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Carbapenem-Resistant Gram-Negative Bacteria: Pathology and Interventions

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Abstract: Carbapenem-resistant Gram-negative bacteria (CR-GNB) can be regarded as one of the significant health issues on the global level. They are carbapenemic resistant i.e. antibiotics which are actually the last resort of treatment of extreme infections. More CR-GNB has largely resulted because of the transmission of mobile resistance determinants, overuse of antibiotics and minimal therapeutic development. This review explains the molecular mechanism of resistance, clinical implications, epidemiology and available treatments as well as emerging treatments. These considerations must be comprehended to be capable of antimicrobial stewardship, controlling infections, and therapeutic innovation.

Keywords: Bacteria , Gram-negative , infection, Clinical.

INTRODUCTION

One of the most effective classes of 2-lactam antibiotics that can be used to treat the severe cases of bacterial infection is the carbapenems. Carbapenems include imipenem, meropenem, doripenem, and ertapenem. Carbapenems have been regarded since ancient times as the foundation of therapy in the case of infection by multidrug-resistant (MDR) Gram-negative bacteria due to their broad-spectrum activity, their stability against the majority of 2-lactamases, and their high affinity to a number of penicillin-binding proteins (PBPs) [Zhuorong, L., & Along, C. 2025]. They are often used as late-line drugs in life-threatening diseases infections of the bloodstream, ventilator associated pneumonia, complex intra-abdominal infections and severe urinary tract infection[Hasan, G. M. *et al*., 2026].

Nevertheless, the high rate of global acquisition and spread of carbapenem-resistant Gram-negative bacteria (CR-GNB) has currently endangered the usefulness of this important line of antibiotics. Some of the major pathogens that are involved in carbapenem resistance are Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, and Acinetobacter baumannii[Mourabiti, F. *et al*., 2025]. The organisms have a significant ratio of healthcare-associated infections all over the world and are especially vestigial in the intensive care unit (ICU), transplant unit, cancer ward, and neonatal unit [Chakraverty, R., & Kundu, A. K. 2025].

The clinical pathology of CR-GNB is immense. Infections by these organisms have been associated with high morbidity and mortality, long hospitalization, reduced therapeutic alternatives and high health care expenditures[Hu, H. *et al*., 2025]. The fatality rate of bloodstream infections caused by carbapenem-resistant Enterobacterales is often higher than 3050 percent, with such patients particularly being critically ill or immunocompromised. In addition to that, older and more toxic treatments like polymyxins are frequently used, which highlights the necessity to work on safer and more effective treatments as soon as possible [De Pascale, G. *et al*., 2025].

The World Health Organization formally recognized CR-GNB as a health issue of global concern, listing carbapenem-resistant Enterobacterales, P. aeruginosa and A. baumannii in its list of Priority 1 (Critical) pathogens on antibiotic-resistant bacteria. This title demonstrates the sheer urgency of research and development of novel antimicrobial agents, fast diagnostic measures and coordinated international containment measures [Antochevis, L. C. *et al*., 2025].

The problem of carbapenem resistance development is a complex of circumstances, with the main factors being the transfer of the resistance determinants in horizontal ways, a selective pressure caused by improper or excessive antibiotic use, a poor practice in infection control, global travel, and the environmental reservoirs [Dadić, B. *et al*., 2025]. Carbapenemase genes are disseminated rapidly in bacterial species and also across geographic boundaries through mobile genetic elements like plasmids, transposons and integrons. This has resulted in resistance no longer being localized and is now a reality in most parts of the globe [Karampatakis, T. *et al*., 2025].

Moreover, there is also a growing incidence of community-acquired infection by carbapenin-resistant organisms besides healthcare-associated

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transmission, which complicates the process of containment. The combination of antimicrobial resistance, movement, and lack of drug development pipelines is a perfect storm in the contemporary management of infectious diseases [Laddad, M. *et al*., 2024].

Because of the rapidly increasing evolution of the resistance mechanisms and the growing clinical implications, a detailed insight on the molecular pathogenesis of carbapenem resistance, epidemiology patterns, diagnosis tools and therapeutic interventions is needed [Li, J. *et al*., 2025]. The purpose of this review is to derive an in-depth examination of the mechanisms of the carbapenem resistance in the Gram-negative bacteria, as well as provide a critical evaluation of the existing and upcoming treatment options, which may lead into an informed clinical practice, antimicrobial stewardship, as well as future research efforts [Mourabiti, F. *et al*., 2025].

MECHANISMS OF CARBAPENEM RESISTANCE

Carbapenem resistance in Gram-negative bacteria is multifactorial and often results from the combined action of enzymatic degradation, reduced drug entry, active efflux, and structural targ*et al*terations. These mechanisms may occur independently but frequently coexist within the same bacterial isolate, leading to high-level resistance and multidrug-resistant phenotypes [Su, Y. *et al*., 2025]. The horizontal gene transfer through the plasmids, integrons, and transposons plays a key role in spreading the resistance determinants between the species and geographical areas. It is necessary to comprehend these mechanisms at a molecular level so that it can be implemented in therapeutic and diagnostic strategies [Kumavath, R. *et al*., 2025].

Carbapenemase Enzymes

Carbapenemases are specific 8 -lactamases that have the ability to hydrolyze carbapenems and other 8 -lactam antibiotics, making them ineffective. They constitute the most clinically relevant carbapenem resistance methodology of the Gram-negative bacteria [Beer, M. 2025]. These enzymes are frequently placed on mobile genetic material which allows them to spread quickly intra and interspecies. According to Ambler classification system, there are Class A, Class B and Class D carbapenemases which have different structural and functional characteristics [Lloyd, S. M. 2024].

Class A Carbapenemases

Class A carbapenemases are serine -lactamases, which exploit a serine residue in their active site to break down 8 -lactam antibiotics. The brightest example is the KPC (Klebsiella pneumoniae carbapenemase) which was first discovered in Klebsiella pneumoniae but is now transferred across the entire world. There is wide resistance profile with KPC enzymes being able to hydrolyze penicillins, cephalosporins, monobactams, and carbapenems. These enzymes are generally plasmid-mediated, and makes them be transmitted rapidly among the members of the order Enterobacterales [Beer, M. 2025].

Class B Metallo-β-Lactamases (MBLs)

Metallo-2-lactamases (MBLs) or class B carbapenemases are catalysts that need the presence of zinc ions over their active site. Notable ones among them are NDM, VIM and IMP enzymes which have been found in various Gram-negatives across the world. All 6 -lactam antibiotics, including carbapenem antibiotics, can be hydrolyzed by MBLs, but not monobactam antibiotics (including aztreonam). Their genetic determinants often are related to integrons and plasmids, which facilitates quick worldwide distribution and constrains efficient treatment possibilities[Ortega-Balleza, J. L. *et al*., 2024].

Class D Oxacillinases

OXA-type enzymes, which are also referred to as class D carbapenemases, are proteins that are capable of hydrolyzing oxacillin. Other Enterobacterales and Acinetobacter baumannii OXA-48 and OXA-23 variants are of specific clinical interest. Although some OXA enzymes have a comparatively low carbapenin resistance level, they carry a big impact with regard to loss of porins or efflux. These enzymes tend to be plasmid-mediated; as a result, they cause both hospital outbreak and local endemicity. [Zdarska, V. *et al*., 2026].

Altered Membrane Permeability

One non-enzymatic mechanism of carbapenem resistance is the reduced membrane permeability which restricts the entry of antibiotics into the bacterial cell. This is usually done by loss, mutation or down regulation of outer membrane porins that ordinarily facilitate uptake of 7-lactam. Reduced expression of certain porins by organisms like the Pseudomonas aeruginosa greatly diminishes the carbapenem susceptibility. Porin changes can lead to elevated-level resistance and failure to respond to treatment, when combined

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with 0 -lactamase generation [Hamzaoui, Z. *et al*., 2025].

Efflux Pump Overexpression

The efflux pumps are membrane-linked transport systems, which actively drive out antibiotics out of the cytoplasm of the bacteria. Multidrug efflux systems amplification, including MexAB-OprM in P. aeruginosa reduces intracellular carbapenem levels below therapeutic levels. These pumps are frequently broad-spectrum in their substrate specificity, and lead to not just carbapenems resistance, but to fluoroquinolones, aminoglycoside and other classes of drugs resistance. The efflux-mediated resistance is especially disastrous as it increases the multidrug resistance and decreases the effect of combination therapy. [Wu, W. *et al*., 2024].

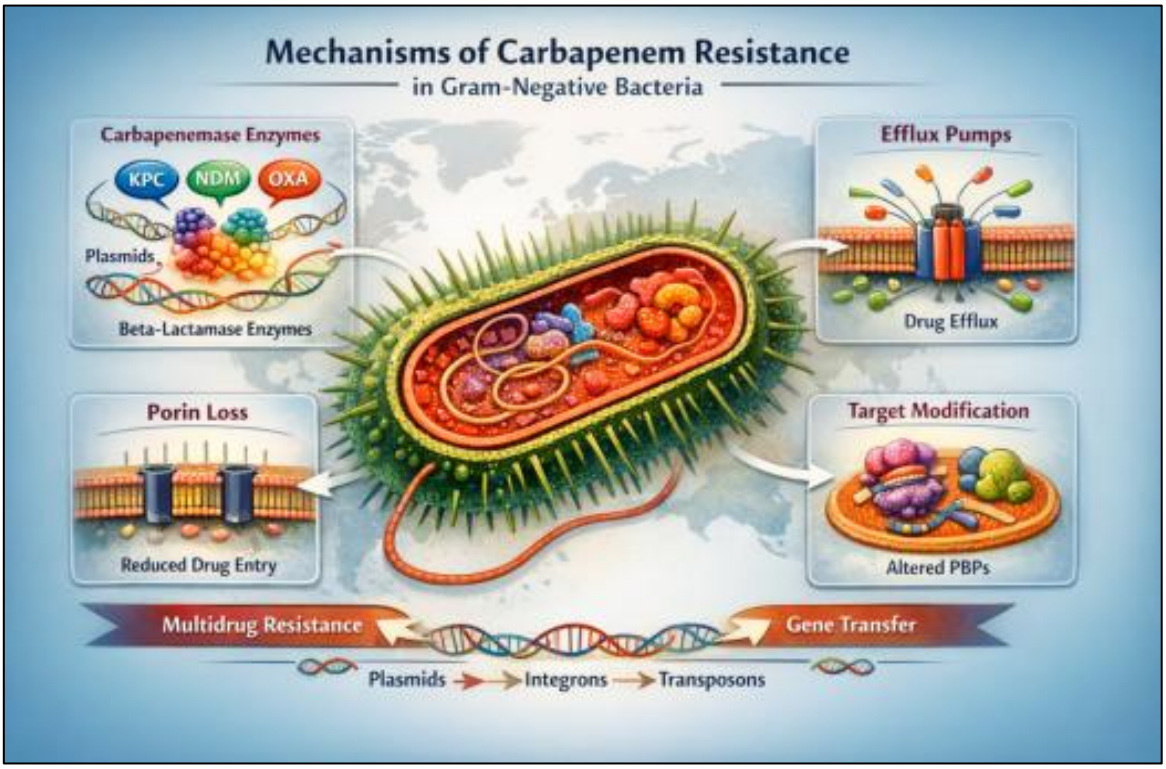

Figure 1: Mechanisms of Carbapenem Resistance

Target Site Modifications

Changes in penicillin-binding proteins (PBPs) which are the major targets of carbapenems may decrease the binding affinity of antibiotics. PBP mutations (although seen less frequently in Gram-negative organisms than in Gram-positive organisms) can be thought to play a role in reduced susceptibility of specific strains. PBPs alteration disrupts the cell wall growth inhibitory effect of carbapenem, enabling bacterial growth to proceed. Target modifications may also be complicated along with other resistance mechanisms, which further restrain the effective treatment and narrow therapeutic index [Dabhi, M. *et al*., 2024].

EPIDEMIOLOGY AND CLINICAL IMPACT

Carbapenem-resistant Gram-negative bacteria (CR-GNB) has become one of the primary health issues of concern in numerous countries of the world with rising prevalence rates noted in healthcare systems. They have dynamic epidemiology, which is dependent on regional patterns of antimicrobial use, infection control measures and mobility of resistance genes. The dissemination of carbapenemase producing organisms has converted the local outbreaks into endemic transmission in most nations. Surveillance data show increasing levels of resistance in the hospital and community based settings. [Li, Q. *et al*., 2024].

Global Distribution

CR-GNB are endemic in some regions and some types of carbapenemase are prevalent in some geographical areas. Most commonly reported KPC-producing organisms are in the United States, parts of South America and China, and most commonly associated with Klebsiella pneumonia. [Li, Q. *et al*., 2024]. The NDM-producing strains are very common in the Indian subcontinent and they are spread to other continents due to travel

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and migration. OXA-48-like enzymes are commonly found in Europe, North Africa, and the Middle East and are usually associated with healthcare-associated epidemics. Moreover, Acinetobacter baumannii that is resistant to carbapenem has turned out to be endemic in most intensive care units across the world. Cross-border dissemination comes across through international travel, medical tourism, the flow of refugees, and international trade in the significant numbers. The spread of resistance determinants all over the world further increases with horizontal gene transfer through plasmids [Talat, A. *et al*., 2024].

Clinical Outcomes

CR-GNB infections are linked to serious clinical outcomes and high case-fatality rates, which may reach more than 3040 percent of critically ill individuals. Deaths are especially high when it comes to cases of septic shock, failure to introduce the proper treatment in time, or highly resistant strains. The patients often need long-term hospitalization involving long intensive care unit and mechanical ventilation services [Abedi, H. *et al*., 2025]. The economic price is excessive, incorporating the increased expenditure of treatment, excessive use of bed rounds and final line antimicrobial agents. Bloodstream infections, ventilator-associated pneumonia, complicated urinary tract infections, and intra-abdominal infections are the common clinical manifestations. The limitation of treatment and toxicity of available treatment agents further complicate treatment leading to poor overall outcome compared to infection by susceptible organisms [Puri, B. *et al*., 2025].

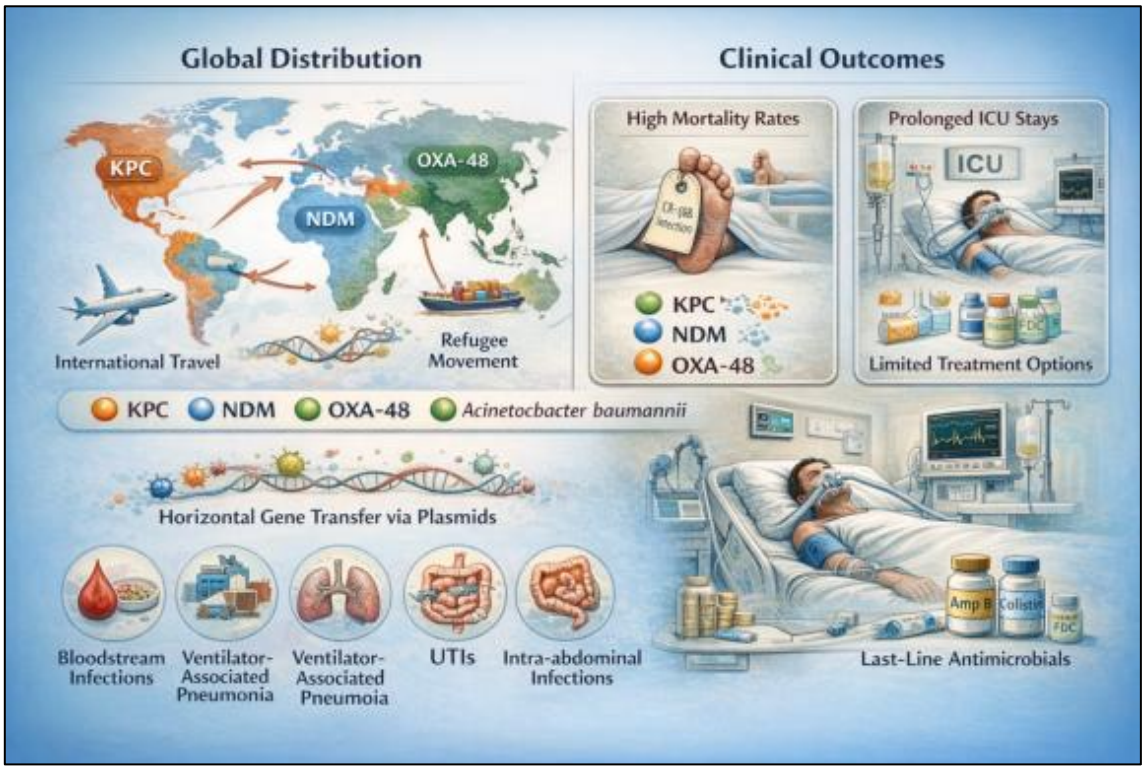

Figure 2 : Global Epidemiology and Clinical Impact of Carbapenem-Resistant Gram-Negative Bacteria (CR-GNB)

LABORATORY DETECTION AND DIAGNOSTICS

Timely and accurate identification of carbapenem resistant Gram-negative bacteria (CR-GNB) is the key factor to proper antimicrobial treatment, infection control, and epidemiological monitoring. The diagnostic methods could be generally divided into two groups, i.e., phenotypic and molecular approaches, both possessing both benefits and drawbacks. Phenotypic tests assess antimicrobial resistance and enzyme activity, and molecular-assay methods determine molecular resistance genes. Combinations of the two methods enhance the accuracy of diagnoses and direct specific treatment. [Al Souheil, A. *et al*., 2025].

Phenotypic Methods

Phenotypic detection is a methodology that evaluates the resistance to carbapenem by observing changes in growth of bacteria on the basis of observable growth patterns of bacteria

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upon the presence of the antibiotics. VITEK 2 and MicroScan WalkAway automated susceptibility testing systems are common in clinical laboratories to establish minimum inhibitory concentrations (MICs). Modified Hodge Test and Carba NP test particularly identify the production of enzymatic hydrolysis as the detection of enzyme carbapenemase production. Also, β-lactamase inhibitors together with gradient diffusion techniques (E-tests) can be used to distinguish between carbapenemase classes. Even though practical and economical, phenotypic tests are sometimes subject to false positives or have limitation in detecting some emerging enzymes [Lathakumari, R. H. *et al*., 2025].

Molecular Methods

Molecular diagnostic methods are sensitive and specific in identifying the specific carbapenemase genes. The detection of genes, including bla_KPC, bla_NDM, and bla_OXA-48, is usually done by polymerase chain reaction (PCR) and multiplex real-time assays directly in clinical isolates. The assays give quick results and enable prompt interventions of the infection control. WGS provides a full resistance profiling which allows both recognized and novel resistance determinants to be identified. In addition to diagnosis, WGS aids in outbreak investigation, transmission tracking and surveillance of epidemiology on the global scale [Abou-assy, R. S. *et al*., 2023].

THERAPEUTIC OPTIONS

CR-GNB infections need a careful choice of treatment according to the factors of susceptibility, location of infection, and patient factors.

Older and Adjunctive Agents

- **Polymyxins (colistin, polymyxin B)**: Active against many CR-GNB but associated with nephrotoxicity and neurotoxicity.
- **Tigecycline**: Broad coverage including some CR-GNB, limited by low serum levels for bloodstream infections.
- **Aminoglycosides** (amikacin, gentamicin): Useful in combination therapy for susceptible isolates [Liu, D. *et al*., 2024].

Newer β-Lactam/β-Lactamase Inhibitor Combinations [Melinte, V. *et al*., 2025**]**

Agent	Target Enzymes	Notes
Ceftazidime-avibactam	KPC, OXA-48	Not active against MBLs
Meropenem-vaborbactam	KPC	No activity vs MBLs, OXA
Imipenem-relebactam	KPC, some AmpC	Restores imipenem activity
Cefiderocol	Broad spectrum including MBL producers	Siderophore cephalosporin; efficacy in difficult-to-treat infections

Combination Therapy

To aid patients with multidrug resistant gram-negative infection with more severe illnesses, combination therapy is usually suggested to improve antibacterial activity and patient outcomes [Umemura, T. *et al*., 2022].

The typical combinations are polymyxin and a carbapenem (when the resistance is low-level) or polymyxin and tigecycline in an attempt to display a synergetic effect via varying mechanisms of action.

In extreme situations, triple therapy can be employed with the addition of an aminoglycoside in order to expand coverage and minimize development of additional resistance. [Gajic, I. *et al*., 2025].

Emerging Therapies and Strategies

Metallo- β-lactamase (MBL)-inhibitors β-lactamase Overproduction of metallo- β-lactamase (MBLs) resistance in bacteria has led to the development of new β-lactamase inhibitors that have the potential to resensitize 6-lactam to highly resistant bacteria, including E. coli (Olsen 2008).

Other options that are being explored involve phage therapy and antimicrobial peptides, which directly act on the pathogens via non-conventional non-traditional mechanisms. [Huang, Y. S., & Zhou, H. 2025].

INFECTION CONTROL AND STEWARDSHIP

Medical institutions are required to adopt evidence-based practices that can help reduce the spread of infection in high-risk environments like the intensive care unit. There is the need to have a multidisciplinary collaboration between clinicians, microbiologists, infection control teams and policymakers. Constant institutional commitment will go a long way in reducing cases of outbreaks

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and enhancing patient outcomes. [Liu, C. *et al*., 2026].

Infection Prevention

First line of defence against the CR-GNB in a healthcare facility is the implementation of infection protection. Close compliance with hand hygiene, contact precaution, and appropriate use of personal protective equipment would greatly minimize the cross-transmission. It is important that the environment be thoroughly cleaned and disinfected especially in the case of intensive care units. Early detection and isolation of colonized patients can be achieved through screening of high-risk patients, which include those that have been hospitalized in a foreign country or those who have been admitted to the ICU recently [Xiao, P. *et al*., 2025].

Antimicrobial Stewardship

Antimicrobial stewardship initiatives focus on maximizing the use of antibiotics, such that selective pressure causing resistance is minimized. They are evidence-based choice of agents, correct dosage, and a restriction of unnecessary broad-spectrum antibiotic administration. Culturally and susceptibility-driven de-escalation of therapy is beneficial in preserving efficacy of carbapenems. Life-long learning, prescription reviews, and feedback systems are all vital to achieving effective stewardship programs. [Karmakar, S. *et al*., 2026].

Surveillance

The constant surveillance systems are essential in tracking the trends of resistance and early detection of outbreaks. Local programs based in hospitals monitor the trends of susceptibility in order to inform empirical interventions of therapy and infection control. National and international monitoring networks offer a wider range of epidemiological information and determine new resistance mechanisms. Evidence-based policies allow government officials in the field of health to adopt specific containment policies [Ingelbeen, B. *et al*., 2025].

CHALLENGES AND FUTURE DIRECTIONS

CR-GNB continue to pose a great health challenge across the globe in spite of the progress in both diagnostics and therapy. Drug development is frequently lagged behind by the fast development of resistance mechanisms. The availability of novel treatment in most regions is restricted by economic, logistical and regulatory aspects. To solve these problems, it needs innovation, long-term financing and international collaboration [Mourabiti, F. *et al*., 2025].

Diagnostic Gaps

Even though quick molecular methodologies to detect carbapenase are increasing in number, they are not yet globally available especially to the low-resource setting. Most healthcare institutions continue to use traditional phenotypic approaches that do not necessarily identify rare or new resistance genes. Inadequate laboratory facilities may also slow down the process of diagnostics and management of infection. The affordable, point-of-care diagnostic devices are a vital area of research that needs to be developed [Chakraborty, S. 2024].

CONCLUSION

One of the most urgent problems of the contemporary infectious disease management is the carbapenem-resistant Gram-negative bacteria. There is a need to adopt a complex strategy incorporating molecular diagnostics, innovative therapeutics agents, infection control, and effective antimicrobial stewardship. Current studies and research collaboration across the globe are important to respond to the changing nature of the resistance and to enhance the clinical outcomes.

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