDR infections, besides causing high mortality, also create a significant healthcare burden, such as extended hospitalization, and research has shown that the length of stay is extended by around 10 to 20 days, as compared to susceptible infections (Kumar *et al*., 2024). The effects of antimicrobial resistance on a worldwide scale are vast, and more recent estimates

indicate that bacterial AMR directly caused about 1.27 million deaths worldwide in 2019, which is why effective therapeutic methods are urgently needed (Jocthan et a., 2025).

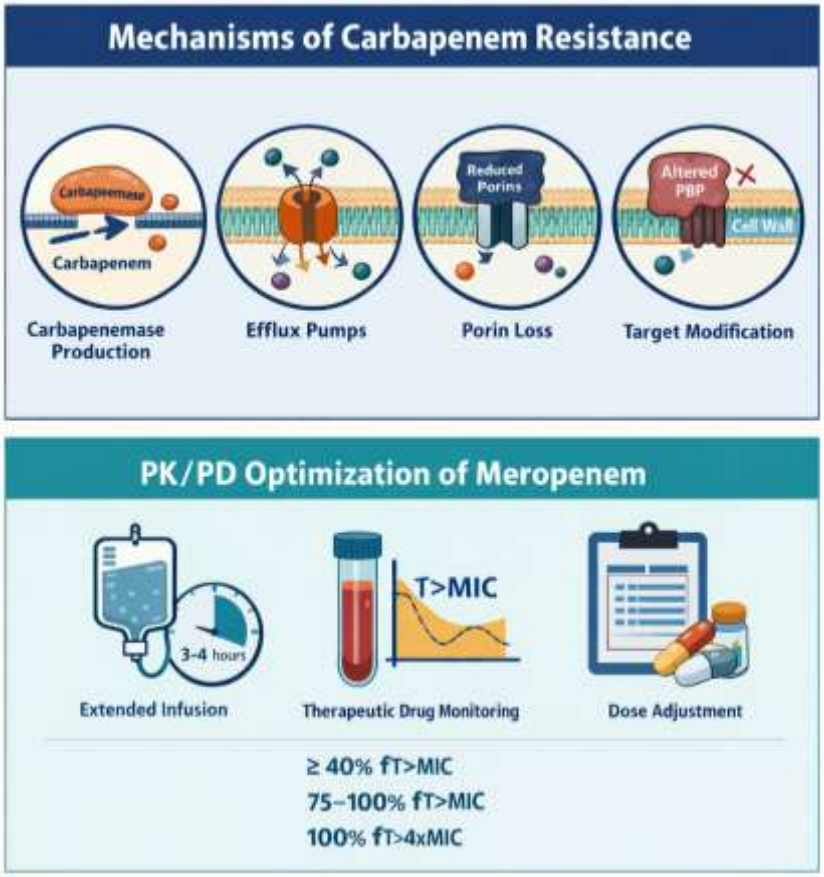


**Figure 1. Mechanisms of carbapenem resistance and pharmacokinetic/pharmacodynamic (PK/PD) optimization of meropenem.**

Figure 1 demonstrates the main carbapenem resistance mechanisms and optimal meropenem therapy approaches. Gram-negative organisms develop resistance mechanisms such as carbapenemase production, an enzymatic process that breaks down the antibiotic; efflux pump overexpression, an active expulsion process to expel the drug out of the bacterial cell; porin loss or modification, which decreases the entry of the antibiotic into the bacterial cell; and target site alterations, which decreases the process by which the antibiotic binds These processes frequently co-occur, leading to resistance on a high level and therapeutic failure. The bottom part focuses on pharmacokinetic/pharmacodynamic (PK/PD) optimization of meropenem with a particular focus on long-term infusion (34 hours), therapeutic drug monitoring, and dose modification to ensure sufficient exposure to drugs. Optimal effects are linked to maintaining free drug concentrations above minimum inhibitory concentration with targets of at least 40% fT>MIC in normal infections or 75-100% or even 100% fT>4%MIC in critically ill patients. Collectively, these ideas highlight the significance of not only mastering the biology of resistance but also using the optimized dosing approaches in order to enhance clinical outcomes.

The rising resistance mechanisms complicate treatment even more. The development of carbapenemase enzymes, such as KPC, NDM, VIM, IMP, and OXA-type beta-lactamases, is widely known to mediate carbapenem resistance (Aurilio *et al*.,2022). Moreover, non-enzymatic mechanisms like decreased membrane permeability and overexpressed efflux pump are often present, especially in non-fermenting Gram-negative bacteria (Lepe *et al*., 2022). The presence of various resistance pathways can frequently lead to high-level resistance and treatment failure (Baquero *et al*., 2021).

MDR infections have significant clinical outcomes. Late administration of effective antimicrobial treatment is closely linked with high mortality especially in sepsis and septic shock (Al-Sunaidar *et al*., 2022). Moreover, MDR infections are associated with long-term hospitalization, high-risk of intensive care support, and high-cost of healthcare. These obstacles highlight the importance of using effective antimicrobials approaches to weigh between quick empiric coverage and evidence-based therapy (Nelson *et al*.,2021).

Antimicrobial activity has also changed with the emergence of more recent agents against resistant Gram-negative pathogens in response to the increasing resistance burden. Nonetheless, access to these therapies is not even throughout various healthcare environments. Consequently, old antibiotics still have a big role to play in clinical practice, especially in resource-restricted setups (Breijyeh *et al*., 2020).

It is in this context that the importance of established therapies in the framework of contemporary resistance patterns needs to be explored. There is a need to conduct a critical assessment of commonly used agents, their clinical utility, and their limitations to inform the best treatment options and direct antimicrobial stewardship efforts.

## LITERATURE SEARCH STRATEGY

Relevant literature search was performed to find relevant studies that would evaluate the role of meropenem in the management of severe multidrug-resistant (MDR) bacterial infections (Perez *et al*., 2025). Systematic searches were done in electronic databases such as PubMed, Scopus and Web of Science.

The search strategy was based on the use of both Medical Subject Headings (MeSH) terms and free-text terms, including: meropenem, multidrug-resistant, carbapenem-resistant *Enterobacterales*, ESBL-producing *Enterobacterales*, *P. aeruginosa*, A. *baumannii*, pharmacokinetics, pharmacodynamics, extended infusion, continuous infusion The search was refined with the help of Boolean operators (AND, OR) to cover it thoroughly.

To ensure the inclusion of the latest and clinically relevant evidence in the dynamic field of antimicrobial resistance, the search was confined to studies published since January 2018 and up to December 2025. Articles published in English were only included.

Only studies that met the following criteria were eligible: randomized controlled trials, systematic reviews, meta-analyses, observational studies, and international clinical guidelines that assessed the efficacy, pharmacokinetics/pharmacodynamics, or clinical role of meropenem in MDR infections. Research specifically on Gram-negative pathogens such as ESBL-producing *Enterobacterales*, carbapenem-resistant *Enterobacterales* (CRE), *P. aeruginosa* and *A. baumannii* were prioritized (Lonergan, 2020).

The exclusion criteria were case reports, small case series, non-peer-reviewed articles, and conference abstracts that lacked comprehensive data, as well as studies that were not directly related to meropenem or MDR bacterial infections. Further, studies that were limited to non-bacterial infections or non-clinical experimental models that lacked translational significance were eliminated.

Manual screening of reference lists of selected articles was performed to extract more relevant studies. The last choice of literature was made on the basis of relevance, the quality of methods, and the contribution to the critical analysis of the role of meropenem in the case of severe MDR infections.

**Table: 10 key studies on meropenem in severe MDR bacterial infections (2018–2025)**

| Year | Study | Design / population | Meropenem-related intervention | Main outcomes | Why it matters for your review | Reference |
|---|---|---|---|---|---|---|
| 2018 | MERINO trial | Multicenter randomized clinical trial; 391 patients with ceftriaxone-resistant E. coli or K. pneumoniae bloodstream infection | Meropenem vs piperacillin-tazobactam for definitive therapy | 30-day mortality: 3.7% with meropenem vs 12.3% with piperacillin-tazobactam | Best trial to support meropenem as preferred therapy in severe ESBL bloodstream infection | Harris PNA, *et al*. *JAMA*. 2018. (jamanetwork.com) |
| 2018 | AIDA trial | Multicenter open-label randomized superiority trial in severe carbapenem-resistant Gram-negative infections | Colistin + meropenem vs colistin alone | Combination therapy was not superior; in severe A. baumannii infection, adding meropenem did not improve clinical failure outcomes | Strong evidence against routine meropenem add-on therapy in CRAB/CRGN when organism is carbapenem-nonsusceptible | Paul M, *et al*. *Lancet Infect Dis*. 2018. (PubMed) |
| 2018 | TANGO II | Phase 3 open-label randomized controlled trial in adults with CRE infections | Meropenem-vaborbactam vs best available therapy | Clinical cure at end of therapy: 64.3% vs 33.3%; test-of-cure: 57.1% vs 26.7% favoring meropenem-vaborbactam | Pivotal study showing meropenem regains value in KPC-CRE when paired with vaborbactam | Wunderink RG, *et al*. *Infect Dis Ther*. 2018. (PubMed) |
| 2020 | Early Experience With Meropenem-Vaborbactam | Retrospective cohort; 20 patients with CRE infections | Meropenem-vaborbactam treatment | 30-day clinical success 65%; 30-day survival 90%; microbiologic failure within 90 | Useful real-world CRE data showing good short-term survival but resistance/recurrence remains a | Shields RK, *et al*. *Clin Infect Dis*. 2020. (PubMed) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | days 35% | concern | |
| 2020 | Real-world multicenter analysis of meropenem-vaborbactam | Multicenter real-world cohort; 40 patients with serious Gram-negative infections, 80% CRE | Meropenem-vaborbactam treatment | Clinical success 70.0%; 30-day mortality 7.5%; 30-day recurrence 12.5% | Strong observational support for meropenem-vaborbactam in real-world CRE practice | Alosaimy S, *et al*. *Open Forum Infect Dis*. 2020. (PubMed) |
| 2021 | APEKS-NP | Randomized double-blind phase 3 non-inferiority trial in Gram-negative nosocomial pneumonia | High-dose extended-infusion meropenem comparator arm vs cefiderocol | Day-14 all-cause mortality in meropenem arm: 11.6%; cefiderocol was non-inferior | Important because it gives robust outcomes for optimized meropenem dosing in severe nosocomial pneumonia | Wunderink RG, *et al*. *Lancet Infect Dis*. 2021. (PubMed) |
| 2022 | Meropenem target attainment in critically ill septic patients | Prospective observational PK study in ICU patients with severe sepsis/septic shock and preserved/increased renal function | Evaluation of meropenem PK/PD attainment | Showed risk of underexposure in patients with preserved/increased renal function, supporting need for dose optimization/TDM | Good study to support your PK/PD section and the problem of augmented renal clearance | Gijsen M, *et al*. *Infect Drug Resist*. 2022. (PubMed) |
| 2023 | MERCY trial | Double-blind randomized clinical trial; 607 critically ill patients with sepsis/septic shock | Continuous meropenem infusion vs intermittent administration | Primary composite outcome: 47% vs 49%; 90-day mortality 42% in both groups | High-quality evidence that routine continuous infusion does not automatically improve mortality despite PK rationale | Monti G, *et al*. *JAMA*. 2023. (PubMed) |
| 2023 | Extended vs intermittent meropenem | Retrospective ICU study of adults treated for nosocomial pneumonia | Extended infusion vs intermittent | Study compared 14-day mortality and other clinical | Helpful as syndrome-specific evidence for pneumonia, though lower | Park HJ, *et al*. *Antibiotics (Basel)*. 2023. (PMC) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | infusion in nosocomial pneumonia | | infusion | outcomes; designed to test whether extended infusion improves pneumonia outcomes | quality than MERCY | |
| 2025 | High-dose vs standard-dose intermittent meropenem in critically ill patients | Observational cohort; 4,210 critically ill patients, propensity-matched analysis | High-dose intermittent meropenem (6 g/day) vs standard-dose therapy | High-dose therapy was associated with lower 90-day all-cause mortality and lower AKI; no major LOS difference | Important recent study supporting intensity optimization in severe infection, especially when PK/PD failure is likely | Bergmann F, *et al*. *AICOJ*. 2025. (PMC) |

**STRENGTHS: PHARMACOLOGICAL ROBUSTNESS AND CLINICAL RELIABILITY**

The main advantage of meropenem is that it is a broad-spectrum antimicrobial agent against Gram-negative and Gram-positive bacteria, including anaerobes. (Zhuorong and Along, 2025) This broad coverage has rendered it especially useful in empiric therapy of critically ill patients, where any delay in the appropriate treatment can greatly increase mortality. Meropenem offers rapid bactericidal effect by blocking bacterial cell wall synthesis, which helps in early microbiological clearance, in severe infections like sepsis, ventilator-associated pneumonia, and intra-abdominal infections (Zahra and Naqvi, 2021).

One of the most significant areas where meropenem still has a high clinical interest is in the treatment of infections caused by *Enterobacterales*, which produce extended-spectrum beta-lactamase (ESBL). The best clinical evidence, such as randomized controlled trials and observational studies, has always shown the superiority of carbapenems over other beta-lactams in severe ESBL infections, and especially in bloodstream infections (Salmon-Rousseau *et al*., 2020). Against this backdrop, meropenem is still considered a standard-of-care agent particularly in the critically-ill populations where failure to respond to treatment has serious consequences (Raza *et al*., 2021).

The other major benefit is that meropenem has a good pharmacokinetic/pharmacodynamic (PK/PD) profile. Being a time-dependent antibiotic, its effect depends highly on the time during which free drug levels are maintained above the minimum inhibitory concentration (fT>MIC). This feature enables flexible dosage plans such as long-term and continuous infusions, which can maximize drug exposure in patients in the critical care unit (Mohun, 2024). These are especially applicable in patients with different physiology, such as augmented renal clearance or increased volume of distribution, which are prevalent in intensive care units (Raza *et al*., 2021).

Moreover, meropenem shows good tissue penetration, even into lung parenchyma, cerebrospinal fluid (inflamed conditions), and intra-abdominal compartments. This makes it more useful in a broad spectrum of severe infection syndromes. Meropenem is a safe agent in most high-risk clinical settings, combined with a relatively favourable safety profile, as compared to older carbapenems (Mengesha, 2025).

## LIMITATIONS: RESISTANCE, REDUCED EFFICACY, AND CLINICAL UNCERTAINTY

Notwithstanding these advantages, the clinical usefulness of meropenem is progressively diminishing due to the increasing carbapenem resistance in the world, especially in Gram-negative pathogens. The development and spread of carbapenemase-producing organisms, including *K. pneumoniae* carbapenemase (KPC), New Delhi metallo-beta-lactamase (NDM), and OXA-type enzymes have greatly diminished the efficacy of meropenem in most environments (Karvouniaris *et al*., 2023). Mercopenem monotherapy is often not effective in infections due to carbapenem-resistant *Enterobacterales* (CRE), even when the in vitro susceptibility is borderline or intermediate (Mohun, 2024).

Besides enzymatic degradation, other mechanisms that resist meropenem activity include loss of porins, overexpression of efflux pumps, and modifications of target sites. These processes are especially applicable in *P. aeruginosa* and *A. baumannii* where resistance can be frequently multifactorial. Consequently, even optimized dosing plans can be ineffective in the treatment of infections by these organisms (Garcia-Bustos *et al*., 2022).

The other drawback is that there is a lack of a consistent benefit of meropenem combination therapy. Previously MDR infections were often treated with combination regimens (e.g., meropenem plus colistin or aminoglycosides) in the hope that this would improve efficacy and overcome the development of resistance (Karvouniaris *et al*., 2023). But recent randomized trials and meta-analyses have yielded mixed results with some studies demonstrating no significant mortality advantage to the newer agents as compared to monotherapy. This also poses significant concerns regarding whether meropenem provides any therapeutic benefit when used in such combinations, or is simply a source of toxicity and complexity (Garcia-Bustos *et al*., 2022).

In addition, the extensively used meropenem has led to selective pressure and rapid development of resistance (Abed and Yousuf, 2021). In the antimicrobial stewardship view, the indiscriminate or extended use of meropenem is a concern because it can facilitate the development of carbapenem-resistant organisms at the individual level, institutional level, as well as in the community. This has seen a growing interest in carbapenem-sparing interventions especially where substitutive agents exist (Breijyeh *et al*., 2020).

## The Central Debate: Backbone Therapy or Targeted Agent?

The changing evidence base has given rise to a paradigm shift in the contemporary role of meropenem: is it still one of the backbone therapies of severe MDR infections or is it time to limit its application to more specific, phenotype-based indications?

Traditionally, meropenem was considered a “last-line” or “backbone” antibiotic, often used empirically in critically ill patients with suspected MDR infections (Abdul-Mutakabbir *et al*., 2021). The reason behind this method was its wide coverage and effectiveness in severe disease. Nonetheless, the development of new beta-lactam/beta-lactamase-inhibitor complexes, which include ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, have dramatically changed the treatment of how things were done. They show enhanced action against some carbapenem-resistant organisms, especially KPC-producing *Enterobacterales*, and are becoming a first-line agent in this regard (Almeida *et al*., 2021; Bassetti *et al*., 2025).

As a result, the role of meropenem is becoming more situation specific and phenotype specific. Meropenem is very effective and commonly used in infections caused by ESBL-producing organisms (Anwar *et al*., 2025). In CRE infections however, it might be restricted to combination use or may be replaced completely by newer agents with more predictable activity. Meropenem can still play a role in some cases of MDR *P. aeruginosa*, especially when there is still susceptibility and PK/PD can be

optimized (Pelegrin *et al*., 2021). Conversely, its efficacy in carbapenem-resistant *A. baumannii* is increasingly doubted, with clinical outcome not always improving with its addition to treatment regimens (Bassetti *et al*., 2025; Yehya *et al*., 2025).

This change is indicative of an overall change in antimicrobial therapy where empiric, broad-spectrum methods are being replaced by precision-based, pathogen-sensitive methods. The value of meropenem in this model is not a fixed value but rather a variable value based on the nature of particular resistance mechanisms in the infecting organism, availability of alternative agents, and the clinical conditions of the patient (CECROPIN, 2023).

A critical assessment of meropenem points out that further use of the drug should be strategic and not a routine. Although its pharmacological advantages make it indispensable in some situations, especially severe infections of ESBL or some cases of MDR, its drawbacks require special attention to its use when and how to use it (Haddad *et al*., 2022).

Notably, the ongoing use of meropenem as an important treatment option is not only a factor of its effectiveness but also indicative of its accessibility gaps, notably in low- and middle-income regions. Meropenem can still be used as de facto backbone therapy, albeit with limitations, in such settings. This highlights the significance of considering real-world constraints in conjunction with clinical evidence to assess its relevance (Keck *et al*., 2025).

Finally, meropenem cannot be considered a universal solution to MDR infections. Rather, it ought to be placed in an active and changing paradigm of treatment, with the utilization of microbiological information, optimization of PK/PD, and stewardship concepts (Moussa *et al*., 2020). The next task is to clarify the clinical situations where meropenem will add real value and not to use it in situations where it is not necessary and will only contribute to the rapid development of the very resistance being targeted.

**Pharmacokinetic/Pharmacodynamic (PK/PD) Optimization of Meropenem**

The pharmacokinetic/pharmacodynamic (PK/PD) characteristics of meropenem are closely associated with its clinical efficacy in severe infections, especially in the critically ill patients whose physiological changes have a strong influence on drug exposure (Moussa *et al*., 2020). Being a time-dependent 8 -lactam antibiotic, the antibacterial performance of meropenem can be most effectively linked to the proportion of time during which free drug concentrations exceed the minimum inhibitory concentration (fT>MIC). Optimal PK/PD targets are thus critical particularly in infections caused by organisms with high MICs or marginal susceptibility (Aldaz *et al*., 2021).

Patients who are in a critical condition pose special problems to normal dosing policies. Subtherapeutic levels of certain drugs may occur with traditional intermittent dosing due to augmented renal clearance, higher volume of distribution, hypoalbuminemia, and organ dysfunction. It is especially applicable to sepsis and septic shock, where both early and sufficient exposure to antibiotics is closely linked with better outcomes. Because of this, the routine dosing regimens of meropenem might be inadequate in attaining optimal PK/PD targets in these groups (Boonpeng *et al*., 2022).

To overcome this, the use of extended infusion (3-4 hours) and continuous infusion strategies has become more and more popular. These strategies seek to increase exposure time of the drug above the MIC, which maximizes bacterial killing and decreases the chances of selecting resistance (Deng *et al*., 2023). A number of clinical trials and meta-analyses indicate that extended administration of 2-lactam antibiotics, such as meropenem, can enhance clinical cure rates and in certain instances, decrease the mortality of critically ill patients. Nevertheless, the outcomes are not fully consistent, and the extent of benefit seems to be determined by the severity of

infections, the susceptibility to pathogens, and the factors specific to patients (Hassanpour *et al*., 2021).

The other new methodology is that of therapeutic drug monitoring (TDM), which enables the personalization of dose, depending on plasma concentrations (Tao *et al*., 2025). TDM has found application especially in patients who's pharmacokinetic is unpredictable, including patients undergoing renal replacement therapy, extracorporeal membrane oxygenation (ECMO), or whose renal function varies (Wenzler and Scoble, 2020). TDM-guided dosing is a potential approach that can be applied to maximize meropenem exposure and reduce toxicity and resistance development, although it is not yet universally applied (He *et al*., 2023).

Even with these developments, PK/PD optimization would not be sufficient to overcome resistance in organisms that express potent carbapenemases (Wang *et al*., 2022). However, in situations when MICs do not exceed a range of treatment, optimized dosing regimens can increase the chances of clinical success and prolong the utility of meropenem in chosen MDR infections (Liao *et al*., 2025a)

**Pathogen-Specific Roles of Meropenem**

The role of meropenem in MDR infections is highly **pathogen-dependent**, and its clinical value varies significantly based on the underlying resistance mechanisms.

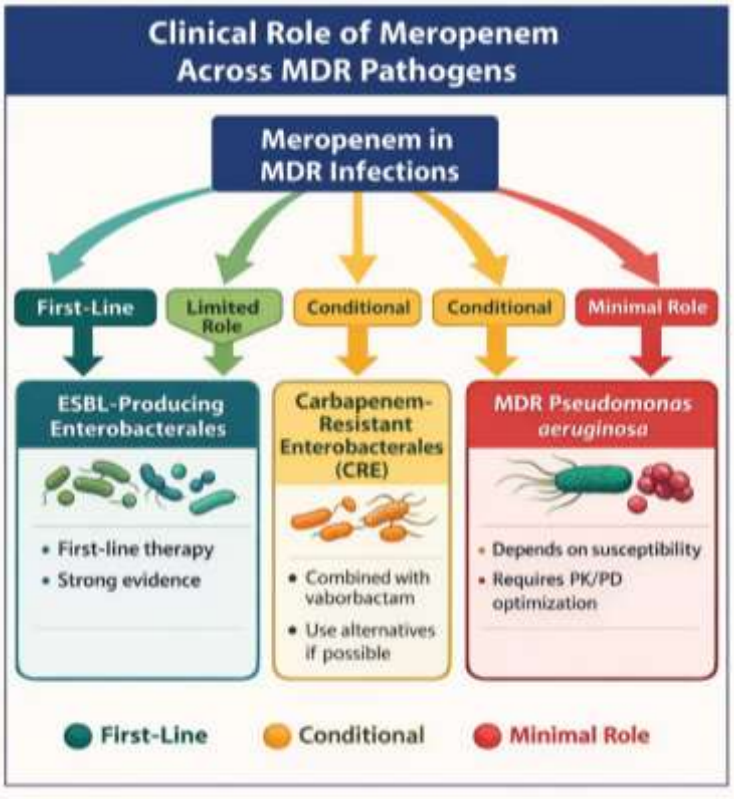


**Figure 2. Clinical role of meropenem across multidrug-resistant Gram-negative pathogens.**

The table 2 provides the overview of the pathogen clinical role of meropenem in the management of multidrug-resistant gram-negative infections. Meropenem continues to be a first-line treatment with solid clinical evidence in infections of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, especially in cases of severe infection, such as bloodstream infections. Conversely, its effect on carbapenem-resistant *Enterobacterales* (CRE) is limited because of resistance mechanisms, but its activity can be reinstated with the use of β-lactamase inhibitors, including vaborbactam. Meropenem can still be used in some cases of multidrug-resistant *P. aeruginosa* with appropriate pharmacodynamics/pharmacokinetic optimization and depending on the susceptibility patterns (Liao *et al*., 2025a).

Nevertheless, its clinical use has not been effective in carbapenem-resistant A. *baumannii*, where the level of resistance is often high and combination therapy has not always shown an increase. This pathogen-specific model underscores the change of meropenem as a broad empiric agent to a more targeted, precision-based therapy based on resistance mechanisms and microbiological information (Liao *et al*., 2025a).

**ESBL-Producing *Enterobacterales***

Meropenem is still a cornerstone therapy in severe infections due to ESBL-producing *Enterobacterales*. Its clinical superiority over other 2-lactams has strong clinical evidence, especially with serious infections, or bloodstream infections (Aydin *et al*., 2025). Meropenem is a better choice in critically ill patients because of its predictability, quick bactericidal effect and low chances of failure of treatment. In this regard, it has a well-established role that is not contested (Bandy and Tantry, 2021).

**Carbapenem-Resistant *Enterobacterales* (CRE)**

Meropenem is significantly reduced in the role in CRE infections. Carbapenemase enzymes normally mediate resistance, making meropenem ineffective in solitude. Nevertheless, meropenem could still have a place in combination therapy or in a combination with β-lactamase inhibitor like vaborbactam. The introduction of meropenem-vaborbactam has increased its use in KPC-producing organisms, but has weak activity against metallo-β-lactamases like NDM (Lonergan, 2020).

High-dose or extended infusion meropenem has been studied as a treatment of CRE infections with low level resistance, with inconsistent clinical success and strongly related to MIC values. This has seen new agents being increasingly preferred where they do exist (Bandy and Tantry, 2021).

**Multidrug-Resistant *P. aeruginosa***

Meropenem has variable activity in MDR *P. aeruginosa*. Mechanisms of resistance are multifactorial in nature, such as efflux pumps, porin mutations, and enzyme production. Optimized dosing of meropenem can still be effective in instances in which there is preserved susceptibility. Nonetheless, its reliability has decreased due to the development of resistance phenotypes that are hard to treat (DTR) (Tamma *et al*., 2021).

The newer anti-pseudomonal agents, including ceftolozane-tazobactam and ceftazidime-avibactam tend to be more active against resistant strains, undermining the role of meropenem as a first-line agent in these infections (Tamma *et al*., 2022).

**Carbapenem-Resistant *A. baumannii* (CRAB)**

The use of meropenem in CRAB is a controversial one. OXA-type carbapenemases and other mechanisms have been identified to drive resistance in A. baumannii, resulting in high-level resistance. The introduction of meropenem-based combination treatment (e.g., with colistin) to clinical studies has not always shown better results.

Consequently, the role of meropenem in CRAB infections has grown to be regarded as limited, and other agents like cefiderocol or combination regimens are considered. Its application in this context must be well justified and based on the susceptibility data (Lonergan, 2020).

## FUTURE PERSPECTIVES AND EMERGING THERAPEUTIC STRATEGIES

The future of meropenem should be viewed in the framework of the fast-changing antimicrobial environment. The introduction of new combinations of 2-lactam/2-lactamase inhibitors has been a significant addition to the treatment of MDR Gram-negative infections. Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam agents have a greater activity against the specific resistance

mechanisms, especially carbapenemase-producing *Enterobacterales* (Lonergan, 2020; Tamma *et al*., 2021).

These more recent treatments are gaining popularity as first-line agents in treating some cases of MDR infections, casting doubt on the future of meropenem as a backbone agent. Meropenem will probably become more selectively used, with pathogen-specific susceptibility data and resistance pathways driving its use, rather than being generally applicable (Tamma *et al*., 2022).

The other critical factor is the incorporation of precision medicine strategies that involve fast molecular diagnostics. With the help of these technologies, resistance genes can be identified early and enable clinicians to be more effective in terms of antimicrobial therapy. The application of meropenem in this context can be optimized or avoided, depending on the real time microbiological data (Aydin *et al*., 2025).

Antimicrobial stewardship will play a critical role in shaping the future use of meropenem. Reducing the exposure to unnecessary carbapenem is critical to reduce the rate of resistance. These involve de-escalation plans, carbapenem-sparing plans and compliance with evidence based recommendations (Wen *et al*., 2025).

The uneven access to newer antimicrobial agents in the world should be taken into consideration. Meropenem will remain an important treatment in most areas because of the lack of access to advanced therapies. Optimization of its use with the help of PK/PD strategies, stewardship programs and better diagnostics is thus necessary.

## DISCUSSION

The treatment of severe multidrug-resistant (MDR) bacterial infections is one of the most demanding fields in modern practice of infectious diseases. Once considered a foundation of treatment of severe Gram-negative infections, its role has been increasingly redefined by the increasing global prevalence of antimicrobial resistance, the development of new therapeutic agents, and an increased focus on antimicrobial stewardship. (Aldaz *et al*., 2021)

The results of this review indicate that meropenem still has considerable clinical value. Meropenem is still a highly effective agent in the treatment of severe cases of ESBL producing *Enterobacterales* infections, where strong clinical evidence still supports its activity and dependability. Meropenem gives predictable results in such infections and is still a choice of therapy, especially in critically ill patients (Liao *et al*., 2025b).

Its activity in carbapenem-resistant infections is greatly reduced, with resistance mechanisms having a direct negative effect on its activity. Moxpenam effectiveness in the context of carbapenem-resistant *Enterobacterales* (CRE) is strongly linked to the resistance mechanism and minimum inhibitory concentration. Although optimized dosing plans and combination regimens provide a certain advantage in the selected cases, the introduction of newer 2-lactam/2-lactamase combinations has changed the treatment patterns in favor of more specific and successful treatments. The same tendency is more dramatic in infections with carbapenem-resistant A. *baumannii*, in which meropenem-based regimens have not always proven to be clinically beneficial, casting doubt on their further use in this scenario (Deng *et al*., 2023; Hassanpour *et al*., 2021).

Its use towards MDR *P. aeruginosa* is not fixed and is determined by the susceptibility, with its utility being variable and strongly context-dependent. Meropenem can still offer effective treatment in situations where susceptibility is maintained, especially optimized PK/PD strategies. Its status as a first-line therapy is however challenged by the growing number of difficult-to-treat resistance phenotypes and the existence of more recent anti-pseudomonal agents (Liao *et al*., 2025a).

The optimization of PK/PD is significant and is not able to break the resistance on high levels. Extended or continuous infusion and, where possible, therapeutic drug monitoring are the strategies which can have a great impact on drug exposure and clinical outcome in critically ill patients. However, these strategies are not able to

completely resist high-level resistance, especially in organisms that generate strong carbapenemases. Therefore, although PK/PD optimization can prolong the usefulness of meropenem, it is not able to replace intrinsic antimicrobial activity (Wang *et al*., 2022; Wenzler and Scoble, 2020).

Proper antimicrobial stewardship is critical. The extensive and frequent empirical use of meropenem has led to the selection and diffusion (spread) of carbapenem-resistant organisms. This emphasizes the importance of using it more judiciously, such as through early de-escalation guided by microbiological data and implementing carbapenem-sparing measures where suitable. This approach is additionally supported by the introduction of rapid diagnostic tools that can provide timely and specific treatment (Almeida *et al*., 2021; CECROPIN, 2023).

The newer drugs are better at resisting certain resistance mechanisms and are gaining an increasing number of recommendations in international guidelines to treat MDR infections. Consequently, meropenem is evolving into a more selectively used, pathogen-oriented therapy, rather than a broadly used, last-line agent (Pelegrin *et al*., 2021).

Global differences in the provision of newer therapies are a significant challenge that is still unresolved. In most low and middle-income countries, meropenem remains an important part of the treatment because of the lack of alternative agents. It is especially relevant to ensure that meropenem is optimally used in such settings, both in terms of dosing strategies and stewardship practices (Abdul-Mutakabbir *et al*., 2021).

The present review shows that the use of meropenem in serious MDR bacterial infections is not universal and outdated. Rather, it is reliant on pathogen and clinical situation. Its further applicability requires selective use of patients, pathogen-specific factors and combination with current antimicrobial approaches.

## CONCLUSION

Meropenem remains a significant part of the treatment of severe multidrug-resistant bacteria infection but its clinical application has been more and more contextual. Although it is still the agent of choice against severe infections with ESBL-producing *Enterobacterales*, it is largely ineffective against carbapenem-resistant pathogens, especially *A. baumannii* and some *Enterobacterales*, with newer antimicrobial agents showing better results. Drug exposure in critically ill patients can be improved by the optimization of meropenem therapy with the use of PK/PD-based approaches, such as the prolongation of the infusion and the use of individual doses. However, high-level resistance cannot be substituted by such methods, and it is crucial to choose a suitable therapy according to the pathogen-specific sensitivity. The changing antimicrobial environment with the emergence of new 2-lactams/2-lactamasase inhibitor patterns and the development of rapid diagnostics is moving treatment models to more focused and precision-oriented strategies. Here, meropenem can no longer be considered a universal last-line agent but a strategically used therapy as part of a more comprehensive, evidence-based approach. Further work should aim at streamlining antimicrobial stewardship, enhancing access to novel therapies, and incorporating both pharmacological and microbiological data in decision-making when it comes to individualized treatments. This practice is necessary to maintain the clinical usefulness of meropenem and to deal with the current threat of antimicrobial resistance that has affected the world.

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