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Carbapenem-Resistant Gram-Negative Bacteria: A Global Perspective on Emergence, Challenges, and Future Directions

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Perspective

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ABSTRACT

Carbapenem–resistant Gram–negative bacteria (CRGNB) have emerged as one of the most critical threats to global health, undermining the efficacy of last–line β–lactam antibiotics and contributing to increased morbidity, mortality, and healthcare costs. These organisms include carbapenem–resistant Enterobacterales (CRE), Pseudomonas aeruginosa (CRPA), and Acinetobacter baumannii (CRAB), all of which have demonstrated rapid geographic dissemination and complex resistance mechanisms. Resistance arises through enzymatic degradation via carbapenemases, efflux pump overexpression, porin mutations, and mobile genetic elements facilitating horizontal gene transfer. CRGNB infections are associated with limited treatment options, often requiring toxic or less effective drugs, and their prevalence highlights gaps in antimicrobial stewardship, diagnostics, infection control, and environmental reservoirs of resistance. This perspective explores the epidemiology, underlying mechanisms, clinical implications, diagnostic challenges, therapeutic strategies, and future research priorities. To address this growing threat, a coordinated global response integrating novel diagnostics, stewardship programs, innovative therapeutics, and environmental surveillance is essential.

Keywords

carbapenem–resistant, Gram–negative bacteria, antimicrobial resistance, carbapenemases, public health

INTRODUCTION

The rise of antimicrobial resistance (AMR) stands as one of the foremost challenges facing modern medicine. Among resistant organisms, carbapenem–resistant Gram–negative bacteria (CRGNB) have garnered particular concern. Carbapenems, including imipenem, meropenem, and ertapenem, have historically served as “last–line” agents for severe infections caused by multidrug–resistant (MDR) pathogens. Their broad spectrum of activity and relative resilience to many β–lactamases made them indispensable in clinical practice. However, extensive use — and often misuse — of these agents has driven the emergence of highly resistant Gram–negative strains that are capable of hydrolyzing carbapenems and evading therapeutic effects. This shift has ushered in a new era of difficult–to–treat infections with profound public health implications.

Global Epidemiology of CRGNB

The spread of CRGNB represents a truly global phenomenon. Carbapenem–resistant Enterobacterales (CRE), initially detected in select geographic regions, have disseminated worldwide and are now commonplace in both healthcare and community settings. Similarly, carbapenem–resistant Pseudomonas aeruginosa (CRPA) and Acinetobacter baumannii (CRAB) have been reported at high frequencies across continents.

In many regions, non–fermenting Gram–negative bacteria such as CRPA and CRAB exhibit even greater resistance rates than CRE, partly due to intrinsic mechanisms and adaptability to hospital environments. These pathogens are frequently isolated from intensive care units, surgical wards, and ventilated patients, where selective pressures from prolonged antibiotic exposure are highest.

Surveillance data indicate significant regional variation, with parts of Asia, Europe, and the Americas reporting increasing car-

bapenem resistance rates among critical pathogens. Enterobacterales producing carbapenemases such as KPC (Klebsiella pneumoniae carbapenemase), NDM (New Delhi metallo–β–lactamase), VIM (Verona integron–encoded metallo–β–lactamase), IMP, and OXA–48 variants have been documented globally, reflecting the mobility of resistance genes and international spread via travel, trade, and healthcare transfers.

These trends underscore the urgency of coordinated global surveillance and reporting systems that can accurately track the emergence and dissemination of CRGNB in human, animal, and environmental reservoirs.

Mechanisms of Carbapenem Resistance

Resistance to carbapenems in Gram–negative bacteria is multifactorial, often involving combinations of mechanisms that synergize to confer high–level resistance.

Carbapenemase Production

The most well–recognized mechanism of resistance is the enzymatic hydrolysis of carbapenems by carbapenemases — β–lactamase enzymes capable of degrading carbapenem antibiotics. Carbapenemases are classified into Ambler classes A, B, and D, with important examples including KPC (class A), NDM and VIM (class B metallo–β–lactamases), and OXA–48 and its variants (class D). These enzymes often reside on mobile genetic elements such as plasmids and transposons, facilitating horizontal gene transfer across species and genera.

Non–enzymatic Mechanisms

In addition to carbapenemases, resistance may arise through alterations in membrane permeability — for instance, loss or modification of porin channels that reduce drug entry — and overexpression of efflux pumps, which expel antibiotics from the bacterial cell. In Pseudomonas aeruginosa, upregulated efflux systems and porin loss frequently contribute to carbapenem resistance even in the absence of carbapenemases.

Co–Resistance and Genetic Plasticity

Resistance genes are often co–located with determinants conferring resistance to other antibiotic classes, such as aminoglycosides and fluoroquinolones. This co–resistance complicates treatment and narrows therapeutic options. The genetic plasticity of Gram–negative bacteria enhances their ability to adapt and accumulate resistance determinants via horizontal gene transfer and mutation.

Clinical Implications and Outcomes

Infections caused by CRGNB are associated with significantly worse clinical outcomes compared with susceptible organisms. Patients with CRGNB infections have higher rates of treatment failure, prolonged hospital stays, increased healthcare costs, and elevated mortality rates. This is partly due to delays in initiating effective therapy, as routine antibiotics often lack activity against resistant strains.

Moreover, colonization with CRGNB — even in the absence of active infection — poses a risk for subsequent invasive disease, particularly in vulnerable populations such as critically ill patients, neonates, and immunocompromised individuals. The presence of resistance also contributes to outbreaks within healthcare settings, challenging infection control practices and resource allocation.

Diagnostics: Challenges and Innovations

Accurate and rapid detection of carbapenem resistance is essential for effective clinical management and infection control. Traditional microbiological methods, while specific, are often slow and may delay critical treatment decisions. Contemporary diagnostic approaches include rapid phenotypic assays, molecular methods such as PCR for carbapenemase genes, and automated systems that can detect resistance markers with greater speed and precision.

Despite advances, diagnostic capacity remains uneven globally. Many resource–limited settings lack access to rapid molecular diagnostics, leading to reliance on slower methods and under–reporting of resistant cases. Enhanced access to and integration of rapid diagnostics — including point–of–care solutions — will be crucial for early detection and containment of CRGNB.

Therapeutic Strategies and Stewardship

The therapeutic landscape for CRGNB infections has historically been bleak, with few effective agents available. Older antibiotics such as polymyxins (e.g., colistin), tigecycline, and fosfomycin have been repurposed despite concerns about toxicity and variable efficacy. Combination therapy — using multiple agents simultaneously — has been employed to enhance activity and prevent further resistance.

Recent years have seen the development and approval of novel β–lactam/β–lactamase inhibitor combinations (e.g., ceftazidime/avibactam, meropenem/vaborbactam) and siderophore cephalosporins such as cefiderocol, offering promising activity against specific resistant phenotypes. However, these agents must be used judiciously to prevent the rapid emergence of resistance.

Antimicrobial stewardship principles — including appropriate empirical therapy, dose optimization, de–escalation based on susceptibility results, and minimization of unnecessary antibiotic use — are fundamental to preserving the efficacy of available therapies and slowing the spread of CRGNB.

Prevention, Control, and One Health Approaches

Infection prevention and control (IPC) strategies within healthcare facilities — such as hand hygiene, environmental cleaning, screening of high–risk patients, and cohorting of colonized individuals — remain cornerstones of containment efforts. Robust surveillance systems capable of real–time monitoring and reporting are equally important to inform IPC and stewardship interventions.

Environmental reservoirs, including wastewater and agricultural ecosystems, have been implicated in the dissemination of carbapenem resistance. Antibiotic residues and resistant bacteria in water matrices facilitate the selection and spread of resistance determinants beyond clinical settings. Addressing these environmental dimensions requires One Health approaches that integrate human, animal, and environmental health sectors to mitigate resistance transmission pathways.

Future Directions and Research Priorities

Looking forward, several key priorities emerge:

Enhanced global surveillance networks to capture resistance trends and inform policy.

Investment in rapid, affordable diagnostics adaptable to low–resource settings.

Development of new antimicrobial classes and non–traditional therapies, including bacteriophages, antimicrobial peptides, and host–directed strategies.

Strengthening antimicrobial stewardship at all levels of healthcare.

Integrating environmental and agricultural reservoirs into resistance monitoring frameworks.

Interdisciplinary collaboration — spanning microbiology, clinical medicine, public health, veterinary science, and environmental science — will be essential to devise sustainable solutions to the crisis of carbapenem resistance.

CONCLUSION

Carbapenem–resistant Gram–negative bacteria represent a formidable and evolving threat to global health. Their capacity to evade last–line antibiotics, disseminate rapidly via mobile genetic elements, and persist in diverse environments underscores the complexity of the challenge. Addressing this crisis requires a multi–faceted response that includes improved diagnostics, stewardship, innovative therapeutics, robust surveillance, and integrated One Health strategies. Only through coordinated, sustained action can the medical community hope to preserve the efficacy of existing treatments, curb the spread of resistance, and safeguard public health for future generations.

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