**INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH**
**(ISSN: 2454-4191)**
www.ijmsdh.org (2026)



**Received:** 11 January 2026
**Revised:** 24 January 2026
**Accepted:** 19 February 2026
**Published:** 28 February 2026

**Page No - 114-120**
**DOI** - 10.55640/ijmsdh-12-02-14

**Article Citation:** Jamel, A. N., Salman, S. B.., Saber, F. O.., & Ali A. Al-fahham. (2026). The Classification of Carbapenemase Genes and Their Role in Bacterial Antimicrobial Resistance: A Review. International Journal of Medical Science and Dental Health, 12(02), 114-120. https://doi.org/10.55640/ijmsdh-12-02-14



# The Classification of Carbapenemase Genes and Their Role in Bacterial Antimicrobial Resistance: A Review

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## Abstract

Antimicrobial resistance (AMR) is a significant worldwide health problem caused by antimicrobial overuse and misuse in different sectors, resulting in the appearance of resistant microbes. Other concerning is the concurrent emergence of dual carbapenem-colistin resistance, defined as no efficacy by both antibiotics that are reserved to treat life-threatening infections due to multidrug-resistant enterobacteriaceae. Carbapenemase genes encode β-lactamase enzymes capable of hydrolyzing carbapenems and other β-lactam antibiotics, offering high-level resistance and promoting treatment failure. This review focuses on molecular features, classification and pathogenic significance of the main carbapenemase genes in clinically important bacteria through data until October 2023. Carbapenemases are mainly classified into Ambler classes A, B, and D including major enzymatic family like KPC, OXA, IMP, VIM, and NDM type carbapenemases. the genes that encode carbapenemases often reside on mobile genetic elements that can be transferred horizontally at a high rate between bacterial species and are responsible for spreading carbapenem resistance globally. Besides their well-characterized links to antimicrobial resistance, emerging data suggest that carbapenemase genes can also

influence bacterial pathogenesis through increased survival in the presence of antibiotic selective pressure, biofilm formation and co-transfer of virulence-associated determinants. It also emphasizes the clinical manifestations of infections with carbapenemase-producing pathogens, which are linked with increased morbidity and mortality, prolonged length of stay and greater healthcare costs. In line with observations made in some bacterial lineages, the co-existence of resistance and virulence traits highlights an urgent need to improve molecular surveillance, rapid diagnostic tools and efficient strategies for infection prevention. In addition, understanding the complex interactions between carbapenemase gene expression and bacterial fitness and host–pathogen dynamics is important for developing new therapeutic and preventive measures. There are many factors that facilitate the pathogenesis and antibiotic resistance of these organisms. To overcome this escalating public health challenge, it will then require integrated approaches between molecular epidemiology, antimicrobial stewardship and novel therapeutic strategies that together will alleviate the burden of carbapenemase-producing organisms on global health.

**Keywords:** carbapenemases, antimicrobial resistance, β-lactam antibiotics

## Introduction

One of the most important mechanisms of carbapenem resistance in gram-negatives is the release of acquired carbapenemases, which are the broadest-spectrum β-lactamase enzymes. In addition to carbapenems, these enzymes have activity against virtually all other members of the β-lactam group with the notable exception of cephamycin. Researchers reported that carbapenemase genes are commonly located on large, mobile genetic elements including plasmids and transposons enabling rapid dissemination of resistance determinants by horizontal gene transfer between species and genera. This mobility can diffuse resistance rapidly across microbial populations and over broad geographic areas which is a major impediment to controlling infections in both hospital-based or outpatient settings (Beig et al., 2023; Shahimi et al., 2025). Undoubtedly, the resist type of carbapenemases is aminoglycosides, nevertheless, there are also other aminoglycoside families along with oxazolidinones, phosphorolysis as well as rifampicin (Tyers & Dalman et al., 2022).

The widespread existence of carbapenemase genes among CRE emphasizes the magnitude of the problem. Multi-center retrospective analysis of Enterobacterales from geographically diverse sites in the United States KPC enzymes remain the most prevalent carbapenemases detected. At the same time, metallo-β-lactamases and OXA-48 variants got a different distribution both from turf and doomed (Caliskan-Aydogan & Alocilja, 2023). Blinded use of carbapenems has led to high levels of resistance that ultimately result from a process of selection that involves a very small fraction of the local pool of multidrug-resistant bacteria, as is clarified by studies at Saudi Arabian hospitals showing that gonorrhoea resistance due to bla_OXA-48 and bla_NDM accounts for most of this resistance. These genes influence the treatment of infection by co-localization which not only raises the resistance but also causes high mortality among the infected patients especially those in Intensive Care Units (ICUs) (Zowawi et al., 2014). Besides Enterobacterales, we also observe the dissemination of carbapenemase genes to other Gram-negative pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The mobility of these genes allows these pathogens to rapidly adapt to antibiotic pressures and to survive diverse environments both inside and outside of the human host. The spread of resistance based on carbapenemases only increases the utility of these pathogens (Beig et al., 2023; Paudel et al., 2024). Thus, pathogens can proliferate in diverse environments, such as hospital wastewater treatment systems, and disseminate widely, as carbapenemase genes are typically harbored on plasmids alongside other resistance determinants. This genetic linkage facilitates the emergence of multidrug-resistant (MDR) phenotypes that are difficult to manage using currently available antibiotics (Bleichenbacher et al., 2020).

In addition to antibiotic resistance, carbapenemase genes could well be responsible for the expression of virulence determinants which could make bacteria more pathogenic. For example, a study of isolates of carbapenemase-producing Escherichia coli showed that certain virulence genes might only be expressed in the presence of the resistance-related genes, This raises the question whether the production of such an enzyme can go together with qualities that enhance fit and severity in bacteria whether it is meant also to cause their disease. These double exigencies of virulence and resistance raise the spectre of more severe clinical effects and greater transmission in health care settings (Jomehzadeh et al., 2022).

While diverse mechanisms are recognized for carbapenemase-mediated resistance, our understanding of these genes mediating bacterial pathogenesis at molecular and clinical levels remains rudimentary. These non-fermenters can harbor carbapenemase genes, but MICs are often only in the range of intermediate and routine susceptibility testing will return a susceptible result, masking their clinical potential and permitting silent transmission within the health care network (Caliskan-Aydogan & Alocilja, 2023). Additionally, the differences between phenotypic resistance profiles and gene presence illustrate both the limitations of current diagnostic approaches as well as further support the need for integrated molecular surveillance methods.

Carbapenemase genes present clinical significance in terms of treatment failure, economically through increased costs and length of hospital stays, as well as being associated with increased mortality. Carbapenemase-producing organism infections frequently demand last-line and combination therapies, which are expensive and have potential for substantial adverse effects. But with new antibiotic development blocked, the problem becomes even greater as a public health issue in terms of antimicrobial resistance than it otherwise would have been. (Gupta et al., 2018). It is constantly changing and its creators billboard on the gene of carbapenem resistence will depend on overcoming these problems. However, continuous surveillance, good molecular diagnostics, and improved stewardship practices are required to mitigate this type of resistance mechanism. Better comprehension of the genetic settings, evolutionary dynamics and clinical context of carbapenemase genes will provide a better platform for more effective therapeutic strategies and containment policies. In this review, we summarize the current knowledge on the prevalence and diversity of carbapenemase genes with respect to their distribution in bacterial pathogens, their molecular characteristics and clinical relevance, aimed at providing up-to-date information about a major challenge for infection control and prevention that may inform both research and implementation in practice (Guchhait et al., 2025).

## Classification of carbapenemase genes

Carbapenemases are β-lactamase enzymes that can hydrolyze the carbapenem class of β-lactam antibiotics, which was previously reserved for use against serious infections resulted from multidrug-resistant Gram-negative bacteria (Bush & Bradford, 2016). These enzymes provide resistance by hydrolyzing the β-lactam ring, thereby inactivating the antibiotic. Carbapenemases are categorized by their molecular mechanism, active site and genetic origin. Amino acid sequence homology forms the basis of the most accepted classification system for β-lactamases, including carbapenemases (Bush & Jacoby, 2010) (Figure 1).

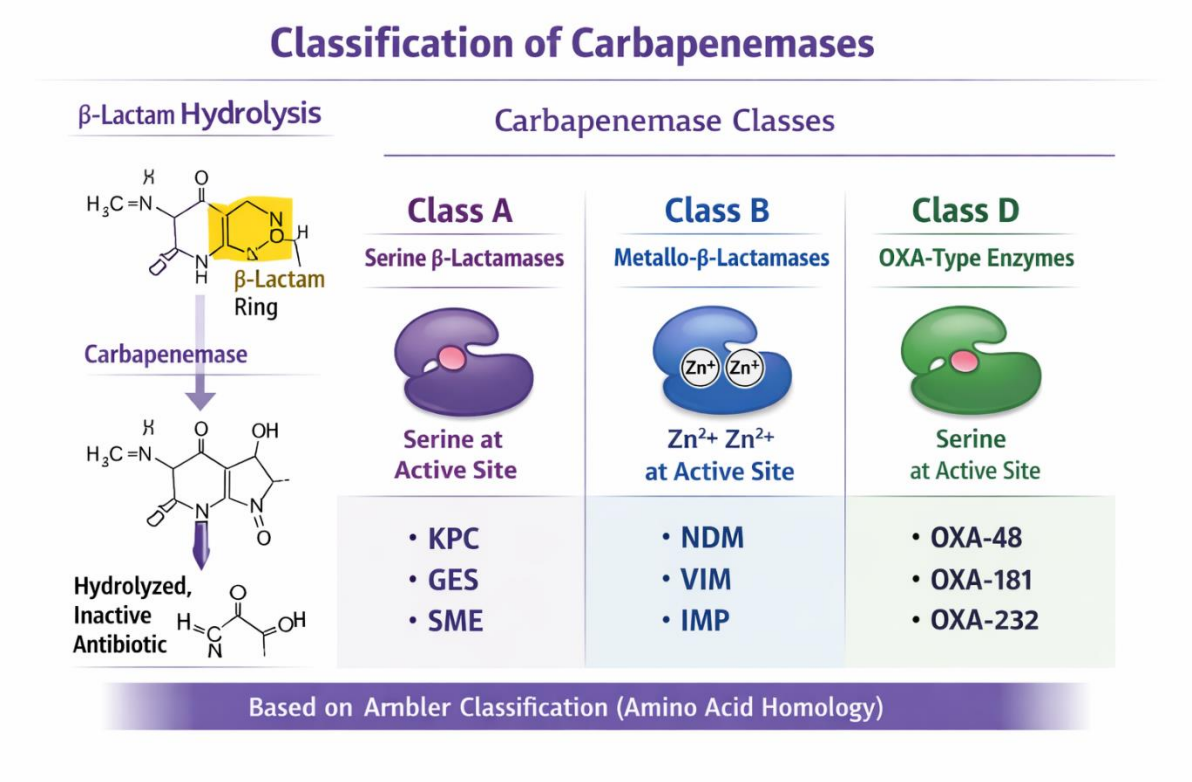


**Figure 1.** Classification of carbapenemases (Bush & Bradford, 2024).

Based on Ambler classification, carbapenemases can be categorized into 3 main classes: Class A (serine β-lactamases), Class B (metallo-β-lactamases) and Class D (oxacillinases). Each class has distinct structural features and substrate specificities that affect clinical treatment outcomes. These classes of recurrent mutations are important for not only diagnostic detection, but also therapeutic decision-making (Ambler, 1980 ; Bush & Bradford, 2024).

Class A carbapenemases are serine- dependent enzymes that utilize a serine residue at the active site to cause hydrolysis of β-lactam antibiotics. The most clinically relevant member of this group is Klebsiella pneumoniae carbapenemase (KPC), which was first recognized in the United States during the late 1990s and then spread throughout the world. KPC enzymes have wide substrate profiles and can efficiently hydrolyze the carbapenems, in addition to penicillins and cephalosporins which are of significant concern (Naas et al., 2016). Usually, KPC enzyme genes, for example, bla_KPC, are harbored by conjugative plasmids including IncF and IncN that facilitate the horizontal spread within Enterobacterales as well as other Gram-negative species. Other class A carbapenemases include variants of GES (Guiana Extended-Spectrum β-lactamase) that have weaker carbapenemase activity but may lower detection thresholds for resistance phenotypes when co-expressed with further β-lactamases (Nordmann & Poirel, 2014).

Class B carbapenemases (the metallo-β-lactamases [MBLs]), which differ from the serine enzymes by requiring one or two zinc ions at their active sites for catalyzing β-lactam hydrolysis. MBLs are a relevant clinical problem as they remain insensitive to ordinary β-lactamase inhibitors like tazobactam and clavulanic acid (Poirel et al, 2011). The New Delhi metallo-β-lactamase (NDM) has emerged from the MBL group and gained worldwide dissemination since it was first recognized in 2008 in India (Kumarasamy et al., 2010). The gene bla_NDM is commonly found on broad-host-range plasmids that coharbor additional resistance determinants, facilitating multidrug resistance (Poirel et al. 2011). Other important families of MBL include IMP (active on imipenem) enzymes and VIM (Verona integron-encoded metallo-β-lactamase), which have been described in multiple settings around the globe and frequently are associated with integrons or transposons promoting gene mobility (Nordmann et al., 2011).

Class D carbapenemases, or oxacillinases (OXA-type enzymes), are another important class of carbapenemases. These have a serine active site characteristic of serine β-lactamases but are structurally unrelated to class A enzymes. Within the OXA family, their OXA-48-like group biocarriers are the most prominent and clinical spread in Mediterranean, Middle Eastern and North African territories (Boyd et al., 2022). OXA-48 has weak carbapenemase activity when analyzed in vitro, but when combined with permeability defects of the bacterial outer membrane this enzyme can confer high-level resistance. Genes encoding OXA-48-like enzymes (bla_OXA-232, bla_OXA-181, bla_OXA-48, etc.) are frequently located on plasmids that disseminate within Enterobacterales. There are currently no effective inhibitors against OXA-type enzymes unlike other carbapenemases, making therapeutic strategies more complicated (Boyd et al., 2022).

In addition to these major classes, newly emerging and hybrid carbapenemases are still being reported. They are multideterminant resistance variants that either merge elements from distinct carbapenemase families, or contain variants that have an increased catalytic efficiency. For example, some derivatives of OXA enzymes have enhanced hydrolysis of extended-spectrum cephalosporins and carbapenems, making their identification even more challenging. Continued emergence of specific types of carbapenemases indicates the need for molecular surveillance and genomic sequencing to track changing epidemiology of resistance (Abouelfetouh et al., 2022).

While the classification of carbapenemases is of a deep academic interest, it has an important clinical relevance. Different classes have different responses to diagnostic tests and inhibitors. Carbapenemase activity can be detected phenotypically with tests such as modified Hodge and Carba NP test (although they do not discriminate between classes of enzymes (Poirel et al., 2011), so for absolute identification molecular assay which target specific genes by PCR may be necessary. Treatment regimens vary as well: regimens with novel β-lactamase inhibitors such as avibactam are active against KPC producers but not against most MBLs. Thus, accurate identification of the carbapenemase class and gene subtype is essential for appropriate therapy (Wong & van Duin, 2017).

Finally, the molecular classification informs infection control strategies. Due to frequent associations between carbapenemase genes, mobile genetic elements and co-resistance determinants, the transmission dynamics of outbreaks are often complex and involve both patients as well as environmental reservoirs. In this regard, surveillance that combines molecular typing and epidemiological data are essential to tracking and controlling carbapenemase-producing strains (Göpel et al., 2025).

## Role of carbapenemase genes in bacterial resistance

Although carbapenemase genes are classically acknowledged for their role in conferring resistance to carbapenem antibiotics, increasing evidence suggests that these genes also exert their impact on bacterial pathogenicity, both directly or indirectly. Pathogenicity includes a bacterium's ability to evade immune defenses, colonize the host, persist in hostile environments and cause tissue damage. The acquisition and expression of carbapenemase genes may modify these processes by impacting on bacterial fitness and virulence factor expression, host–pathogen interaction, and the clinical outcomes of disease (Meletis, 2016).

The pathogenicity mechanism whose role may be played by antibiotic resistance in particular is increased bacterial survival under antibiotic pressure, which is a prominent pathway used by carbapenemase genes. The selective pressure for carbapenemase-producing organisms in the healthcare environment is potent, driven by pervasive use of broad-spectrum β-lactams. This enables prolonged colonization and greater opportunity for invasion and transmission as these bacteria can survive exposure to antimicrobials that would kill a susceptible strain. The close relationship between resistance and pathogenicity, including the ability of carbapenemase-producing Enterobacterales to persistently colonise mucosal surfaces (most notably the gastrointestinal tract) prior to causing bloodstream and respiratory infections (Nordmann et al., 2011).

Moreover, most carbapenemase genes are mapped to mobile genetic elements, such as transposons, integrons and plasmids, that frequently co-localize determinants of virulence. Such genetic linkage enables simultaneous transmission of resistance and pathogenic traits. Gene for adhesion, iron acquisition, toxin production and biofilm formation were represented in studies analyzing plasmids carrying bla_OXA-48, bla_NDM or bla_KPC. This may confer enhanced fitness and increased capacity to infect versus non-producing strains (Beig et al., 2023).

Biofilm formation is important virulence factor of carbapenemase-producing bacteria. Biofilms afford bacteria protection from the immune responses of the host and greatly decrease their susceptibility to antibiotics, leading to chronic and recurrent infections. Increased biofilm-forming capacity has been observed among carbapenemase-producing *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and isolates. The co-existence of carbapenemase genes and biofilm-associated determinants results in a synergistic effect that allows for increased persistence, as well as pathogenicity, especially in relation to cases such as VAP (ventilator-associated pneumonia) and CRBSI (catheter-related bloodstream infection) which are device-associated infections (Jomehzadeh et al., 2022; Paudel et al., 2024).

Besides inducing persistence, carbapenemase genes may alter the metabolic fitness and stress responses of bacteria. Notably, the expression of resistance genes may result in global regulatory changes influencing membrane permeability, efflux pump activation and energy metabolism. These adaptations might promote bacterial viability in hostile host environments, such as oxidative stress and nutrient limitation faced during infection (Poirel et al., 2011). While the expression of carbapenemase genes can have a metabolic cost, compensatory mutations often restore or even increase bacterial fitness permitting resistant strains to effectively outcompete susceptible populations (Andersson & Hughes, 2014).

It is the production of carbapenemase and immune evasion that will contribute towards pathogenicity. These modifications could change the way the host immune system interacts with and/or recognizes outer membrane proteins linked to carbapenem resistance, and/or capsule overproduction, as occurs with some of the carbapenemase producers, could evade phagocytosis or complement-mediated killing (or both) as well. This results in increasingly identification of hypervirulent lineages producing carbapenemase genes. Such a combination that is simultaneously highly resistance and highly virulent could be present in a single organism (Naas et al., 2016), which is a cause of fear.

Moreover, this correlation of carbapenemase genes with severity of illness has also been substantiated among clinical studies. Many clinical infections due to carbapenemase-producing organisms are associated with a consistently greater odds of morbidity and mortality, increased lengths of stay, and increased costs for health services compared to carbapenem-susceptible strains (Wong & van Duin, 2017). Despite these limited treatment options contributing to poor outcomes, both experimental and epidemiological data confirm that the innate virulence capacity of carbapenemase-producing strains also has a role to play. For instance, carbapenemase-producing strains of A. baumannii have exhibited increased cytotoxic activity and adhesion to epithelial cells in vitro compared with non-carbapenemase-producing isolates (Beig et al., 2023).

The role of carbapenemase genes in pathogenicity is best illustrated in nosocomial outbreaks. In patient populations completely susceptible to the drug, a single resistant strain rapidly sweeps through the population. Giving rise to an ideal breeding ground for the selection and spread of carbapenemase-producing Enterobacteriaceae in intensive care, with their high exposure to antibiotics, invasive devices or immunocompromised patients. The retention of such organisms as sink contaminants, in medical devices, or whatever, may also only further perpetuate onward transmission and disease. Typically, these outbreaks are clonal strains with a presence of resistance determinants and virulence factors, and consequently comprise a double burden (Nordmann & Poirel, 2014; Wahwah and AL-Hussaini, 2026).

The impacts of the genes conferring these carbapenemase phenotypes on virulence are surprisingly species and genetic background-dependent. While the majority of strains may be hypervirulent, acquisition of resistance may result in a temporary fitness cost and, so not all carbapenemase-producing strains are more virulent. But those costs are often minimized by evolution-adaptive behavior, allowing the resistant strains to persist and thrive. This process highlights the complex relationship between resistance and pathogenicity, and highlights the importance of species-specific research. (Andersson & Hughes, 2014).

## Conclusion

The classification of carbapenemase genes based on their biochemical mechanism, genetic organization and catalytic action. Examples include KPC which belongs to Class A serine β-lactamases, metallo-β-lactamases including NDM/ VIM/ IMP which belong to Class B, while OXA-type enzymes belong to class D, all of which present unique challenges on the global carbapenem resistance burden. Another critical element of this new paradigm for response to this major antimicrobial challenge is the rapid detection of new variants, allowing swift adjustment of diagnostics and development of targeted therapeutics. Carbapenemase genes is better known for its classic well-documented potential to confer antimicrobial resistance, yet it constitutes a multidimensional virulence determinant a far more complex clinical pathophysiologic process. Their significance for the pathogenesis of bacterial pathogens is particularly emphasized by their contribution to survival under antibiotic pressure, co-transfer of virulence determinants, biofilm formation and evasion of the immune system. This knowledge is essential for optimizing strategies to prevent hospital-acquired infection, for guiding clinical decision making, and for addressing the evolutionary threat of carbapenemase-producing organisms.

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