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# MOLECULAR CHARACTERIZATION OF COLISTIN-RESISTANT *KLEBSIELLA PNEUMONIAE*: A COMPREHENSIVE REVIEW

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## ABSTRACT

The rapid emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Klebsiella pneumoniae* has become one of the most significant public health concerns worldwide. Colistin has traditionally served as the antibiotic of last resort for treating carbapenem-resistant *K. pneumoniae* infections. However, the increasing occurrence of colistin-resistant isolates has substantially reduced available therapeutic options, leading to increased morbidity, mortality, prolonged hospitalization, and healthcare costs. Molecular characterization has become indispensable for understanding resistance mechanisms, epidemiology, and transmission pathways of these resistant pathogens. The principal mechanisms of colistin resistance include chromosomal mutations affecting lipopolysaccharide modification pathways and plasmid-mediated mobilized colistin resistance (*mcr*) genes. Advanced molecular diagnostic techniques, including polymerase chain reaction (PCR), whole genome sequencing (WGS), multilocus sequence typing (MLST), pulsed-field gel electrophoresis (PFGE), and next-generation sequencing (NGS), have significantly improved the detection and surveillance of resistant strains. This review summarizes recent advances in molecular mechanisms, epidemiology, diagnostic techniques, resistance genes, clinical implications, and infection control strategies for colistin-resistant *K. pneumoniae*. Furthermore, it highlights existing research gaps and future perspectives for effective surveillance and antimicrobial stewardship.

**KEYWORDS:** *Klebsiella pneumoniae*, Colistin resistance, Molecular characterization, Antimicrobial resistance, mcr genes, PCR, Whole genome sequencing

## 1. INTRODUCTION

*Klebsiella pneumoniae* is a Gram-negative opportunistic pathogen belonging to the family Enterobacteriaceae and is responsible for a broad spectrum of healthcare-associated infections, including bloodstream infections, urinary tract infections, pneumonia, wound infections, neonatal sepsis, and ventilator-associated pneumonia. The increasing prevalence of multidrug-resistant strains has transformed this organism into one of the most problematic ESKAPE pathogens worldwide.

Carbapenem-resistant *K. pneumoniae* (CRKP) has emerged due to the widespread dissemination of carbapenemase enzymes such as KPC, NDM, VIM, IMP, and OXA-48. Consequently, colistin became the preferred salvage therapy. Unfortunately, excessive and inappropriate colistin use has accelerated the emergence of colistin-resistant isolates, creating pan-drug resistant strains with extremely limited therapeutic options.

Molecular characterization plays a crucial role in identifying resistance determinants, monitoring epidemiological trends, tracing outbreak sources, and guiding infection prevention strategies. Understanding these molecular mechanisms is essential for designing targeted therapeutic interventions and implementing antimicrobial stewardship programs.

## 2. Molecular Mechanisms of Colistin Resistance

Colistin exerts bactericidal activity by binding to lipid A within lipopolysaccharide (LPS) molecules of Gram-negative bacteria, disrupting the bacterial outer membrane. Resistance develops primarily through structural modifications of lipid A that reduce the affinity of colistin.

The most common chromosomal mechanisms involve mutations in regulatory genes including **pmrA**, **pmrB**, **phoP**, **phoQ**, **mgrB**, **crrA**, and **crrB**. These mutations activate signaling pathways that promote the addition of phosphoethanolamine or 4-amino-4-deoxy-L-arabinose to lipid A, decreasing the negative charge of the bacterial membrane and reducing colistin binding.

Another important mechanism involves plasmid-mediated **mobilized colistin resistance (mcr)** genes. Since the first discovery of **mcr-1** in China in 2015, several variants (**mcr-1** to **mcr-10**) have been identified globally. These genes encode phosphoethanolamine transferases capable of modifying lipid A and facilitating horizontal transfer of resistance among bacterial populations.

The coexistence of carbapenemase genes with **mcr** genes has significantly increased therapeutic challenges, emphasizing the need for continuous molecular surveillance.

## 3. Molecular Diagnostic Techniques

Accurate molecular identification is fundamental for early diagnosis and epidemiological surveillance.

### Polymerase Chain Reaction (PCR)

PCR remains the most widely used molecular technique for detecting **mcr** genes and chromosomal resistance determinants. Multiplex PCR enables simultaneous detection of multiple resistance genes, providing rapid and reliable diagnostic information.

### Whole Genome Sequencing (WGS)

Whole genome sequencing offers comprehensive characterization of resistance genes, virulence factors, plasmid profiles, and phylogenetic relationships. WGS has become the gold standard for outbreak investigations and genomic surveillance.

### Multilocus Sequence Typing (MLST)

MLST classifies bacterial isolates into sequence types (STs), allowing researchers to monitor global dissemination of high-risk clones such as ST11, ST258, ST15, ST147, and ST231.

### Pulsed Field Gel Electrophoresis (PFGE)

PFGE has traditionally been employed for outbreak investigations by comparing chromosomal DNA restriction patterns among bacterial isolates.

### Next-Generation Sequencing (NGS)

NGS platforms enable rapid sequencing of complete bacterial genomes and have become increasingly important for detecting emerging resistance genes and understanding evolutionary dynamics.

## 4. Global Epidemiology of Colistin Resistance

Colistin-resistant *K. pneumoniae* has now been reported across Asia, Europe, Africa, North America, and South America. Countries such as China, India, Italy, Greece, Brazil, and the United States have documented increasing prevalence rates.

In India, the emergence of New Delhi Metallo-β-lactamase (NDM)-producing *K. pneumoniae* combined with colistin resistance has become a significant concern. Hospital outbreaks involving intensive care units have demonstrated rapid clonal dissemination facilitated by inadequate infection control practices and excessive antibiotic usage.

The global spread of plasmid-mediated **mcr** genes further complicates surveillance because these mobile genetic elements can transfer between bacterial species.

## 5. Clinical Significance

Colistin-resistant *K. pneumoniae* infections are associated with:

- Increased mortality rates
- Longer hospital stays
- Higher healthcare expenditure
- Limited treatment options
- Increased risk of hospital outbreaks

Patients admitted to intensive care units, transplant recipients, immunocompromised individuals, and patients receiving prolonged antibiotic therapy are particularly susceptible.

Combination antimicrobial therapy involving tigecycline, ceftazidime-avibactam, fosfomycin, aminoglycosides, and novel β-lactam/β-lactamase inhibitor combinations is increasingly explored; however, treatment outcomes remain variable depending on resistance mechanisms.

## 6. Infection Control and Antimicrobial Stewardship

Effective containment requires comprehensive infection prevention strategies including:

- Active surveillance cultures
- Rapid molecular diagnosis
- Contact precautions
- Environmental disinfection
- Hand hygiene compliance
- Isolation of colonized patients
- Antimicrobial stewardship programs
- Routine molecular surveillance

Hospitals should establish molecular epidemiological monitoring programs to rapidly detect emerging resistant clones and prevent nosocomial transmission.

## 7. Future Perspectives

Future research should focus on:

- Development of rapid point-of-care molecular diagnostics.
- Comprehensive genomic surveillance using whole genome sequencing.
- Discovery of novel antimicrobials against pan-drug resistant pathogens.
- CRISPR-based antimicrobial approaches.
- Bacteriophage therapy.
- Machine learning applications for antimicrobial resistance prediction.

- One Health surveillance integrating human, animal, and environmental reservoirs.

Understanding resistance evolution at the molecular level will facilitate precision medicine and improve infection control policies.

## CONCLUSION

The emergence of colistin-resistant *Klebsiella pneumoniae* represents a major challenge to global healthcare systems. Molecular characterization has significantly enhanced understanding of resistance mechanisms, transmission dynamics, and epidemiological patterns. Both chromosomal mutations and plasmid-mediated **mcr** genes contribute substantially to resistance development. Advanced molecular technologies, particularly whole genome sequencing and next-generation sequencing, have revolutionized surveillance and outbreak investigations. Continuous monitoring, antimicrobial stewardship, rapid molecular diagnostics, and coordinated global surveillance remain essential for limiting the spread of these highly resistant pathogens. Future research should prioritize novel therapeutic approaches and genomic surveillance to combat the escalating burden of antimicrobial resistance.

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