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COLISTIN RESISTANCE: MECHANISMS AND GLOBAL PERSPECTIVE

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ABSTRACT

Colistin (polymyxin E) is a last-resort antibiotic used to treat infections caused by multidrug-resistant (MDR) Gram-negative bacteria. The emergence of colistin resistance, mainly through chromosomal mutations and plasmid-mediated mcr genes, has become a major global health concern. This review summarizes the mechanism of action of colistin, resistance mechanisms, global epidemiology, laboratory detection methods, clinical impact, and strategies for prevention and control. It also discusses emerging therapeutic approaches, including novel antibiotics, bacteriophage therapy, CRISPR-based technologies, and artificial intelligence. Strengthening antimicrobial stewardship, surveillance, and the One Health approach is essential to preserve the effectiveness of colistin.

2. INTRODUCTION

2.1 Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR) occurs when microorganisms become resistant to drugs that were previously effective, making infections difficult to treat and increasing illness, mortality, and healthcare costs. Gram-negative bacteria such as Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa are major causes of severe infections and frequently develop multidrug resistance. The misuse of antibiotics in human medicine, veterinary practice, agriculture, and aquaculture, together with poor infection control and global travel, has accelerated the spread of resistant organisms. Based on resistance patterns, bacteria are classified as multidrug-resistant (MDR), extensively drug-resistant (XDR), or pandrug-resistant (PDR).

2.2 Colistin as a Last-Resort Antibiotic

Colistin (polymyxin E) is a cyclic polypeptide antibiotic active against Gram-negative bacteria. Although its clinical use declined because of nephrotoxicity and neurotoxicity, the emergence of carbapenem-resistant pathogens has led to its reintroduction as a last-resort treatment. It is widely used against carbapenem-resistant Enterobacterales, Pseudomonas aeruginosa, and Acinetobacter baumannii. However, increasing resistance threatens its clinical effectiveness.

2.3 Rationale and Objectives

The rapid global spread of colistin resistance, driven by chromosomal mutations and plasmid-mediated mcr genes, has become a significant public health concern. These transferable resistance genes circulate among humans, animals, food, and the environment, emphasizing the importance of the One Health approach. This review summarizes the mechanism of action of colistin, resistance mechanisms, molecular genetics, epidemiology, laboratory detection, clinical impact, and current strategies for prevention and control of colistin resistance.

3. Colistin: Structure and Mechanism of Action

3.1 Chemical Structure of Colistin

Colistin (polymyxin E) is a cationic cyclic polypeptide antibiotic produced by Paenibacillus polymyxa. It is active mainly against Gram-negative bacteria by targeting the lipopolysaccharide (LPS) layer of the outer membrane. Structurally, colistin consists of a positively charged cyclic peptide ring, a linear peptide side chain, and a hydrophobic fatty acid tail, which together enable binding to and disruption of the bacterial membrane. Clinically, it is available as colistin sulfate (oral/topical) and colistimethate sodium (CMS), an inactive prodrug used intravenously or by inhalation.

3.2 Mechanism of Action

Colistin exerts bactericidal activity by binding to the negatively charged lipid A component of LPS through electrostatic interactions. It displaces membrane-stabilizing divalent cations (Mg^{2+} and Ca^{2+}), allowing its fatty acid tail to disrupt the outer membrane. This increases membrane permeability, causes leakage of intracellular contents, and ultimately leads to bacterial cell death.

3.3 Spectrum of Activity

Colistin is active against important Gram-negative pathogens, including Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter cloacae, and Salmonella enterica. It has little or no activity against Gram-positive bacteria because they lack the LPS-containing outer membrane targeted by colistin.

3.4 Clinical Significance

Colistin is an essential last-resort antibiotic for treating severe infections caused by carbapenem-resistant Gram-negative bacteria. However, the emergence of plasmid-mediated mcr genes and other resistance mechanisms threatens its effectiveness, emphasizing the need for antimicrobial stewardship, continuous surveillance, and prudent clinical use.

4. Clinical Applications of Colistin

4.1 Use of Colistin in Human Medicine

Colistin is a last-resort antibiotic used to treat severe infections caused by multidrug-resistant (MDR) and carbapenem-resistant Gram-negative bacteria when other antibiotics are ineffective. It is commonly used against Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa. Major clinical indications include hospital-acquired and ventilator-associated pneumonia, bloodstream infections, complicated urinary tract infections, intra-abdominal infections, and selected central nervous system infections.

4.2 Use in Veterinary Medicine

Colistin has been widely used in livestock, poultry, and aquaculture to treat Gram-negative bacterial infections. However, extensive veterinary use has contributed to the emergence and spread of plasmid-mediated mcr genes, facilitating transmission of resistant bacteria among animals, humans, food, and the environment.

4.3 Routes of Administration

Depending on the infection, colistin can be administered intravenously (as colistimethate sodium), by inhalation for respiratory infections, orally for intestinal decontamination, or topically for localized infections. The route of administration depends on the site and severity of infection.

4.4 Limitations and Adverse Effects

The clinical use of colistin is limited by significant nephrotoxicity and neurotoxicity. In addition, excessive or inappropriate use in humans and animals has accelerated the development of colistin-resistant bacteria, reducing its therapeutic effectiveness.

4.5 Clinical Significance

Despite its toxicity, colistin remains a critical last-resort antibiotic for life-threatening infections caused by carbapenem-resistant Gram-negative bacteria. Its effectiveness can be preserved through appropriate dosing, antimicrobial stewardship, infection prevention and control, and continuous surveillance of antimicrobial resistance.

5. Mechanisms of Colistin Resistance

5.1 Overview

Colistin resistance develops when bacteria modify the lipid A component of lipopolysaccharide (LPS), reducing the binding of colistin to the bacterial outer membrane. The two major mechanisms are chromosomal mutations and plasmid-mediated mobile colistin resistance (mcr) genes. Other contributing mechanisms include lipid A modification, capsule overproduction, biofilm formation, efflux pumps, and heteroresistance.

5.2 Chromosomal-Mediated Resistance

Chromosomal mutations in regulatory genes such as pmrAB, phoPQ, mgrB, and crrAB alter lipid A by adding phosphoethanolamine (pEtN) or 4-amino-4-deoxy-L-arabinose (L-Ara4N). These modifications reduce the negative charge of the bacterial surface, decreasing colistin binding and resulting in resistance.

5.3 Plasmid-Mediated Resistance (mcr Genes)

The discovery of the mcr-1 gene in 2015 marked the first transferable mechanism of colistin resistance. Mcr genes, located on plasmids, encode phosphoethanolamine transferase, which modifies lipid A and reduces colistin affinity. To date, multiple mcr variants (mcr-1 to mcr-10) have been identified in bacteria from humans, animals, food, and environmental sources, enabling rapid horizontal spread of resistance.

5.4 Additional Resistance Mechanisms

Lipid A modification remains the central mechanism of resistance. Other factors, including capsule overproduction, biofilm formation, efflux pumps, and heteroresistance, further decrease colistin susceptibility and contribute to persistent infections and treatment failure.

5.5 Summary

Colistin resistance is a multifactorial process involving chromosomal mutations, plasmid-mediated mcr genes, and additional adaptive mechanisms. The rapid dissemination of mcr genes through horizontal gene transfer represents a major global concern, highlighting the need for effective surveillance, accurate diagnostics, antimicrobial stewardship, and infection control measures.

6. Molecular Genetics of Colistin Resistance

6.1 Introduction

The rapid emergence and global spread of colistin resistance are primarily driven by genetic mechanisms, including chromosomal mutations, plasmid-mediated mcr genes, and mobile genetic elements (MGEs). These mechanisms facilitate the acquisition and dissemination of resistance among Gram-negative bacteria, making molecular understanding essential for surveillance, diagnosis, and control.

6.2 Mobile Genetic Elements (MGEs)

Mobile genetic elements play a central role in the spread of colistin resistance.

Plasmids are self-replicating DNA molecules that carry mcr genes and transfer them between bacteria through conjugation. Common plasmid groups associated with mcr dissemination include IncI2, IncHI2, IncX4, and IncP.

Transposons (“jumping genes”) move resistance genes between plasmids and chromosomes, promoting their spread.

Insertion sequences (IS), particularly ISApl1, facilitate the mobilization and persistence of mcr-1 by transferring resistance genes between different genetic locations.

6.3 Horizontal Gene Transfer (HGT)

Horizontal gene transfer is the major mechanism responsible for the dissemination of plasmid-mediated colistin resistance. It occurs through:

Conjugation: Direct transfer of mcr-carrying plasmids between bacterial cells (most important mechanism).

Transformation: Uptake of free DNA containing resistance genes from the environment.

Transduction: Transfer of resistance genes by bacteriophages, although this is less common for mcr genes.

6.4 Evolution and Dissemination of Mcr Genes

Since the discovery of mcr-1 in 2015, multiple variants (mcr-1 to mcr-10) have been reported worldwide in clinical isolates, livestock, food products, and environmental samples. The widespread use of colistin in human and veterinary medicine, together with international travel, food trade, and environmental contamination, has accelerated their global dissemination.

6.5 One Health Perspective

The spread of colistin resistance is closely linked to the interaction between humans, animals, and the environment. A One Health approach promotes prudent antibiotic use, continuous surveillance, improved infection prevention, monitoring of food and environmental reservoirs, and international collaboration to reduce the global spread of resistance.

6.6 Summary

The molecular genetics of colistin resistance involves chromosomal mutations, plasmid-mediated mcr genes, and mobile genetic elements that facilitate horizontal gene transfer. Understanding these genetic mechanisms is essential for developing effective diagnostic tools, surveillance programs, and strategies to limit the spread of colistin resistance.

7. Global Epidemiology of Colistin Resistance

7.1 Introduction

Colistin resistance has become a major global public health concern since the discovery of the plasmid-mediated mcr-1 gene in 2015. Resistant bacteria have now been reported in more than 100 countries from humans, animals, food products, and environmental sources. The widespread use of colistin in healthcare and livestock production, together with horizontal gene transfer, has accelerated its global dissemination.

7.2 Global Distribution

The prevalence of colistin resistance varies across different regions.

Asia has the highest reported burden, with resistant Escherichia coli, Klebsiella pneumoniae, and Acinetobacter baumannii frequently isolated from hospitals, livestock, poultry, seafood, and wastewater.

Europe continues to detect mcr genes despite strong antimicrobial stewardship and surveillance programs.

North America reports relatively lower prevalence, with most cases associated with healthcare settings, international travel, or imported food.

South America has documented resistant isolates in hospitals and food-producing animals, particularly in Brazil and neighboring countries.

Africa has increasing reports of resistance, although limited laboratory capacity may underestimate its true burden.

Oceania reports comparatively low resistance because of strict antibiotic regulations and effective stewardship, but ongoing surveillance remains essential.

7.3 One Health Perspective

The epidemiology of colistin resistance reflects the interconnectedness of human, animal, food, and environmental health. Hospitals serve as major reservoirs of resistant bacteria, while the use of colistin in livestock contributes to the selection and transmission of resistant organisms through food chains and environmental contamination. This highlights the importance of the One Health approach, integrating healthcare, veterinary medicine, agriculture, and environmental management to control resistance.

7.4 Summary

Colistin resistance is now a worldwide problem, with mcr genes and resistant Gram-negative bacteria detected across all inhabited continents. Asia remains the most affected region, while other continents continue to report emerging resistance through surveillance programs. Strengthening antimicrobial stewardship, global surveillance, and One Health initiatives is essential to limit the further spread of colistin resistance.

8. Detection and Characterization of Colistin Resistance

8.1 Introduction

Accurate detection of colistin resistance is essential for appropriate patient management, antimicrobial stewardship, infection control, and surveillance. Because colistin diffuses poorly in agar, reliable laboratory methods are required. Detection methods are broadly classified into phenotypic and molecular (genotypic) techniques.

8.2 Phenotypic Detection Methods

Phenotypic methods determine bacterial susceptibility by assessing growth in the presence of colistin.

Broth Microdilution (BMD): The gold-standard method for determining the minimum inhibitory concentration (MIC). It is highly accurate and reproducible but labor-intensive and time-consuming.

Rapid Polymyxin NP Test: A rapid colorimetric assay that detects glucose metabolism in the presence of colistin. It provides results within 2–4 hours and is mainly used for Enterobacterales

Colistin Broth Disk Elution (CBDE): A simple and cost-effective alternative suitable for routine clinical laboratories.

Selective agar media (e.g., CHROMagar™ COL-APSE and SuperPolymyxin) are useful for screening colistin-resistant isolates but are not recommended for definitive susceptibility testing.

8.3 Molecular Detection Methods

Molecular techniques detect resistance genes rather than bacterial growth.

Conventional PCR identifies mcr genes with high specificity.

Multiplex PCR simultaneously detects multiple mcr variants.

Real-Time PCR (qPCR) provides rapid, sensitive, and quantitative detection.

Loop-Mediated Isothermal Amplification (LAMP) is a rapid and simple method suitable for resource-limited laboratories.

Whole Genome Sequencing (WGS) offers comprehensive identification of resistance genes, chromosomal mutations, and epidemiological relationships but requires specialized expertise and is relatively expensive.

8.4 Advanced Diagnostic Techniques

Emerging diagnostic methods include MALDI-TOF Mass Spectrometry, which can detect lipid A modifications associated with colistin resistance, and CRISPR-based diagnostic platforms, which enable highly sensitive and specific detection of mcr genes with potential for rapid point-of-care testing.

8.5 Summary

Broth Microdilution remains the reference standard for colistin susceptibility testing, while molecular techniques such as PCR, qPCR, LAMP, and WGS provide rapid identification of resistance genes. Advanced methods, including MALDI-TOF MS and CRISPR-based diagnostics, further improve the speed and accuracy of detection. Combining phenotypic and molecular approaches provides the most reliable strategy for diagnosing and monitoring colistin resistance.

9. Clinical Impact of Colistin Resistance

9.1 Introduction

The emergence of colistin resistance has significantly reduced the effectiveness of one of the last-resort antibiotics for treating multidrug-resistant (MDR) Gram-negative infections. As a result, colistin-resistant infections are associated with prolonged hospitalization, increased healthcare costs, limited treatment options, and higher morbidity and mortality, posing a major threat to global public health.

9.2 Clinical Consequences

Colistin resistance frequently leads to treatment failure, particularly in infections caused by Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa. Patients often require combination therapy or newer antimicrobial agents, which may be more expensive and less accessible. Resistant infections are associated with prolonged illness, longer hospital and ICU stays, increased complications, and higher mortality, especially in critically ill patients.

9.3 Economic and Infection Control Challenges

Colistin-resistant infections increase healthcare expenditure because of extended hospitalization, intensive care, advanced diagnostic testing, and the use of costly antimicrobial therapies. In healthcare settings, resistant bacteria can spread through direct contact, contaminated equipment, and inadequate infection control practices. Effective management requires early laboratory detection, patient isolation, strict hand hygiene, environmental cleaning, and appropriate use of personal protective equipment (PPE).

9.4 Public Health Implications

The spread of colistin resistance extends beyond hospitals, with resistant bacteria and mcr genes detected in humans, animals, food products, wastewater, and the environment. International travel, food trade, and environmental contamination further facilitate global dissemination, emphasizing the importance of coordinated surveillance, antimicrobial stewardship, and the One Health approach.

9.5 Summary

Colistin resistance has serious clinical and public health consequences, including treatment failure, increased morbidity and mortality, prolonged hospitalization, higher healthcare costs, and limited therapeutic options. Strengthening infection prevention, antimicrobial stewardship, early laboratory diagnosis, and global surveillance is essential to reduce its impact and preserve the effectiveness of colistin.

10. Prevention and Control of Colistin Resistance

10.1 Introduction

The increasing global spread of colistin resistance threatens the effectiveness of this last-resort antibiotic. Preventing and

controlling resistance requires a multidisciplinary approach involving healthcare professionals, veterinarians, researchers, policymakers, and the public. Key strategies include antimicrobial stewardship, infection prevention and control, surveillance, rational antibiotic use, and the One Health approach.

10.2 Antimicrobial Stewardship (AMS)

Antimicrobial stewardship promotes the appropriate use of colistin to improve patient outcomes while minimizing the development of resistance. Core principles include prescribing colistin only when necessary, using antimicrobial susceptibility testing (AST) to guide therapy, selecting the correct dose and duration, avoiding unnecessary empirical use, and reviewing treatment regularly. Effective AMS programs reduce inappropriate antibiotic use and improve clinical outcomes.

10.3 Infection Prevention and Control (IPC)

Strict infection prevention measures are essential to limit the spread of colistin-resistant bacteria in healthcare settings. These include proper hand hygiene, early identification and isolation of infected patients, appropriate use of personal protective equipment (PPE), regular environmental cleaning and disinfection, sterilization of medical equipment, and continuous education of healthcare workers.

10.4 Surveillance and Rational Antibiotic Use

Continuous surveillance enables early detection of resistant bacteria, monitoring of resistance trends, outbreak identification, and informed antimicrobial policies. Surveillance should include human, animal, food, and environmental sectors. In veterinary medicine, colistin should be restricted to therapeutic use under professional supervision, with emphasis on improved farm hygiene, vaccination, biosecurity, and monitoring of antimicrobial use to reduce selection pressure.

10.5 One Health and Future Strategies

The One Health approach recognizes the interconnectedness of human, animal, and environmental health and promotes coordinated action across these sectors. Public education on responsible antibiotic use, avoidance of self-medication, and good hygiene practices is essential. Emerging strategies such as novel antimicrobial agents, combination therapy, bacteriophage therapy, antimicrobial peptides, CRISPR-based technologies, rapid diagnostics, and artificial intelligence offer promising approaches for combating colistin resistance.

10.6 Summary

Preventing colistin resistance requires coordinated implementation of antimicrobial stewardship, infection prevention and control, surveillance, responsible antibiotic use in humans and animals, public awareness, and the One Health

11. Future Perspectives and Emerging Therapeutic Strategies

11.1 Introduction

The increasing prevalence of colistin-resistant Gram-negative bacteria highlights the urgent need for alternative therapeutic strategies. Future approaches focus on developing novel antimicrobial agents, improving diagnostic methods, and strengthening antimicrobial stewardship to preserve the effectiveness of existing antibiotics.

11.2 Emerging Therapeutic Strategies

Several promising strategies are being explored to combat colistin resistance:

Novel antibiotics offer new treatment options against multidrug-resistant (MDR) Gram-negative bacteria, although high development costs and emerging resistance remain challenges.

Combination antibiotic therapy (e.g., colistin with meropenem, tigecycline, fosfomycin, or rifampicin) may improve bacterial killing and reduce resistance development when guided by antimicrobial susceptibility testing.

Antimicrobial peptides (AMPs) disrupt bacterial membranes and represent potential alternatives to conventional antibiotics because of their broad-spectrum activity and lower risk of resistance.

Bacteriophage therapy specifically targets resistant bacteria with minimal effects on normal microbiota but requires further clinical development.

CRISPR-Cas technologies have potential applications in removing mcr genes, eliminating resistance plasmids, restoring colistin susceptibility, and improving molecular diagnostics.

Nanotechnology-based drug delivery may enhance antibiotic penetration, improve drug delivery, reduce toxicity, and increase efficacy against biofilm-associated infections.

Artificial intelligence (AI) is increasingly used to predict antimicrobial resistance, discover new antimicrobial compounds, optimize antibiotic therapy, and strengthen surveillance systems.

Vaccines targeting major Gram-negative pathogens may reduce antibiotic use and decrease the selection pressure driving resistance.

11.3 Global Collaboration and Policy Development

Effective control of colistin resistance requires international collaboration through strengthened antimicrobial stewardship, expanded surveillance networks, responsible antibiotic use in human and veterinary medicine, continued research, and implementation of the One Health approach.

11.4 Summary

Future management of colistin resistance will depend on integrating novel antibiotics, combination therapy, antimicrobial peptides, bacteriophage therapy, CRISPR-based technologies, nanotechnology, AI, and vaccine development with robust antimicrobial stewardship, global surveillance, and One Health initiatives. These combined strategies offer the greatest potential to preserve the effectiveness of colistin and improve the management of resistant infections.

12. CONCLUSION

Colistin remains one of the most important last-resort antibiotics for treating infections caused by multidrug-resistant (MDR) and carbapenem-resistant Gram-negative bacteria. However, the rapid emergence of resistance through chromosomal mutations and plasmid-mediated mcr genes has significantly reduced its clinical effectiveness and poses a major global public health challenge.

Accurate detection of colistin resistance using phenotypic and molecular methods, together with continuous surveillance, is essential for effective patient management and infection control. Preventing further dissemination requires antimicrobial stewardship, rational antibiotic use in human and veterinary medicine, strict infection prevention measures, and coordinated implementation of the One Health approach.

Future strategies, including the development of novel antibiotics, combination therapies, antimicrobial peptides, bacteriophage therapy, CRISPR-based technologies, nanotechnology, and artificial intelligence, offer promising opportunities to combat colistin resistance. Sustained global collaboration, research, and responsible antimicrobial use

are essential to preserve the effectiveness of colistin and reduce the burden of antimicrobial resistance worldwide.

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