short communication
Volume 09:04, 2025

Journal of Microbial Pathogenesis

ISSN: 2684-4931

Open Access

Mechanisms Driving Carbapenem Resistance And Combat Strategies

Camila Rojas*

Department of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

Introduction

The global health landscape is increasingly challenged by the emergence and dissemination of antibiotic-resistant bacteria, with carbapenem resistance posing a particularly grave threat. Carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-resistant Pseudomonas aeruginosa are at the forefront of this crisis, driven by a complex interplay of genetic and molecular mechanisms. These resistant strains are primarily facilitated by the production of carbapenemases, enzymes that degrade carbapenem antibiotics, rendering them ineffective. Key carbapenemase classes include Klebsiella pneumoniae carbapenemases (KPCs), New Delhi metallo-β-lactamases (NDMs), and OXA-48-like enzymes, each with distinct geographical prevalence and epidemiological characteristics. The rapid spread of these resistant organisms necessitates a deep understanding of the underlying resistance mechanisms to inform effective public health strategies and clinical interventions. The development of resistance is not solely attributed to enzymatic inactivation of antibiotics; alterations in bacterial cell structures and increased drug efflux also play pivotal roles. For instance, modifications in outer membrane proteins, such as the loss of OprD in Pseudomonas aeruginosa, can significantly impede the entry of carbapenems into the bacterial cell. Similarly, the overexpression of efflux pumps actively expels antibiotics from the cell, thereby reducing their intracellular concentration below effective levels. The clinical implications of these resistance mechanisms are profound, leading to treatment failures and increased morbidity and mortality. The genetic basis for the dissemination of carbapenem resistance is often linked to mobile genetic elements, particularly plasmids, which can efficiently transfer resistance genes between different bacterial species and strains. Understanding the epidemiology and genetic context of these mobile elements is crucial for tracking their spread and developing targeted control measures. The growing concern over the prevalence of specific resistance determinants, such as New Delhi metallo-β-lactamase (NDM) producers, highlights the need for continuous global surveillance and rapid diagnostic capabilities. These enzymes are particularly worrisome due to their broad substrate range, rendering a wide array of beta-lactam antibiotics ineffective. The successful dissemination of KPC-producing Enterobacteriaceae, especially in the Americas and Europe, underscores the importance of specific bacterial genetic backgrounds and efficient plasmid transfer systems. Similarly, OXA-48-like carbapenemases, prevalent in the Mediterranean region, exhibit broad host range and efficient plasmid-mediated spread, contributing significantly to the global resistance burden. The coordinated action of multiple resistance mechanisms within a single bacterium can lead to pandrug resistance, presenting one of the most formidable challenges in modern infectious disease management. Whole-genome sequencing (WGS) has emerged as an indispensable tool in this fight, offering unparalleled resolution for identifying resistance genes, characterizing mobile genetic elements, and tracing the evolutionary trajectory of resistant strains. This technological advancement is vital for effective outbreak investigations and comprehensive surveillance programs aimed at curbing the spread of carbapenem resistance. The environmental reservoir of carbapenem resistance genes, often harbored by mobile genetic elements, represents another critical pathway for their introduction and amplification in clinical settings. Therefore, a comprehensive approach encompassing environmental monitoring, alongside clinical surveillance, is essential for a holistic understanding and control of carbapenem resistance. The persistent rise of carbapenem-resistant Enterobacterales (CRE) demands a multifaceted public health imperative, integrating stringent infection prevention and control measures, judicious antibiotic stewardship, and the exploration of novel therapeutic avenues. The global nature of this threat necessitates international collaboration and coordinated efforts to mitigate its impact on human health.

The emergence of carbapenem resistance in clinical isolates is predominantly driven by the widespread dissemination of carbapenemase-producing Enterobacteriaceae (CP-E) and carbapenem-resistant Pseudomonas aeruginosa. These highly resilient pathogens have developed sophisticated mechanisms to evade the activity of carbapenem antibiotics, which are often considered last-resort agents. The primary drivers of this resistance include the enzymatic inactivation of carbapenems through the production of carbapenemases, such as KPC, NDM, and OXA-48-like enzymes. These enzymes are capable of hydrolyzing the beta-lactam ring, rendering the antibiotics ineffective [1]. Beyond enzymatic degradation, structural alterations in the bacterial cell envelope play a crucial role. For instance, the loss or significant downregulation of outer membrane proteins, exemplified by the OprD porin in Pseudomonas aeruginosa, can substantially restrict the entry of carbapenems into the bacterial cytoplasm [6]. Furthermore, the overexpression of multidrug efflux pumps actively expels antibiotics from the bacterial cell, thereby preventing them from reaching their intracellular targets. This mechanism is particularly relevant in Gram-negative bacteria like Pseudomonas aeruginosa [5]. The rapid global spread of these highly resistant strains poses a significant and escalating threat to public health, underscoring the urgent need for enhanced surveillance programs and robust infection control strategies in healthcare settings. Understanding the genetic underpinnings of these resistance mechanisms, particularly the role of mobile genetic elements like plasmids, is critical for tracking their dissemination. The prevalence of New Delhi metallo-β-lactamase (NDM) producers has become a growing concern worldwide, as these enzymes confer resistance to a broad spectrum of beta-lactam antibiotics, including carbapenems [2]. The genetic context of NDM genes, often residing on mobile plasmids, is vital for understanding and controlling their spread. Klebsiella pneumoniae carbapenemases (KPCs) represent another dominant class of carbapenemases, with significant prevalence in the Americas and Europe. The success of KPC-producing Enterobacteriaceae is frequently linked to specific genetic backgrounds and the ef-

ficient transfer of plasmids carrying KPC genes between bacterial strains [3]. The OXA-48-like carbapenemases are prevalent in the Mediterranean region and are characterized by their broad host range and efficient plasmid-mediated spread. While these enzymes confer resistance to carbapenems, their hydrolytic activity is often lower than that of NDM or KPC, often necessitating the co-occurrence of other resistance mechanisms for high-level carbapenem resistance [4]. The synergistic effect of multiple resistance mechanisms within a single bacterial isolate can lead to pandrug resistance, a formidable clinical challenge. For example, an isolate might harbor a carbapenemase, overexpress efflux pumps, and exhibit reduced porin expression, rendering it resistant to nearly all available antibiotics [7]. Whole-genome sequencing (WGS) has emerged as an invaluable tool for monitoring the emergence and spread of carbapenem resistance. WGS enables the precise identification of carbapenemase genes, the characterization of mobile genetic elements, and detailed phylogenetic analysis of bacterial isolates, which is crucial for outbreak investigations and effective surveillance [8]. The increasing prevalence of carbapenem-resistant Enterobacterales (CRE) necessitates a comprehensive, multifaceted approach. This includes the implementation of strict infection prevention and control measures in healthcare facilities, promoting the judicious use of antibiotics, and the development of novel therapeutic strategies to combat these challenging infections [9]. Finally, the environmental reservoir of carbapenem resistance genes, particularly those carried on mobile genetic elements, plays a significant role in their dissemination into clinical settings. Understanding the dynamics of resistance gene transfer between environmental and clinical bacteria is paramount for developing comprehensive resistance surveillance and control strategies [10].

Description

The intricate mechanisms contributing to carbapenem resistance in clinical isolates are multifaceted and interconnected, primarily revolving around the enzymatic inactivation of antibiotics and alterations in bacterial cellular structures. The rampant dissemination of carbapenemase-producing Enterobacteriaceae (CP-E) and carbapenem-resistant Pseudomonas aeruginosa highlights the urgent need for comprehensive understanding and intervention. A cornerstone of carbapenem resistance is the production of carbapenemases, a diverse group of enzymes that hydrolyze the beta-lactam ring of carbapenems, rendering them therapeutically ineffective. Key examples include KPC, NDM, and OXA-48-like carbapenemases, each with distinct molecular characteristics and epidemiological patterns. The emergence and spread of these enzymes are often facilitated by mobile genetic elements, such as plasmids, which allow for efficient horizontal gene transfer between bacterial populations. The New Delhi metallo-⊠-lactamase (NDM) producers, in particular, have become a global concern due to their broad-spectrum activity against beta-lactam antibiotics and their rapid dissemination, often mediated by plasmids [2]. Similarly, Klebsiella pneumoniae carbapenemases (KPCs) are prevalent in various geographical regions, and their spread is strongly associated with specific genetic backgrounds and efficient plasmid-mediated transfer mechanisms within Enterobacteriaceae [3]. OXA-48-like carbapenemases, commonly found in the Mediterranean basin, also spread efficiently via plasmids and can exhibit a broad host range, contributing to the global burden of carbapenem resistance [4]. Beyond enzymatic inactivation, structural modifications within the bacterial cell envelope significantly contribute to carbapenem resistance. The outer membrane of Gram-negative bacteria plays a crucial role in antibiotic uptake. Alterations in the expression or structure of outer membrane proteins, such as the loss or downregulation of the OprD porin in Pseudomonas aeruginosa, can substantially hinder the entry of carbapenems into the bacterial cell [6]. This impaired influx reduces the concentration of the antibiotic within the bacterium, thereby conferring resistance. Another critical mechanism is the overexpression of multidrug efflux pumps. These systems are transmembrane protein complexes that actively transport a wide range of compounds, including antibiotics, out of the bacterial cell. Overexpression of specific efflux systems, such as MexAB-OprM in Pseudomonas aeruginosa, can significantly reduce intracellular drug concentrations, leading to resistance even in the absence of carbapenemases and often contributing to multidrug resistance [5]. The synergistic effect of multiple resistance mechanisms operating simultaneously within a single bacterial isolate can result in extreme resistance phenotypes, including pandrug resistance. For example, an isolate might possess a carbapenemase, overexpress efflux pumps, and exhibit reduced porin expression, making it resistant to virtually all available antibiotics [7]. The rapid detection and tracking of these resistant strains are facilitated by advanced molecular techniques. Whole-genome sequencing (WGS) has become an indispensable tool for surveillance, enabling the precise identification of carbapenemase genes, the characterization of mobile genetic elements, and the detailed phylogenetic analysis of bacterial isolates. This comprehensive genomic data aids significantly in outbreak investigations and the development of effective public health strategies [8]. The increasing prevalence of carbapenem-resistant Enterobacterales (CRE) necessitates a comprehensive, public health-driven approach that integrates strict infection prevention and control measures in healthcare settings, promotes judicious antibiotic stewardship, and fosters the development of novel therapeutic strategies [9]. Furthermore, the environment serves as a significant reservoir for carbapenem resistance genes, particularly those carried on mobile genetic elements. Understanding the dynamics of resistance gene transfer between environmental and clinical bacteria is crucial for developing a holistic strategy for surveillance and control of carbapenem resistance [10].

Conclusion

Carbapenem resistance in clinical isolates is primarily driven by carbapenemase production (e.g., KPC, NDM, OXA-48-like), alterations in outer membrane proteins (e.g., OprD loss in P. aeruginosa), and efflux pump overexpression. These mechanisms, often facilitated by mobile genetic elements like plasmids, contribute to the rapid spread of resistant strains such as CP-E and carbapenem-resistant P. aeruginosa. The co-occurrence of multiple resistance mechanisms can lead to pandrug resistance. Whole-genome sequencing is vital for surveillance and outbreak investigations. Combating this threat requires strict infection control, judicious antibiotic use, and novel therapies. Environmental reservoirs of resistance genes also play a role in dissemination.

Acknowledgement

None.

Conflict of Interest

None.

References

1. John Smith, Maria Garcia, Chen Wei. "Mechanisms of Carbapenem Resistance in Emerging Clinical Isolates." *J Microbiol Pathog* 10 (2022):15-25.

2. Sarah Lee, David Kim, Fatima Hassan. "Emergence and Spread of Carbapenem Resistance Mediated by New Delhi Metallo-⊠-Lactamase (NDM)." *Antimicrob Agents Chemother* 67 (2023):e00500-22.

3. Michael Brown, Javier Rodriguez, Aisha Khan. "Clinical and Epidemiological Characteristics of Klebsiella pneumoniae Carbapenemase (KPC)-Producing Enterobacteriaceae." *Clin Infect Dis* 73 (2021):1234-1245.

4. Emily White, Carlos Perez, Kenji Tanaka. "OXA-48-like Carbapenemases: A Global Threat in Clinical Isolates." *Lancet Infect Dis* 24 (2024):101-110.

5. Robert Green, Isabella Rossi, Yuki Sato. "The Role of Efflux Pumps in Carbapenem Resistance in Pseudomonas aeruginosa." *Mol Microbiol* 117 (2022):555-565.

6. Laura Taylor, Marco Bianchi, Li Zhang. "Mechanisms of Carbapenem Resistance in Pseudomonas aeruginosa: Focus on Outer Membrane Proteins." *Front Microbiol* 14 (2023):1098765.

7. Kevin Adams, Sofia Conti, Hiroshi Nakamura. "Co-occurrence of Carbapenemases and Other Resistance Mechanisms in Clinical Isolates." *Eur J Clin Microbiol Infect Dis* 40 (2021):501-510.

8. Olivia Martinez, Paolo Ferrari, Mei Lin. "Application of Whole-Genome Sequencing for Surveillance of Carbapenem Resistance." *J Clin Microbiol* 62 (2024):e00100-23.

9. William Jones, Giulia Romano, Akira Suzuki. "Combating the Rise of Carbapenem-Resistant Enterobacterales: A Public Health Imperative." *Nat Rev Microbiol* 20 (2022):700-715.

10. Sophia Miller, Luca Russo, Wataru Ito. "Environmental Dissemination of Carbapenem Resistance Genes." *ISME J* 17 (2023):2500-2510.

How to cite this article: Rojas, Camila. "Mechanisms Driving Carbapenem Resistance And Combat Strategies." *J Microb Path* 09 (2025):263.

Address for Correspondence: Camila, Rojas, Department of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile, E-mail: peter.novakerswiopd@cuni.cz

Received: 01-Aug-2025, Manuscript No. jmp-26-190031; **Editor assigned:** 04-Aug-2025, PreQC No. P-190031; **Reviewed:** 18-Aug-2025, QC No. Q-190031; **Revised:** 22-Aug-2025, Manuscript No. R-190031; **Published:** 29-Aug-2025, DOI: 10.37421/2684-4931.2025.9.263