Emergence of High-Level Antibiotic Resistance in *Klebsiella pneumoniae*: A Narrative Review

ABSTRACT

In an era marked by remarkable advancements in medicine, the persistent emergence of high-level antibiotic resistance in *Klebsiella pneumoniae* poses a critical threat to public health globally. As the worldwide spread of extensively drug-resistant (XDR) and pan-drug-resistant (PDR) *K. pneumoniae* strains continues to grow, a significant shift in how we approach treatment is on the horizon. The complex interaction of genetic factors, which encompasses a wide range of beta-lactamases, aminoglycoside-modifying enzymes, and chromosomal mutations, creates a dynamic resistance mechanism that counters the effects of antibiotics. These intricate adaptations, arising from both gene transfers facilitated by plasmids and changes in the genome itself, present a challenging obstacle to our efforts in managing antimicrobial effectiveness. *Klebsiella* infections come back stronger armed with molecular tactics that challenge healthcare systems, prolong hospital stays, and increase mortality. Beyond healthcare settings, the economic and social dimensions grow as resources are redirected, intensifying the impact on vulnerable groups. This review delves into the intricate mechanisms behind the high-level antibiotic resistance in *K. pneumoniae*, examining its epidemiological, molecular, and clinical facets. Highlighting the necessity for coordinated research, medical protocols, and policies, the review underscores the importance of judicious antibiotic utilization, drug innovation, and rigorous infection management.

Keywords: *Klebsiella pneumoniae, Antibiotic resistance, extensively drug-resistant (XDR), Pandrug-resistant (PDR), Beta-lactamases, Aminoglycoside-modifying enzymes.*

1. INTRODUCTION

Over the decades, antibiotics have revolutionized the practice of medicine, ushering in an era where once-deadly bacterial infections could be tamed (Sagar et al.,2019). However, this triumph has not been without consequences. The widespread use and misuse of antibiotics have exerted immense selection pressure on bacterial populations, driving the evolution of resistance traits. *K. pneumoniae*, a member of the Enterobacteriaceae family, has been at the forefront of this resistance arms race, steadily acquiring genetic determinants that render it impervious to our most potent antibiotics (Capita & Alonso (2013).

Klebsiella pneumoniae plays a significant role in the challenge of antimicrobial resistance, emerging as a formidable adversary. This bacterium is known for its ability to adapt and develop resistance to a wide range of antibiotics, making it difficult to treat infections effectively. As *K. pneumoniae* continues to elude standard treatments, it emphasizes the pressing need for innovative strategies to combat the growing threat of antibiotic resistance. This requires coordinated efforts from the scientific community and healthcare professionals(Li *et al.,* 2023; Navon-Venezia*et al*.,2017).

The rapid and substantial global increase in multi-drug-resistant *Klebsiella pneumoniae* (MDRKP) represents an urgent and pressing risk to public health in recent decades. This surge in prevalence underscores the critical need for immediate attention and intervention strategies to effectively address this escalating threat, which poses significant challenges to healthcare systems worldwide (Sharma *et al.,* 2023, WHO 2015).

Klebsiella pneumoniae has become notorious for its complex and diverse mechanisms of antibiotic resistance, which contribute to its ability to evade the effects of various antimicrobial agents. High-level antibiotic resistance in *K. pneumoniae* is primarily driven by the acquisition of genes encoding enzymes that can inactivate or modify antibiotics. Extended-spectrum β-lactamases (ESBLs), the key contributors to resistance against broad-spectrum β-lactam antibiotics, including cephalosporins and penicillins (Paterson & Doi 2007). Moreover, the emergence of carbapenemase, enzyme has rendered carbapenems, the "last resort" antibiotics, ineffective against many *K. pneumoniae strains* (Munoz *et al*., 2013). Additionally, aminoglycoside modifying enzymes, further diminish the utility of aminoglycoside antibiotics. The global dissemination of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *K. pneumoniae* strains havevery limited therapeutic options (Zhou2023).
This narrative review mainly focuses on the factors contributing to the rise of high-level antibiotic resistance in *K. pneumoniae*. We will explore the key mechanisms employed by this bacterium to withstand the onslaught of antibiotics, including the production of carbapenemases. These carbapenemase-producing strains have rapidly disseminated worldwide, posing formidable challenges to clinicians and healthcare systems alike.

In addition to addressing the molecular intricacies of resistance, this review will provide a comprehensive overview of the epidemiology of *K. pneumoniae* strains that are transferred into superbugs. We will examine the geographical variations in prevalence, shedding light on the global distribution of these resistant strains. Furthermore, we also emphasized the role of major *K. pneumoniae* clones, in the dissemination of resistance, unraveling the genetic interplay that underpins their global prevalence.

Ultimately, our endeavorsare twofold: to provide a brief understanding of the multifaceted challenges posed by high-level antibiotic resistance in *K. pneumoniae* and to lighten the way for innovative therapeutic approaches that can mitigate the impact of this global health crisis. Through a meticulous examination of the mechanisms, epidemiology, and treatment options, this review aims to enlighten healthcare professionals, researchers, and policymakers with the knowledge needed to address thispublic health issue effectively.

2. Antibiotic Resistance in *Klebsiella pneumoniae*

Due to the increasing significance of multidrug-resistant *Klebsiella pneumoniae* (MDR *K. pneumoniae*), it is crucial to comprehend its population characteristics and the connection between these traits and the genetic variability related to antibiotic resistance. Nevertheless, despite gaining improved insights into the worldwide variety of this bacterium and outbreaks within individual healthcare facilities, we still have limited knowledge about where MDR *K. pneumoniae* originates and how it spreads within countries in the context of hospital infections (Moradigaravand*et al*.,2017).

Klebsiellapneumoniae, among a selected group of bacteria, is currently grappling with a substantial surge in antibiotic resistance, primarily stemming from modifications in its core genetic makeup. The origins of this resistance can be traced back to 1929 when Alexander Fleming first identified beta-lactam antibiotic resistance in gram-negative organisms. In the ensuing years, extensive research has revealed that *K. pneumoniae* produces beta-lactamase enzymes, which catalyze the hydrolysis of the crucial beta-lactam ring in antibiotics.

The emergence of Extended-Spectrum Beta-Lactamase (ESBL) producing *K. pneumoniae* strains was documented in Europe in 1983 and later in the United States in 1989. ESBLs possess the ability to enzymatically degrade oxyimino cephalosporins, rendering third-generation cephalosporin antibiotics ineffective in treating infections caused by these strains. Consequently, clinicians turned to carbapenem

antibiotics as a treatment alternative for ESBL-producing *K. pneumoniae*.However, a concerning trend emerged, as evidenced by data from the Centers for Disease Control and Prevention (CDC) in 2013. Among approximately 9,000 reported infections due to carbapenem-resistant Enterobacteriaceae, roughly 80% were attributed to *K. pneumoniae*. This rise in carbapenem resistance has been linked to various factors within the bacterium, including the up-regulation of efflux pumps, alterations in the outer membrane structure, and augmented production of ESBL enzymes (Ashurst & Dawson (2018)).

Klebsiella pneumoniae predominantly finds its primary reservoir within the human population. In the broader community context, a notable percentage of individuals, ranging from 5% to 38%, harbored this bacterium in their stool, with an additional 1% to 6% carrying it in the nasopharynx. The gastrointestinal tract of patients and the hands of healthcare personnel stand as the principal sources of infection, posing a significant risk for nosocomial outbreaks.It's worth noting that individuals of Chinese ethnicity and those struggling with chronic alcoholism exhibit higher rates of colonization. Within hospital settings, the prevalence of *K. pneumoniae* carriage far surpasses that observed in the general community. Remarkably, in one study, carrier rates as high as 77% were detected among hospitalized patients, and this correlated with the number of antibiotics administered (Esposito *et al*.,2018: Walter *et al*.,2018).

Examining the Indian scenario, the rising cases of antibiotic resistance and the emergence of new strains are causing concern among medical practitioners and healthcare policymakers. A study by Kumarasamy *et al*.,(2010) highlights the increasing significance of multidrug-resistant *Klebsiellapneumoniae* (MDR *K. pneumoniae*), it is crucial to comprehend its population characteristics and the connection between these traits and the genetic variability related to antibiotic resistance. Nevertheless, despite gaining improved insights into the worldwide variety of this bacterium and outbreaks within individual healthcare facilities, we still have limited knowledge about where MDR *K. pneumoniae* originates and how it spreads within countries in the context of hospital infections.

2.1. Mechanisms of Antibiotic Resistance

The multidrug-resistant organisms were once primarily confined to healthcare settings, but their presence is now increasingly pervasive in community environments. This shift implies that reservoirs of antibiotic-resistant bacteria extend beyond the boundaries of healthcare institutions. The ability of bacteria to mount a response to the antibiotic "challenge" serves as a quintessential example of bacterial adaptation and underscores the pinnacle of their evolutionary prowess. The concept of "survival of the fittest" arises from the extraordinary genetic adaptability inherent in bacterial pathogens. This adaptability triggers distinct responses, leading to mutational adjustments, acquisition of new genetic elements, or modulation of gene expression, ultimately culminating in resistance to virtually all antibiotics currently utilized in clinical medicine. Hence, gaining a profound comprehension of the biochemical and genetic underpinnings of antibiotic resistance assumes paramount significance. Such understanding forms the foundation for crafting strategies aimed at curbing the emergence and dissemination of resistance and devising pioneering therapeutic interventions to combat multidrug-resistant organisms (Munita *et al*.,2016).

To unravel the genomic underpinnings of this resistance phenomenon, several studies undertook a rigorous genome sequencing endeavor and the results were interesting.

Lee *et al*.,(2021) conducted a study encompassing 70 clinical isolates, all exhibiting an alarming extent of drug resistance. The isolates were meticulously collected from hospitals in Brasília, Brazil, spanning the time frame from 2010 to 2014. Strikingly, the preponderance of these strains (60 out of 70) clustered within a singular clonal complex, denoted as CC258, which has conspicuously disseminated across the global landscape over the past two decades. Among these CC258 strains, 44 were attributed to sequence type 11 (ST11) and intriguingly bifurcated into two distinct clades, while ST258 strains were notably absent. The comprehensive genomic analysis of this cohort, comprising 10,366 genes in the pan-genome and approximately 4,476 core genes found in 95% of the isolates, unveiled a diverse array of resistance mechanisms at play. These mechanisms encompassed the production of multidrug efflux pumps, enzymes exhibiting the same target function but with diminished or null affinities to the drugs, as well as

proteins that either shielded the drug's target or inactivated the drug altogether. Notably, the production of β-lactamases emerged as the most prominent and conspicuous mechanism intertwined with *K. pneumoniae* resistance. Intriguingly, each strain manifested a repertoire of two to three distinct β-lactamase enzymes, spanning class A (including SHV, CTX-M, and KPC), class B, and class C AmpC enzymes. However, the absence of class D β-lactamases in this cohort was conspicuous. Furthermore, among the strains harboring the formidable NDM enzyme, a trio of distinct sequence types (STs) was observed, implying a lack of a common genetic ancestry underpinning this resistance mechanism. This comprehensive genomic scrutiny underscores the multifaceted and dynamic nature of antibiotic resistance mechanisms within *K. pneumoniae*, shedding vital insights into the formidable challenges posed by this pathogen in clinical settings.

2.2. Beta-Lactam Resistance

K. pneumoniae is known for its robust resistance to beta-lactam antibiotics due to the production of extended-spectrum beta-lactamases (ESBLs), carbapenemases, and other beta-lactamase enzymes (Surger*set al.,* 2016). The extended-spectrum beta-lactamase strains carrying diverse ESBL genes such as *blaCTX-M, blaSHV*, and *blaTEM*, including the dominant *CTX-M-15* type, possess a global challenge. The rapid horizontal transfer of ESBL genes via plasmids has amplified their spread. While ESBL-producing and hypervirulent *K. pneumoniae* strains have been studied globally, however exploring the genomes of these strains will provide crucial insights into the mechanisms driving drug resistance, informing targeted strategies to confront this escalating threat (Chong *et al.,* 2011)

The study of Pathak *et al*.(2023) reported a concerning outbreak of multi-drug resistant *Klebsiella pneumoniae* in an Indian hospital NICU, affecting 5 out of 7 neonates. The isolates showed resistance to critical antibiotics and were categorized into three different sequence types (ST-11, ST-16, and ST-101), carrying carbapenemase genes like *blaNDM-1, blaNDM-5*, and *blaOXA-232*, along with extended-spectrum β-lactamases, While colistin resistance genes (mcr-1, mcr-2, mcr3) were absent, *K. pneumoniae* ST101 was isolated from incubator water, carrying *blaNDM-5, blaOXA-232*, and *ESBL* genes.

Sikarwar & Batra (2011) conducted a study in India that sheds light on a critical healthcare concern: the emergence of multidrug-resistant strains of *Klebsiella pneumoniae*. They collected clinical isolates from various regions of India, primarily from cases involving respiratory, urinary tract, and pus infections. Notably, nearly half of the isolates were found to be multidrug-resistant, highlighting the prevalence of this issue in Indian healthcare setups. Statistical analysis using the SPSS package highlighted the significant resistance of antibiotics such as piperacillin, carbenicillin, ofloxacin, ampicillin, co-trimoxazole, and chloramphenicol, with some showing moderate resistance, including cefotaxime and tetracycline.

Their study highlighted the global concern of antimicrobial resistance, emphasizing that it not only leads to increased healthcare costs but also poses significant threats to patient care. The conclusion, which suggests focusing on the genetic makeup of multidrug-resistant bacteria to understand gene mutations and their effects on antibiotic resistance, aligns with the need for more comprehensive research in this area. Encouraging rapid detection methods for infectious microorganisms and strengthening surveillance and laboratory capacity are crucial steps in addressing this issue. Additionally, promoting rational antibiotic use and fostering collaboration among healthcare professionals, pharmacists, and laboratory personnel are essential strategies to mitigate the growing problem of antibiotic resistance in India and globally.

In the face of a growing global health threat posed by carbapenem-resistant Gram-negative pathogens, *Klebsiella pneumoniae* stands out as a major concern. A study conducted by Lee *etal*.(2016) discussed the emergence of high-level antibiotic resistance in K. pneumoniae, focusing on its ability to produce carbapenemases, including *K. pneumoniae*carbapenemases (KPCs), oxacillinase-48 (OXA-48) type carbapenemases, and New Delhi metallo-β-lactamase (NDM) carbapenemases. These carbapenemase-

producing strains have rapidly disseminated worldwide, presenting significant challenges in terms of treatment. Their study also explored the epidemiology of *K. pneumoniae* strains carrying these carbapenemases, examining variations in prevalence across different geographic regions. Additionally, it delves into the mechanisms underlying the global prevalence of these carbapenemase-producing strains, including the role of major *K. pneumoniae* clones such as ST258 and ST11. Treatment options for infections caused by these highly resistant strains are very limited, primarily involving colistin, polymyxin B, fosfomycin, tigecycline, and select aminoglycosides. While combination therapy has been suggested for severe infections, clinical evidence remains scarce, necessitating further research through rigorous randomized controlled trials.

2.3. Aminoglycoside Resistance

The emergence of aminoglycoside-modifying enzymes (AMEs) in bacteria can develop resistance to aminoglycosides. These enzymes chemically modify aminoglycoside antibiotics, rendering them inactive. Aminoglycosides are frequently used in combination therapy for severe infections caused by Gram-negative bacteria, including *Klebsiella pneumoniae*. When these strains develop resistance to aminoglycosides, the treatment options will become limited. In healthcare settings, where *Klebsiella pneumoniae* is a common cause of hospital-acquired infections, aminoglycoside resistance poses an added concern, as patients in these settings are often more vulnerable to infections (Banerjee *et al.,* 2021; Talat *et al.,* 2023).

Jones *et al.* (2005) conducted a study involving 51 strains of *Klebsiella spp*. that produced extended-spectrum beta-lactamases (ESBLs), 37 (72.5%) were found to harborintegrons. Detection was achieved using PCR targeting integrase genes and cassette regions. Subsequent PCR and amplicon sequencing of the cassette regions revealed the presence of *aadB* and *aadA2* gene cassettes, both conferring resistance to various aminoglycosides. Specifically, *aadB* was associated with a class 1 integron located on a 28-kb plasmid denoted as pES1. Remarkably, this plasmid not only carried *aadB* but also harbored the blaSHV-12 gene and the insertion sequence IS26. This finding underscores the significance of integrons as carriers of antibiotic-resistance genes in ESBL-producing*Klebsiella spp*. and highlights the potential for genetic elements like pES1 to disseminate multidrug resistance within bacterial populations.

The study of Grutke*et al*.(2003) examined a nosocomial outbreak caused by multi-drug-resistant *Klebsiella pneumonia*. Genetic typing confirmed clonality and detected the SHV-5 ESBL gene in most outbreak strains. Notably, the presence of aminoglycoside resistance genes *aadB* and *aadA2* within variable integrons were identified. The study highlights the challenge of detecting low-level ESBL expression and suggests tailored screening based on ciprofloxacin MICs for optimal sensitivity. It emphasizes the need for comprehensive outbreak control, including isolation measures, improved hand hygiene, environmental sanitation, and antibiotic policy revision.

2.4. Fluoroquinolone resistance

Fluoroquinolone resistance in *Klebsiella pneumoniae* is a growing concern in healthcare due to its impact on treatment options and patient outcomes. This resistance can arise through mechanisms like target site mutations, efflux pump overexpression, and plasmid-mediated resistance genes. When *Klebsiella pneumoniae* becomes resistant to fluoroquinolones, treatment choices are limited, especially for serious infections. Risk factors for resistance include the overuse and misuse of fluoroquinolones and the hospital environment, which can facilitate the spread of resistant strains. Preventing fluoroquinolone resistance requires prudent antibiotic use through antibiotic stewardship programs, rigorous infection control measures in healthcare settings, and ongoing research into new antibiotics with different mechanisms of action.

Klebsiella oxytoca and *Klebsiella pneumoniae*, are known for their production of extended-spectrum β-lactamase (ESBL) and cephalosporinase enzymes. These pathogens pose a significant threat in both

hospital-acquired (HA) infections and non-hygienic community settings, with a concerning prevalence of ESBL positivity and fluoroquinolone resistance. The broad spectrum of antibiotic resistance, including critical drugs like imipenem and ciprofloxacin, raises serious concerns for patients. Rath*et al.* (2014) have clearly underscored the pressing global challenge of antimicrobial resistance and the urgent need for comprehensive strategies, including prudent antibiotic use, rigorous infection control, and the development of alternative treatment options, to address this growing public health threat.

The study of Shrestha *et al.*(2023) highlighted the presence of various quinolone resistance-determining region (QRDR) mutations in genes *gyrA*and *parC.* Notably, a strong association between TMQR and β-lactamase genes like *blaCTX−M* and *blaTEM* was identified, adding another layer of complexity to the multidrug resistance.

3. CONCLUSION

The emergence of high-level antibiotic resistance in *Klebsiella pneumoniae* is a grave concern that cannot be underestimated, as it poses substantial challenges to both clinical practice and public health. The importance of addressing this crisis cannot be overstated. Such studies hold a pivotal role in illuminating the ever-evolving landscape of antimicrobial resistance, equipping healthcare professionals and policymakers with the knowledge necessary to make informed decisions in clinical practice and public health policy. Furthermore, all reviewed studies underscore the urgent need to prioritize antibiotic resistance as a paramount global health concern, emphasizing the imperative for coordinated efforts to curb its proliferation. Equally critical is the recognition that high-level antibiotic resistance in pathogens like *K. pneumoniae* underscores the crucial role of research and innovation in the development of new treatment strategies and therapeutic agents. It is through such endeavors that we can hope to counteract the inexorable rise of resistant pathogens and secure effective treatment options for the well-being of both current and future generations. In conclusion, Together, we must safeguard the efficacy of antibiotics, an invaluable resource, to ensure the health and welfare of individuals and communities worldwide.

4. ABBREVIATIONS

MDRKP- Multidrug-resistant*Klebsiella pneumoniae*
ESBLs- Extended-spectrum β-lactamases
CDC- Center for Disease Control and Prevention
XDR- Extensively drug-resistant *K. pneumoniae*
SHV- Sulf- hydryl variable active site
NICU- Neonatal intensive care unit
AMEs- Aminoglycoside-modifying enzymes

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6. AUTHORS' CONTRIBUTIONS

Sona P H[1]designed the study, managed the literature searches,and wrote the first draft of the manuscript. Dr. Pavan Chand Attavar[2]and M Shashidhar Kotian[4] managed the analyses of the study. Rasmi T R[3]and Delna N S[5] managed the literature searches. All authors read and approved the final manuscript.

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