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Antimicrobial Resistance Mechanisms in Bacteria: A Review

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Abstract: Antimicrobial resistance (AMR) in bacteria is a major global public health challenge that threatens the effective treatment of infectious diseases and increases morbidity, mortality, healthcare costs and treatment failure. This review examines the major mechanisms by which bacteria develop and disseminate resistance to antimicrobial agents, with emphasis on their molecular and physiological basis. Bacterial resistance may be intrinsic or acquired through spontaneous genetic mutations and horizontal gene transfer involving transformation, transduction and conjugation. The principal mechanisms discussed include enzymatic inactivation of antimicrobial agents, modification and protection of antimicrobial targets, reduced membrane permeability, active efflux, metabolic pathway modification, biofilm-associated resistance, persistence and antimicrobial tolerance. Particular attention is given to β-lactamases, including extended-spectrum β-lactamases and carbapenemases, as well as aminoglycoside-modifying enzymes, altered penicillin-binding proteins, ribosomal modification, fluoroquinolone target mutations and transferable colistin resistance. The review also highlights resistance mechanisms associated with major antibiotic classes, including β-lactams, aminoglycosides, macrolides, tetracyclines, fluoroquinolones, glycopeptides, sulfonamides, trimethoprim, polymyxins and rifampicin. The emergence of multidrug-resistant organisms results from the accumulation and interaction of multiple resistance mechanisms, thereby severely limiting therapeutic options.

Keywords: *Antimicrobial resistance, bacteria, antibiotic resistance, multidrug resistance, resistance mechanisms*

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Introduction

Antimicrobial resistance (AMR) is one of the most important challenges confronting modern medicine and public health. Antimicrobial resistance occurs when microorganisms develop the ability to survive or grow in the presence of antimicrobial agents that would normally inhibit or kill them. Although resistance occurs in bacteria, viruses, fungi, and parasites, bacterial antimicrobial resistance is particularly important because bacterial infections are responsible for a large proportion of infectious diseases and because bacteria can acquire and disseminate resistance determinants through several genetic and biochemical mechanisms (Smith *et al*., 2023).

The global burden of bacterial AMR is substantial. A systematic analysis estimated that bacterial AMR was directly attributable to approximately 1.14 million deaths and associated with approximately 4.71 million deaths globally in 2021 (Sati *et al*., 2025). The World Health Organization (WHO) consequently identifies AMR as a major global health threat requiring coordinated action involving surveillance, infection prevention, antimicrobial stewardship, research and development, and improved access to appropriate diagnostics and treatment.

The 2024 WHO Bacterial Priority Pathogens List contains 24 antibiotic-resistant bacterial pathogens distributed across 15 families and classified into critical, high and medium priority categories. Critical-priority organisms include carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant and third-generation-cephalosporin-resistant Enterobacterales, and rifampicin-resistant *Mycobacterium tuberculosis* (WHO, 2024).

Resistance may be intrinsic or acquired. Intrinsic resistance is naturally present in a bacterial species because of its structural, physiological or genetic characteristics. Acquired resistance develops when a previously susceptible bacterium obtains new resistance determinants or undergoes mutations that reduce antimicrobial susceptibility. Acquired resistance can occur through spontaneous mutation or horizontal transfer of genetic material through transformation, transduction and conjugation (Smith *et al*., 2023).

The emergence of multidrug-resistant (MDR), extensively drug-resistant (XDR) and, in some circumstances, pandrug-resistant bacteria has further complicated treatment. Gram-negative bacteria are particularly concerning because their outer membranes, efflux systems, enzymatic resistance mechanisms and capacity to acquire mobile genetic elements can combine to produce resistance to several antibiotic classes. The WHO has emphasized that resistant Gram-negative bacteria remain among the most urgent priorities because of their ability to transfer resistance genes and their increasing resistance to last-resort antibiotics (WHO, 2024).

Concept of Antimicrobial Resistance

Antimicrobial resistance refers to the ability of a microorganism to withstand the inhibitory or lethal effects of an antimicrobial agent. In bacterial infections, the more specific term antibiotic resistance is commonly used. Resistance should be distinguished from tolerance and persistence. Resistance generally involves an increase in the minimum inhibitory concentration (MIC), whereas tolerance may allow bacteria to survive antimicrobial exposure without necessarily increasing the MIC. Persister cells represent a subpopulation that enters a physiological state allowing survival during antimicrobial exposure (Smith *et al*., 2023).

Resistance can be classified into:

1. **Intrinsic resistance:** resistance naturally present in a bacterial species.
2. **Acquired resistance:** resistance obtained through mutation or horizontal gene transfer.
3. **Phenotypic resistance or tolerance:** temporary changes associated with physiological or environmental conditions.
4. **Multidrug resistance:** resistance to several antimicrobial classes.
5. **Extensive drug resistance:** susceptibility to only a limited number of antimicrobial options.
6. **Pan-drug resistance:** resistance to essentially all available antimicrobial agents in the relevant categories (Smith *et al*., 2023).

Significance of Antimicrobial Resistance

AMR has consequences at individual, institutional, national and global levels. Resistant infections can lead to delayed effective therapy, prolonged hospitalization, increased healthcare expenditure, treatment failure and increased mortality. AMR also threatens medical interventions that depend on effective infection prevention and treatment. The problem is particularly significant in low- and middle-income countries because of limitations in diagnostic capacity, antimicrobial stewardship, infection prevention infrastructure, surveillance systems, access to quality medicines and healthcare resources. The WHO global research agenda emphasizes that AMR research must address prevention, diagnosis, treatment, epidemiology, policies, education and other knowledge gaps (WHO, 2024).

Overview of Bacterial Resistance Mechanisms

Bacterial resistance can arise through several interconnected mechanisms. Four broad mechanisms are traditionally emphasized: antimicrobial inactivation, modification of the antimicrobial target, reduced intracellular antimicrobial concentration and metabolic or physiological adaptation. These mechanisms may occur independently or simultaneously. For example, a Gram-negative bacterium may possess reduced outer-membrane permeability, an extended-spectrum β-lactamase, an aminoglycoside-modifying enzyme and an efflux pump. The combined effects can result in high-level multidrug resistance (Laxminarayan *et al*., 2013).

Enzymatic Inactivation of Antimicrobial Agents

Enzymatic destruction or modification of antibiotics is one of the most important resistance mechanisms. β-lactam antibiotics include penicillins, cephalosporins, monobactams and carbapenems. They inhibit bacterial cell-wall synthesis by binding penicillin-binding proteins (PBPs). Bacteria can resist β-lactams by producing β-lactamases that hydrolyse the β-lactam ring. Important β-lactamases include penicillinases, extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases. Klebsiella pneumoniae carbapenemases (KPC), metallo-β-lactamases such as NDM, VIM and IMP and OXA-type carbapenemases (Murray *et al*., 2022). ESBLs can hydrolyse many penicillins and cephalosporins, while carbapenemases can compromise carbapenems, which are frequently used for serious infections caused by ESBL-producing organisms (Murray *et al*., 2022). Aminoglycosides such as gentamicin, amikacin and tobramycin interfere with bacterial protein synthesis. Bacteria may produce enzymes that chemically modify aminoglycosides, reducing their ability to bind the ribosome. Major enzyme families include aminoglycoside acetyltransferases, aminoglycoside phosphotransferases and aminoglycoside nucleotidyltransferases. These enzymes may be encoded on plasmids, transposons or integrons, facilitating dissemination between bacteria (Smith *et al*., 2023). Although target modification is a major mechanism of macrolide resistance, enzymatic modification can also occur. Bacteria can produce enzymes that modify macrolide molecules and decrease their antimicrobial activity (Blair *et al*., 2015).

Modification of Antimicrobial Targets

Antibiotics act by interacting with specific bacterial targets. Alteration of these targets can reduce antimicrobial binding. Methicillin resistance in *S. aureus* is principally associated with acquisition of the mecA or related resistance determinants, producing an altered PBP known as PBP2a. PBP2a has reduced affinity for many β-lactam antibiotics, allowing cell-wall synthesis to continue despite antimicrobial exposure. MRSA is recognized as a high-priority resistant bacterial pathogen by the WHO (WHO, 2025). Macrolides, lincosamides and streptogramins interfere with bacterial ribosomes. Resistance may occur through methylation of ribosomal RNA. The **erm** genes encode methyltransferases that modify the 23S rRNA component of the 50S ribosomal subunit. This mechanism can produce resistance to macrolides, lincosamides and streptogramins, commonly described as MLSB resistance (Sati *et al*., 2025). Fluoroquinolones target DNA gyrase and topoisomerase IV. Mutations in genes encoding these enzymes, particularly gyrA, gyrB, parC and parE, may decrease fluoroquinolone binding. Accumulation of mutations may produce progressively higher levels of resistance (Sati *et al*., 2025). Trimethoprim inhibits bacterial dihydrofolate reductase. Acquisition or modification of alternative dihydrofolate reductase enzymes can reduce drug effectiveness (Smith *et al*., 2023).

Reduced Permeability

For an antibiotic to act, it must reach its intracellular or periplasmic target. Bacteria can therefore resist antimicrobial agents by reducing drug entry. Gram-negative bacteria possess an outer membrane that provides an additional permeability barrier. Porin proteins facilitate the movement of molecules across this membrane. Mutations, loss or downregulation of porins can decrease antimicrobial penetration. Loss or alteration of porins is particularly important in resistance to β-lactams and carbapenems. When reduced permeability occurs simultaneously with β-lactamase production, very high-level resistance can result.

Reduced permeability is one of the four major mechanisms of environmental and bacterial antibiotic resistance identified in contemporary resistance literature (Smith *et al*., 2023).

Active Efflux Pumps

Efflux pumps are membrane-associated transport systems that actively remove antimicrobial agents from bacterial cells. By reducing intracellular drug concentration, efflux systems can prevent antibiotics from reaching effective concentrations at their targets. Major efflux-pump families include major Facilitator Superfamily (MFS), resistance-Nodulation-Division (RND), ATP-Binding Cassette (ABC), small Multidrug Resistance (SMR); and multidrug and Toxic Compound Extrusion (MATE). The RND family is particularly important in Gram-negative organisms such as *P. aeruginosa*, *A. baumannii* and Enterobacterales. Efflux pumps can confer resistance to multiple antimicrobial classes simultaneously. Their importance is therefore particularly evident in multidrug-resistant bacteria (Murray *et al*., 2022).

Modification of Metabolic Pathways

Some bacteria evade antibiotic action by modifying metabolic pathways targeted by antimicrobial drugs. Instead of simply changing the antibiotic target, bacteria may develop alternative biochemical pathways or acquire enzymes that perform similar functions but are less susceptible to the antibiotic. For example, resistance to sulfonamides and trimethoprim can occur through acquisition of alternative enzymes involved in folate metabolism (Smith *et al*., 2022).

Target Protection

Target protection involves proteins that shield an antimicrobial target from antibiotic action without necessarily modifying the target itself. For example, certain proteins can protect ribosomes from antibiotics that normally inhibit translation. Target-protection mechanisms have been described for tetracyclines and fluoroquinolones. This mechanism demonstrates that resistance does not always require destruction of the drug or alteration of its binding site (Sati *et al*., 2025).

Biofilm-Associated Resistance

Biofilms are structured microbial communities embedded within an extracellular polymeric substance matrix. Bacteria within biofilms can be substantially less susceptible to antimicrobial treatment than planktonic bacteria. Biofilm-associated reduced susceptibility may result from limited antimicrobial penetration, altered metabolic activity, slow growth, nutrient limitation, oxygen gradients, stress responses, increased efflux activity, extracellular matrix interactions and presence of persister cells. Biofilms are therefore important in chronic infections involving medical devices, wounds, catheters, prosthetic materials and respiratory infections. Bacterial defence systems have evolved under diverse ecological pressures and can provide protection against antibiotics as well as other microbial threats (Smith *et al*., 2023).

Persister Cells and Tolerance

Persister cells are phenotypic variants within bacterial populations that survive antimicrobial exposure without necessarily possessing conventional genetic resistance. They often enter metabolically inactive or slow-growing states. Because many antibiotics preferentially target actively growing cells, reduced metabolic activity can increase survival. After removal of the antimicrobial pressure, persister cells may resume growth and cause recurrence of infection (Blair *et al*., 2015).

Resistance Mechanisms Against Major Antibiotic Classes

Resistance to β-Lactam Antibiotics

Resistance to β-lactams may result from β-lactamase production modification of PBPs, reduced permeability, increased efflux and combinations of these mechanisms. ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* are important examples. Carbapenem-resistant Enterobacterales and carbapenem-resistant *A. baumannii* are particularly concerning because therapeutic alternatives may be limited. The WHO 2024 priority list identifies carbapenem-resistant *A. baumannii* and resistant Enterobacterales as critical-priority pathogens (WHO, 2024).

Resistance to Aminoglycosides

Aminoglycoside resistance can occur through enzymatic modification, alteration of ribosomal targets, reduced uptake, efflux and mutations affecting transport and metabolism. Enzymatic modification is one of the most important mechanisms (Smith *et al*., 2023).

Resistance to Macrolides

Macrolide resistance commonly occurs through ribosomal methylation, active efflux and enzymatic drug modification. The **erm** genes are particularly important because they can produce methylation of the ribosomal target (Smith *et al*., 2023).

Resistance to Tetracyclines

Tetracycline resistance frequently involves efflux pumps; and ribosomal protection proteins.

Efflux pumps decrease intracellular tetracycline concentrations, whereas ribosomal protection proteins interfere with antibiotic-mediated inhibition of translation (Smith *et al*., 2023).

Resistance to Fluoroquinolones

The principal mechanisms include mutations in DNA gyrase mutations in topoisomerase IV, reduced permeability and increased efflux. Resistance can increase when multiple mutations accumulate. Fluoroquinolone-resistant *Salmonella*, *Shigella* and *Neisseria gonorrhoeae* are among the resistant pathogens prioritized by WHO (WHO, 2025).

Resistance to Glycopeptides

Vancomycin resistance is particularly important among *Enterococcus* species. Vancomycin-resistant *Enterococcus faecium* can acquire genetic determinants that alter the peptidoglycan precursor targeted by vancomycin. Vancomycin-resistant *E. faecium* is categorized as a high-priority pathogen in the 2024 WHO bacterial priority list (WHO, 2025).

Resistance to Sulfonamides and Trimethoprim

Resistance involves changes in folate biosynthesis pathways. Bacteria can acquire alternative forms of enzymes targeted by these drugs or overproduce target enzymes, thereby reducing antimicrobial effectiveness (Sati *et al*., 2025).

Resistance to Polymyxins

Polymyxins such as colistin interact with bacterial outer membranes. Resistance may arise through modifications of lipopolysaccharide, reducing antimicrobial binding. The emergence of transferable colistin-resistance genes, particularly **mcr** genes, is a major concern because they can facilitate dissemination of resistance through plasmids (Sati *et al*., 2025).

Resistance to Rifampicin

Rifampicin targets bacterial RNA polymerase. Mutations in the **rpoB** gene can alter the target and decrease antibiotic binding. Rifampicin-resistant *M. tuberculosis* is categorized as a critical-priority pathogen by WHO (WHO, 2025).

Multidrug Resistance

MDR occurs when bacteria become resistant to multiple antimicrobial classes. MDR commonly results from accumulation of several resistance mechanisms. For example, a single bacterium may simultaneously possess ESBL production, aminoglycoside-modifying enzymes, quinolone target mutations, efflux pumps, reduced porin expression and biofilm-forming capacity. The combination produces resistance that is considerably more difficult to manage than resistance caused by a single mechanism (Sati *et al*., 2025).

Clinical Implications of Multidrug Resistance

The clinical consequences of bacterial AMR include treatment failure, prolonged illness, recurrent infections, longer hospital stays, increased mortality, increased healthcare expenditure, need for more toxic or expensive antibiotics, increased risk of complications; and increased transmission of resistant organisms (Blair *et al*., 2015). AMR can spread within hospitals, communities, households, farms, food systems and the environment. Resistant organisms can circulate between humans, animals and environmental reservoirs, supporting the One Health concept. The WHO has emphasized that resistance should be addressed using coordinated approaches involving human health, animal health, food systems and environmental sectors (Sati *et al*., 2025).

Conclusion

Antimicrobial resistance in bacteria is a complex and evolving phenomenon driven by genetic variation, natural selection, antimicrobial exposure and bacterial adaptation. The principal mechanisms include enzymatic inactivation of antimicrobial agents, alteration or protection of drug targets, reduced permeability, active efflux, metabolic bypass, biofilm formation, persistence and acquisition of resistance genes through horizontal gene transfer. The ability of bacteria to combine multiple resistance mechanisms has contributed to the emergence of multidrug-resistant organisms that are increasingly difficult to treat. Particularly concerning are carbapenem-resistant *A. baumannii*, resistant Enterobacterales, rifampicin-resistant *M. tuberculosis*, MRSA, vancomycin-resistant *E. faecium* and carbapenem-resistant *P. aeruginosa*, several of which are included in the WHO 2024 bacterial priority pathogen framework. The future control of bacterial AMR cannot depend solely on discovering new antibiotics. Effective management requires an integrated strategy involving antimicrobial stewardship, infection prevention and control, vaccination, rapid laboratory diagnosis, molecular surveillance, environmental monitoring, public education and continued research into new antimicrobial and non-antimicrobial therapies. Ultimately, understanding the molecular mechanisms of bacterial antimicrobial resistance is essential for developing effective diagnostic, therapeutic and preventive interventions. Continued multidisciplinary research and implementation of One Health strategies are necessary to slow the emergence and spread of resistant bacteria and preserve the effectiveness of antimicrobial medicines.

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