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Carbapenem Resistance In Gram Negative Bacterial Infections – A Review On Risk Factors

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ABSTRACT

This review provides a comprehensive overview of carbapenem resistance in gram-negative bacterial infections, emphasizing the critical role of carbapenem antibiotics in treating severe infections caused by resistant pathogens such as Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacteriaceae. It details the mechanism of action of carbapenems, which involves penetrating bacterial cell walls and inhibiting penicillin-binding proteins, leading to cell lysis. The review also outlines various mechanisms of resistance, including decreased permeability, active efflux pumps, target mutation, and hydrolysis by carbapenemases. Furthermore, it identifies significant risk factors for carbapenem-resistant gram-negative bacterial (CRGNB) infections, such as prolonged hospitalization, prior antibiotic use, and invasive procedures. The limited treatment options for CRGNB are discussed, highlighting the emergence of new antibiotics and the importance of antimicrobial stewardship in managing these infections. Overall, the review underscores the urgent need for effective prevention and control measures to combat the rising threat of carbapenem resistance.

Keywords: Carbapenem resistant gram-negative bacteria, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacteriaceae

INTRODUCTION

Carbapenems, bactericidal β-lactam antimicrobials, have been shown to effectively treat severe infections caused by ESBL-producing bacteria. Examples of carbapenem antibiotics are meropenem, imipenem, doripenem, ertapenem, panipenem and biapenem. (1)

Carbapenem antibiotics are the first line of treatment for infections caused by the most resistant bacteria, including Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacteriaceae (Klebsiella pneumonia, Escherichia coli, Enterobacter spp., Serratia spp., Proteus spp.), Enterococcus faecium, Streptococcus pneumoniae, Haemophilus influenzae, Shigella spp., and Mycobacterium tuberculosis. (2) Compared to penicillins, cephalosporins, and combinations of β-lactam/β-lactamase inhibitors, carbapenems exhibit a more comprehensive antibacterial range in vitro. (3)

Carbapenems starts their action by entering through the porins that is the outer membrane proteins of gram-negative bacteria. Penicillin binding proteins are present in the bacterial cell wall, it catalyses the synthesis of peptidoglycan in bacterial cell wall. Once carbapenems cross the periplasmic space, they permanently acylates the penicillin binding proteins which leads to inhibition of peptide cross linking and inhibition of other peptide reaction takes place. Carbapenems has the ability to bind multiple penicillin binding proteins. Facilitation of formation of cell wall and autolysis takes place at the same time, eventually leads to weakening of peptidoglycan due to the autolysis caused by the continuous inhibition of penicillin binding proteins. All these leads to the burst of cell wall caused by osmotic pressure. (4)

Mechanisms lead to carbapenem resistance includes the decreased permeability to the antibiotics that is the drug is not able to enter through the porins of bacteria and reach their site of action e.g. *P. aeruginosa.* Another mechanism of resistance is the active efflux pump, removing the drug from site of action before it can act e.g. *P. aeruginosa,* E. coli *and Neisseria gonorrhoeae.* Mutation of antibiotic target structure also leads to antibiotic resistance. Another major mechanism of antibiotic resistance is the hydrolysis of the antibiotic molecule and inactivate its antimicrobial ability. The enzymes that facilitate the hydrolysis are known as carbapenemases. They are classified as class A, B, C and D. (5)

RISK FACTORS

Understanding the risk factors associated with CRGNB infections is crucial for implementing effective prevention and control measures. This review aims to explore the various risk factors contributing to the emergence and spread of CRGNB, focusing on patient-related factors, healthcare-related factors, and environmental factors. By identifying these risk factors, healthcare professionals can implement targeted interventions to mitigate the burden of CRGNB infections. *Tulay Orhan Kuloglu et al.* conducted a retrospective study on risk factors and mortality rates of carbapenem-resistant gram-negative bacterial infections in intensive care units in Erciyes University Hospital Kayseri, Turkey between January 2017 and December 2021. Case group consisted of the patients who had CRGNB infection 48–72 h after ICU admission and control group comprised of the patients who were not infected by CRGNB infection. During the active follow-up period, 1449 patients (8.97%) were observed, 1171 of whom were included in this study. 14 (70.00%) patients who had CRGNB colonization upon admission developed CRGNB infection; 162 (78.26%) were colonized during hospitalization and 515 (54.56%) were not infected. There was no significant difference in age, gender, or comorbidity. Risk factors identified from the study were Prolonged hospitalization, the time from intensive care unit admission to the development of infection, the presence of CRGNB colonization at

admission, transfer from other hospitals, previous antibiotic use, enteral nutrition, transfusion, hemodialysis, mechanical ventilation, tracheostomy, reintubation, central venous catheter, arterial catheterization, chest tube, total parenteral nutrition, nasogastric tube use, and bronchoscopy procedures were significantly associated ($P < 0.05$).(6)

In another study *Priyanka Gupta et al.* conducted a retrospective study on Risk factors associated with carbapenem-resistant Klebsiella pneumoniae bloodstream infections in a tertiary-care hospital in India. The study was conducted at Medanta–The Medicity, a tertiary-care hospital in North India between the time period August 2014 and July 2015. A total number of 111 patients who were having *K. pneumoniae* blood stream infection was admitted to the study. Out of 111 patients 85 (77%) had CRKP. Prior carbapenem usage, the presence of a Foley catheter, and admission to a gastroenterology service all increased the likelihood of CRKP BSI. In-hospital mortality was greater among CRKP patients, although it did not reach statistical significance in multivariate analysis. (7)

There is only little evidence for geographical influence for causing CRGNB, *Marie-Hélène Nicolas-Chanoine et al.* conducted a prospective study on Risk factors for carbapenem-resistant Enterobacteriaceae infections: a French case-control-control study and found out that several factors, including gender, travel history, hospitalization, recent infections, and antibiotic use, are associated with the risk of developing Carbapenem-Resistant Enterobacteriaceae (CRE). Among CRE cases, those with Carbapenem-Producing Enterobacteriaceae (CPE) were more likely to have travelled or been hospitalized abroad. (8)

There are only limited treatment options available for CRGNB. Colistin and tigecycline have been the primary treatments for infections caused by carbapenem-resistant pathogens, but their effectiveness is uncertain, even when combined with other drugs. Recently, several new antibiotics have been approved or are in development for these infections. They include ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, plazomicin, eravacycline, and cefiderocol. Fosfomycin has also been reformulated for intravenous use. Early data suggest that these newer antibiotics may be more effective than older treatments for carbapenem-resistant infections. As more treatment options become available, it's essential to use them wisely through antimicrobial stewardship to ensure the best outcomes. (9)

CONCLUSION

Carbapenem resistance in gram-negative bacterial infections poses a significant challenge to public health, necessitating urgent attention from healthcare professionals and researchers alike. The data reviewed highlights the critical role of carbapenems as a first-line treatment for severe infections caused by resistant bacteria, while also detailing the complex mechanisms that contribute to resistance. Identifying and understanding the risk factors associated with carbapenem-resistant gram-negative bacteria (CRGNB) is essential for implementing effective prevention and control strategies. As the landscape of antibiotic resistance continues to evolve, the development of new therapeutic options and the prudent use of existing antibiotics through antimicrobial stewardship are vital to ensure successful treatment outcomes. Collaborative efforts

among healthcare providers, researchers, and policymakers are crucial to mitigate the impact of carbapenem resistance and safeguard the efficacy of these important antibiotics for future generations.

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CONFLICT OF INTEREST

There is no conflict of interest.

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