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Genetic Insights Into Carbapenem Resistance In Klebsiella Pneumoniae: A Brief Review

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Abstract: The increasing incidence of antibiotic-resistant bacteria, particularly carbapenem-resistant Klebsiella pneumoniae (CR Kpn), poses significant public health threats due to limited treatment options and high morbidity. This review identified prevalent resistance genes such as blaCTXM-1, blaSHV, and blaNDM-1 in CR Kpn isolates, highlighting deficiencies in outer membrane proteins crucial for carbapenem uptake. A rapid recombinase-aided amplification (RAA) assay for detecting blaKPC genes can be used to manage infections especially to prevent outbreaks. Genomic tools such as Molecular typing methods such as multilocus sequence typing (MLST) and whole-genome sequencing (WGS) are essential for epidemiological surveillance and outbreak investigations. Animal models have been used to understand Rapid changes in CR Kpn gene expression within the intestine as an adaptive strategy to survive and create gut colonization. The prevalence of virulence genes on plasmids further facilitates the spread of resistance traits.

Promising alternative treatment options included ceftazidime-avibactam and aztreonam-avibactam, which have shown potential against carbapenem-resistant bacteria. Fosfomycin, another viable treatment option, inhibits bacterial growth by disrupting replication and has been noted for its efficacy and low toxicity. Tigecycline, known for its high sensitivity against carbapenem-resistant Enterobacteriaceae, and cefiderocol, a siderophore cephalosporin antibiotic, demonstrated strong activity against CR Kpn. Exploring alternative testing approaches, including the combination of multiple methods, automated systems, genotypic methods, new susceptibility tests, Broth dilution methods in different concentrations of antibiotics, and customized testing protocols, can enhance the accuracy of antibiotic susceptibility determination in CR Kpn. This review underscores the urgent need for integrating genetic insights with novel therapeutic strategies to combat CR Kpn, ultimately aiming to improve patient outcomes and public health. Understanding the molecular mechanisms of carbapenem resistance and exploring alternative treatment options are crucial for managing this formidable pathogen effectively.

Index Terms **-** Antibiotic resistance, Carbapenem resistance, Resistance gene,*Klebsiella pneumoniae* (CR-Kpn), Carbapenems.

I. INTRODUCTION

The increasing incidence of bacterial resistance to antibiotics is emerging as a critical issue for global public health [1]. The increase in carbapenem-resistant gram-negative bacteria, including Klebsiella pneumoniae (Kpn), is particularly concerning because it poses a significant threat to health systems worldwide [2]. K. pneumoniae, a member of the Enterobacteriaceae, is commonly found in various environments, such as water, soil, food, and the intestines of animals and humans. This bacterium can act as an opportunistic pathogen, causing a range of infections, including urinary tract infections, skin infections, pneumonia, and sepsis. These conditions often result in high morbidity and mortality rates due to bacterial virulence factors and significant antibiotic resistance [3].

One of the most dangerous aspects of Klebsiella pneumoniae is its ability to produce carbapenemases, enzymes that confer resistance to a broad range of antibiotics, including carbapenems, which are typically used as a last resort antibiotic [4]. The presence of these enzymes poses significant challenges in healthcare settings, where infections caused by carbapenemase-producing strains often result in high mortality rates, severe outbreaks, and complicated treatment options. This resistance makes Klebsiella pneumoniae especially dangerous and difficult to manage [5]. The combined impact of these factors underscores the urgent need for effective strategies to combat the spread and impact of this formidable pathogen.

Understanding the molecular mechanisms underlying carbapenem resistance in K. pneumoniae is crucial for developing effective diagnostic, therapeutic, and preventive strategies [6]. This review aims to provide a concise overview of the genetic basis of carbapenem resistance in K. pneumoniae, highlighting key resistance mechanisms, the epidemiology of carbapenem resistance, and potential approaches to combat this formidable threat.

II. GENETIC BASIS OF CARBAPENEM RESISTANCE

Genetic studies are pivotal in unraveling the mechanisms of antibiotic resistance, yet the role of bacterial metabolism in this context has historically been overlooked. Genetic investigations are instrumental in bridging this gap by pinpointing mutations and variations in metabolic genes that underpin resistance mechanisms [7][8]. Moreover, molecular-based studies, including genomic sequencing, have elucidated diverse pathways and mutations involved in resistance evolution. This approach reveals adaptive strategies beyond traditional mechanisms, offering evolutionary and mechanistic insights crucial for developing new therapeutic strategies [8][9]. Understanding the metabolic contributions to antibiotic resistance through genetic studies opens new avenues for combating drug-resistant infections. These findings will facilitate the development of targeted therapies that exploit metabolic vulnerabilities in resistant bacteria, potentially circumventing traditional resistance mechanisms. The integration of genetics into resistance mechanisms related to metabolism advances strategies for effective antibiotic stewardship and the management of drug-resistant bacterial infections in clinical settings, thereby improving patient outcomes [10].

Carbapenem-resistant Klebsiella pneumoniae (CRKP) is a serious public health issue due to its rapid spread, high mortality rates, and limited treatment options. Carbapenem antibiotics are often the last line of defense against severe bacterial infections, so resistance to these drugs leaves few alternatives left for treatment. The widespread dissemination of CRKP, is coupled with the high death rates associated with infections [11].

Indrajith et al. (2021) conducted a detailed analysis of CRKP isolates from central Tamil Nadu, India, highlighting alarming rates of multidrug resistance (MDR). They identified prevalent resistance genes such as blaCTXM-1, blaSHV, and blaNDM-1, as well as deficiencies in outer membrane proteins crucial for carbapenem uptake. Molecular typing elucidated the genetic relationships among MDR strains, emphasizing complex resistance mechanisms and the critical need for robust surveillance and control strategies in healthcare settings [12].

A study of carbapenem-resistant Klebsiella pneumoniae has focused on the pivotal role of blaKPC genes in antibiotic resistance. These genes are responsible for the production of carbapenemase enzymes that degrade carbapenem antibiotics, thus negating their effectiveness. The ST11 strain, which carries the blaKPC-2 gene, emerged as the most common strain in the analyzed genomes. This strain is particularly concerning due to its extensive distribution and its association with severe infections. Its multidrug-resistant nature complicates treatment efforts and results in increased morbidity and mortality rates. To address this issue, researchers have developed a rapid recombinase -aided amplification (RAA) assay for detecting blaKPC genes. This assay stands out for its high sensitivity and specificity, allowing for the swift identification of blaKPC-positive strains, which is critical for effective infection control and clinical management. The ability to quickly detect these resistant strains is essential for managing infections and preventing outbreaks in healthcare environments [13].

The blaOXA-48-like and blaNDM-1/5 resistance genes are critical for carbapenem resistance in Klebsiella pneumoniae. blaOXA-48-like genes encode enzymes that hydrolyze carbapenems and other beta-lactam antibiotics, while blaNDM-1/5 genes encode New Delhi metallo-β-lactamases, which also degrade a wide range of beta-lactams. These genes are often carried on IncF and Col group plasmids, which facilitate their rapid spread among bacteria through horizontal gene transfer. This widespread dissemination complicates treatment options and highlights the need for effective surveillance and control strategies to manage carbapenem-resistant infections [11][14]. These genes encode enzymes that hydrolyze carbapenems, significantly limiting therapeutic options and necessitating vigilant surveillance to curb their dissemination.

Genomic surveillance of Klebsiella pneumoniae in India revealed that antimicrobial resistance (AMR) genes are different between environmental and clinical strains. Using tools such as ResFinder, Virulence Factor Database, Plasmid Finder, and CSI phylogeny, genomic data from 153 strains were analyzed. The predominant serotypes included K51 and K64, with ST231 being prevalent among the K51 isolates. Virulence genes such as rmpA, magA, entB, ybtS, iutA, and allS were highly present, notably in the ST231-KL51 and ST23-KL1 isolates. Over 97% of the clinical strains carried yersiniabactin and aerobactin genes. The ESBL and carbapenemase-producing isolates harbored the genes ybtS, iutA, rmpA, and magA, which contribute to antibiotic resistance. The IncF plasmids facilitated resistance gene transfer. Phylogenetic analysis distinguished environmental from clinical strains by sequence type (ST) and serotype, stressing the need for genomic surveillance to understand K. pneumoniae evolution, AMR, and virulence, and to guide treatment strategies in India [15].Molecular typing methods such as multilocus sequence typing (MLST) and whole-genome sequencing (WGS) are essential for epidemiological surveillance and outbreak investigations [16]. Pulsed-field gel electrophoresis (PFGE) is well- known for creating unique DNA banding patterns through the digestion of whole genomic DNA with restriction enzymes, and has traditionally been crucial for identifying clonal clusters during outbreaks, indicating potential common sources or transmission routes. MLST focuses on specific housekeeping genes to assign sequence types (STs), providing insights into the population structure and transmission mechanisms of Klebsiella strains, and aiding in epidemiological tracking. However, WGS excels by sequencing the entire genome of bacterial isolates, offering detailed genetic information such as single-nucleotide polymorphisms (SNPs) and resistance genes such as blaKPC, blaNDM and blaOXA [17].Using an in vivo model in which mice were treated with an anti-CD3 antibody to simulate immune activation, researchers investigated how carbapenem-resistant Klebsiella pneumoniae (CR-Kp) adapts at the transcriptional level within the intestine. They observed rapid changes in CR-Kp gene expression just 6 hours after treatment, which correlated with increased oxidative species and amino acids in the intestine. Surprisingly, deleting genes encoding proteins with a domain of unknown function (DUF) 1471 did not affect the fitness of CR-Kp during immune activation, suggesting a nuanced role for these proteins. Transcription analysis highlighted the global regulator cAMP receptor protein (CRP) as pivotal in orchestrating CR-Kp transcriptional responses, which are crucial for CR-Kp survival and gut colonization. This study provide a foundation for understanding CR-Kp's adaptive strategies and potential targets for combating antibiotic resistance [18]. Plasmids carrying virulence genes were prevalent among the CP-Kpn isolates. Plasmids are mobile genetic elements that can be transferred between bacteria, spreading both resistance and virulence traits. This genetic mobility means that the CP-Kpn strains can rapidly adapt and enhance their pathogenic capabilities [19][20]. The alignment of mobile genetic elements (MGEs) with the phylogenetic tree indicated that these elements play a significant role in the transmission of resistance and virulence traits. This correlation suggests that the spread of MGEs is a major driver of the clonal expansion and dissemination of these dangerous strains. The combination of multidrug resistance and increased virulence in CP-Kpn strains makes infections particularly challenging to treat and control. The high rate of clonal transmission, as revealed by the SNP analysis, highlights the importance of stringent infection control measures to prevent the spread of these strains in healthcare settings [21].The fosAKP gene was found to be highly conserved in certain sequence types of carbapenem-resistant Klebsiella pneumoniae, such as CC258/11, ST15, ST307, and ST101, showing 100% sequence identity within each sequence type or clonal complex. This high level of conservation means that the genetic sequence of fosAKP is identical among all the isolates within these specific groups. Because of this uniformity, the fosAKP gene can serve as a reliable genetic marker for accurately identifying these particular types of K. pneumoniae. This makes fosAKP sequencing a useful tool for epidemiological studies, as it allows for precise classification and tracking of these strains in clinical and public health settings. Hence, fosAKP sequencing is a practical alternative to traditional typing methods such as multilocus sequence typing (MLST), offering a simpler, faster, and more cost-effective approach for the epidemiological typing of CR-KPN [22].

A study by de Moraes et al., (2022) identified key carbapenemase genes in Klebsiella pneumoniae that contribute to its resistance to carbapenems. The predominant gene detected was blaKPC (Klebsiella pneumoniae carbapenemase), which was present in 90.4% of the resistant samples. This gene encodes an enzyme that hydrolyzes carbapenems, rendering them ineffective. Additionally, the blaNDM (New Delhi metallo-β-lactamase) gene was identified. This gene also encodes an enzyme that degrades beta-lactam antibiotics, contributing to resistance. These findings highlight the critical role of blaKPC and blaNDM in the molecular mechanisms underlying carbapenem resistance in Klebsiella pneumoniae [23].

Tian et al., (2023) investigated the prevalence, risk factors, and molecular epidemiology characteristics of carbapenem-resistant Enterobacteriaceae (CRE) fecal carriage among patients with liver disease. Klebsiella pneumoniae (KPN) and Escherichia coli were the main strains isolated, with KPN dominating the molecular epidemiology, particularly ST11. Additionally, most CRE strains exhibited high resistance to antimicrobials, except for polymyxin B and tigecycline, with blaKPC-2 being the major carbapenemase gene detected. These findings underscore the importance of regular CRE screening for hospitalized patients with liver disease to limit the spread of CRE strains and mitigate the associated risks, particularly in patients with ACLF and a recent history of pulmonary infections or antibiotic usage [24].

THERAPEUTIC OPTIONS

It is essential to explore alternative treatment options for carbapenem-resistant bacteria (CRB) due to the limited effectiveness of traditional antibiotics [25]. Ceftazidime–avibactam (CZA) and aztreonam–avibactam (AZA) have emerged as promising choices. In a study conducted by Yu et al in 2021, it was discovered that CZA has higher resistance rates against carbapenem-resistant Escherichia coli (CR-Eco) compared to carbapenem-resistant Klebsiella pneumoniae (CR-Kpn) and Pseudomonas aeruginosa (CR-Pae). However, the study found that increasing avibactam concentrations improved the susceptibility of both combinations to CRB, especially CR-Eco and CR-Kpn. The resistance rates of CZA against CR-Eco, CR-Kpn, and CR-Pae were 75.0%, 12.6%, and 18.5%, respectively. The MIC90 values of AZA against CR-Eco, CR-Kpn, and CR-Pae were 2/4, 1/4, and 64/4 mg/L, respectively. Furthermore, the study revealed that among the CZA-resistant CROs, 100% of CR-Eco, 60% of CR-Kpn, and 8.3% of CR-Pae isolates harbored metallo-β-lactamase genes, suggesting the importance of optimized dosing strategies for treating carbapenem-resistant infections. This approach can improve therapeutic outcomes effectively [26].

Another approach involves Fosfomycin, a phosphonic antibiotic that offers a viable treatment option for carbapenem-resistant Klebsiella pneumoniae (CRKP). Fosfomycin inhibiting N-acetylglucosamine enolpyruvyl transferase (murA), disrupts replication and prevents bacterial growth. Clinical studies underscore its efficacy and low toxicity, making it a valuable therapeutic option. Since the emergence of resistance is a natural phenomenon, continuous antibiotic sensitivity surveillance and alternative strategies are crucial for combating CRKP strains and their spread [27].

An important alternative is tigecycline which exhibits high sensitivity against carbapenem-resistant Enterobacteriaceae (CRE), making it valuable when other antibiotics fail [28]. Levofloxacin is another drug effective against Enterobacter species (Enterobacter spp.), and inhibits bacterial DNA replication. Clinicians can consider these antibiotics for managing infections caused by resistant bacteria, aligning treatment with local resistance patterns to preserve efficacy and minimize resistance risks [29]. Cefiderocol which is a novel siderophore cephalosporin antibiotic also shows promising activity against carbapenem-resistant Klebsiella pneumoniae (CR-KP) as well as carbapenem-resistant Pseudomonas aeruginosa (CR-PA). Its siderophore mechanism enhances bacterial cell penetration, and helps to improve the action of the drug [30].

A combination of meropenem combined with ciprofloxacin demonstrated limited effectiveness across tested isolates. However, meropenem combined with colistin combination showed synergistic effects in a subset of patients, highlighting its potential utility against certain carbapenem-resistant Klebsiella pneumoniae isolates. The susceptibility to cefiderocol was notably high, indicating its relevance in managing multidrug-resistant pathogens [31]. Carbapenem resistance represents one of the biggest challenges for clinicians managing severe infections. The best way to treat carbapenem-resistant infections has not been firmly established yet. New treatments have been approved recently or are in late-stage development and have shown promising results. However, there are still some concerns about these new antibiotics, including gaps in their effectiveness, especially against MBL-producing bacteria, and limited real-world data about how well they work [32].

CONCLUSION

Carbapenem resistance in Klebsiella pneumoniae poses a critical challenge in healthcare settings worldwide, demanding necessitating urgent action to reduce its impact. Genetic studies have revealed diverse mechanisms of resistance, emphasizing the pivotal role of carbapenemases and mobile genetic elements in dissemination. Proper monitoring strategies and Effective management could help to identify resistance patterns and guide treatment decisions. The development of novel antibiotics and optimized dosing strategies, coupled with stringent infection control measures, offers hope for managing CR-Kpn infections. Continued research into bacterial genetics and metabolism will be crucial for understanding evolving resistance mechanisms and ensuring effective therapeutic interventions against this persistent public health threat.

.Abbreviationsand Acronyms

1. Kpn - Klebsiella pneumoniae
2. CR-Kpn - Carbapenem-resistant Klebsiella pneumoniae
3. CRKP - Carbapenem-resistant Klebsiella pneumoniae
4. BSI - Bloodstream Infection
5. ICU - Intensive Care Unit
6. CRE - Carbapenem-resistant Enterobacteriaceae
7. CR-Eco - Carbapenem-resistant Escherichia
8. CR-Pae - Carbapenem-resistant Pseudomonas aeruginosa
9. ST - Sequence Type
10. RAA - Recombinase aided Amplification
11. CRB - carbapenem-resistant bacteria
12. MDR - Multidrug resistance
13. CZA - Ceftazidime-Avibactam
14. AZA - Aztreonam-Avibactam
15. MLST - Multilocus Sequence Typing
16. WGS - Whole-Genome Sequencing
17. PFGE - Pulsed-Field Gel Electrophoresis
18. MGEs - Mobile Genetic Elements
19. AMR - Antimicrobial resistance
20. BMD - Broth Microdilution
21. DUF - Domain of Unknown Function
22. CRP - cAMP-Receptor Protein

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