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A Mini Review on Mechanisms of Antimicrobial Resistance in Human Pathogenic Bacteria: Challenges and Emerging Therapeutic Strategies

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Abstract

Antimicrobial resistance (AMR) is one of the major global health challenges of the current century, resulting from the inappropriate and excessive use of antibiotics in the fields of medicine, agriculture and the environment. Reports from the World Health Organization show that resistant infections have increased morbidity, mortality and treatment costs. With the slow pace of discovery of new antibiotics, a more detailed understanding of the mechanisms of resistance and the development of new therapeutic methods are essential. The main mechanisms of resistance include the production of drug-inactivating enzymes, changes in the location of drug targets, efflux pumps and reduced penetration of drugs into the cell. Horizontal gene transfer causes the rapid spread of resistance in bacterial populations. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains have created serious treatment problems. In addition, the shortage of new drugs and the misuse of antibiotics have exacerbated this crisis. New therapeutic approaches such as phage therapy, antimicrobial peptides, pump inhibitors and CRISPR-Cas systems have brought new hope. Tackling drug resistance requires global collaboration, the development of new drugs and the implementation of careful antibiotic stewardship policies. These measures can prevent the spread of resistance and maintain the effectiveness of antimicrobial therapies in the future.

Key words: Antibiotic resistance, Pathogenic bacteria, Resistance mechanisms, Novel therapies, Multidrug resistance

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Introduction

Since the discovery of antibiotics, bacterial infections that were once fatal have become treatable. However, the widespread and often inappropriate use of antimicrobials in human medicine, veterinary practice, and agriculture has accelerated the evolution of resistant bacterial strains. Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) pathogens are now reported worldwide. Common human pathogens such as *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Mycobacterium tuberculosis* exhibit alarming resistance patterns (Elshobary et al.,2025).Antimicrobial resistance arises through intrinsic properties or acquired genetic changes that enable bacteria to survive antibiotic exposure. A clear understanding of resistance mechanisms is fundamental to designing effective therapeutic and preventive strategies (Gajic et al.,2025).

Major Mechanisms of Antimicrobial Resistance

Bacteria employ diverse and often overlapping strategies to evade antimicrobial action.

Enzymatic Inactivation of Antibiotics

One of the most common resistance mechanisms is the production of enzymes that degrade or modify antibiotics.β-lactamases, including extended-spectrum β-lactamases (ESBLs) and carbapenemases, hydrolyze β-lactam antibiotics such as penicillins, cephalosporins, and carbapenems. Aminoglycoside-modifying enzymes (acetyltransferases, phosphotransferases, and nucleotidyltransferases) chemically alter aminoglycosides, reducing their activity-(Qadri et al.,2021).

Modification of Antibiotic Targets

Bacteria can alter the molecular targets of antibiotics, reducing drug binding affinity. Mutations in penicillin-binding proteins (PBPs) confer resistance to β-lactams (e.g., PBP2a in MRSA). Alterations in DNA gyrase and topoisomerase IV lead to fluoroquinolone resistance.Methylation of ribosomal RNA can cause resistance to macrolides, lincosamides, and *streptogramins* (Belay et al.,2024).

Efflux Pumps

Efflux systems actively expel antibiotics from bacterial cells, lowering intracellular drug concentrations. These pumps may be specific or multidrug in nature. For example, the AcrAB-TolC system in Gram-negative bacteria contributes to resistance against β-lactams, tetracyclines, chloramphenicol, and fluoroquinolones (Sharma et al.,2024).

Active Efflux and Reduced Permeability

The RND Superfamily

In Gram-negative bacteria, the Resistance-Nodulation-Division (RND) family of efflux pumps (e.g., AcrAB-TolC in E. coli) is a major contributor to multi-drug resistance. These pumps can expel structurally diverse compounds, including detergents, dyes, and multiple antibiotic classes.

Porin Loss

Bacteria like *Pseudomonas aeruginosa* often downregulate the expression of OprD porins, effectively closing the "gates" to carbapenems (Adefisoye et al.,2023).

Target Site Alteration and Protection

PBP2a in MRSA: *Staphylococcus aureus* acquired the mecA gene, which encodes a modified Penicillin-Binding Protein (PBP2a) with low affinity for beta-lactams, allowing cell wall synthesis even in the presence

of methicillin.Ribosomal Protection: Proteins like Tet(M) bind to the ribosome and physically displace tetracycline molecules, a common strategy in _*Streptococcus* species (Chinemerem et al.,2022).

Pathogen Focus: The ESKAPE Group

The WHO has identified the ESKAPE pathogens (_*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter* species) as priority targets. A. baumannii: Often termed "Iraqibacter," it is notorious for its ability to survive on dry hospital surfaces for weeks and its "Pan-drug resistance" (PDR) profileb (Miller et al.,2024).

Reduced Membrane Permeability

Gram-negative bacteria can limit antibiotic entry by altering porin channels in the outer membrane. Loss or modification of porins decreases uptake of hydrophilic drugs such as β-lactams and carbapenems (Delcour,2009).

Biofilm Formation

Biofilms are structured bacterial communities embedded in an extracellular matrix. Cells in biofilms exhibit increased resistance due to limited drug penetration, altered metabolic states, and the presence of persister cells(Grande et al.,2020). Beyond genetic resistance lies Antimicrobial Tolerance.Physical Barrier,The Extracellular Polymeric Substance (EPS) acts as a molecular sieve, slowing the diffusion of positively charged antibiotics (like aminoglycosides). Metabolic Heterogeneity, Deep within a biofilm, oxygen and nutrients are scarce. Bacteria enter a slow-growing or dormant state. Since most antibiotics target active processes (like cell wall synthesis), these "persister cells" remain unharmed, only to re-awaken and repopulate the infection site once treatment ceases (Arasu,2025).

Horizontal Gene Transfer (HGT)

Resistance genes spread rapidly via conjugation, transformation, and transduction. Mobile genetic elements such as plasmids, transposons, and integrons play a central role in disseminating resistance determinants across species and environments(Von et al.,2016).

AI and Machine Learning in Drug Discovery

AI algorithms can screen the "chemical space" of billions of molecules. This led to the discovery of Halicin, which works by dissipating the transmembrane electrochemical gradienta mechanism to which bacteria find it extremely difficult to evolve resistance(Goel et al.,2023).

Challenges in Combating Antimicrobial Resistance

Overuse and Misuse of Antibiotics Inappropriate prescribing, self-medication, and agricultural use accelerate selective pressure for resistant strains.

Slow Antibiotic Development Pipeline

The discovery of new antibiotics has declined due to scientific, regulatory, and economic barriers.

Global Spread of Resistant Pathogens

International travel, trade, and inadequate infection control facilitate rapid dissemination of resistant bacteria.

Diagnostic Limitations

Delayed or inaccurate diagnostics often result in broad-spectrum antibiotic use, promoting resistance.

Biofilm-Associated and Chronic Infections

Biofilm-related infections on medical devices and tissues are difficult to eradicate with conventional antibiotics.

Emerging Therapeutic Strategies
To counter AMR, alternative and adjunctive approaches are being explored.

Bacteriophage Therapy
Phages specifically infect and lyse bacteria. They offer high specificity and the ability to evolve alongside bacterial targets.

Antimicrobial Peptides (AMPs)
AMPs disrupt bacterial membranes and modulate immune responses, making resistance less likely compared to conventional drugs.

CRISPR-Cas-Based Approaches
Gene-editing tools can be engineered to selectively target and eliminate resistance genes in bacterial populations.

Anti-virulence Therapies
Instead of killing bacteria, these strategies inhibit virulence factors such as toxins, adhesion molecules, or quorum sensing, reducing selective pressure for resistance.

Antibiotic Adjuvants
Compounds like β-lactamase inhibitors restore the activity of existing antibiotics by blocking resistance mechanisms.

Nanotechnology and Drug Delivery Systems
Nanoparticles can enhance drug stability, improve targeting, and overcome permeability barriers.

Vaccination and Prevention
Vaccines reduce infection incidence, thereby decreasing antibiotic use and resistance development.

Conclusion
Antimicrobial resistance in human pathogenic bacteria is driven by complex molecular mechanisms and exacerbated by clinical, environmental, and socioeconomic factors. Traditional antibiotics alone are no longer sufficient to control resistant infections. A multifaceted approach combining antimicrobial stewardship, rapid diagnostics, infection prevention, and innovative therapies such as phages, AMPs, and gene-based tools is essential. Continued research into resistance mechanisms and novel interventions will be critical to mitigating the global AMR crisis.

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