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# Mechanisms of Antibiotic Resistance in Bacteria: A Review

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**Abstract**

The discovery and production of antibiotics in the first half of the previous century was a great medical achievement. Antimicrobial agents have reduced morbidity and mortality due to bacterial infections, substantially contributing to the increased overall life span of humans. Given the emergence and rapid expansion of antibiotic-resistant pathogenic bacteria, this issue has received considerable attention. Antibiotic resistance can be intrinsic, acquired, or adaptive. Therefore, efforts for antibiotic development and studies on the mechanisms of resistance should be continuous and resilient. In the following sections, we will focus on the molecular and biochemical mechanisms underlying the bacterial resistance to antibiotics and describe the related specific situations often encountered in clinical practice.

## INTRODUCTION

In the first half of the previous century, the discovery and production of antibiotics was a great medical achievement (1). Antimicrobial agents have reduced morbidity and mortality due to bacterial infections, substantially contributing to the increased overall life span of humans. The discovery, commercialization, and routine administration of antimicrobial agents for infection treatment have revolutionized modern medicine and changed the therapeutic paradigm (2). Penicillin, a β-lactam antibiotic, was the first discovered antimicrobial agent (3).

Various types of antimicrobials agents have been introduced. Antibiotics are classified based on their mechanisms of action. These agents have cytotoxic or cytostatic effects on microorganisms, allowing the body's natural defenses, such as the immune system, to eliminate them. Their mechanisms of action include inhibiting the bacterial proliferation and synthesis of proteins, Deoxyribonucleic Acids (DNA), or Ribonucleic Acids (RNA) through a membrane-disorganizing agent or other specific actions (4,5). Antibiotics can bind TO the bacterial cell wall, enter the host cell, and use the energy-dependent transport mechanisms in ribosomes, inhibiting protein synthesis. Moreover, antibiotics and other antimicrobial agents are widely used in veterinary medicine for treating or preventing animal diseases, restricting the spread of disease, preventing food chain contamination, and increasing productivity (6).

Given the emergence and rapid expansion of antibiotic-resistant pathogenic bacteria, this issue has received considerable attention (6, 7, 8). Antimicrobial Resistance (AMR) occurs when bacteria, parasites, viruses, and fungi become resistant to the antimicrobial drugs used for treating their related infections. However, the common perception is exclusively associated with the overuse or misuse of antibiotics in humans and animals (9).

Antibiotic resistance and circulation of the related genes in the virulent bacterial populations is the most important issue in infectious disease treatment (10). In the early era of antibiotic use, mutations in the genes that were the target of antibiotics were the primary cause of antibiotic resistance; however, it soon became evident that the acquisition of antibiotic resistance-related genes through horizontal gene transfer has a major role in the antibiotic resistance development and spread in the pathogenic bacteria (10, 11).

Resistance against antibiotics (medicinesThe medications used for bacterial infection treatment and prevention, antibiotics, are the cornerstone of modern medicine. A majority of therapeutic procedures in human and animal healthcare rely on functioning antibiotics. Thus, resistance against

these agents is an urgent problem (12).

Conservative estimates show that at least 23,000 annual deaths occur in the USA due to infections with antibiotic-resistant organisms. According to a recent report, antibiotic resistance is estimated to cause around 300 million premature deaths by 2050, and impose a burden of up to $100 trillion (£64 trillion) on the global economy (14,15).

Application of antimicrobial agents in veterinary medicine creates a selective pressure leading to the emergence of antimicrobial-resistant bacteria. These bacteria can be animal pathogens, human pathogens with animal reservoirs, or commensal bacteria from animals (16). They can spread to humans through direct contact with the infected animals or food products or indirect environmental contact with non-food-producing animals. Thus, in the following sections, we will focus on the molecular and biochemical mechanisms underlying the bacterial resistance to antibiotics and describe the related specific situations often encountered in clinical practice (17).

## TYPES OF ANTIBIOTIC RESISTANCE: INTRINSIC, ACQUIRED, AND ADAPTIVE

Even before the introduction of antibiotics, resistance to them existed in some bacteria. However, the process is being accelerated by the misuse and overuse of antimicrobial agents. Antibiotic resistance exhibited by bacteria can be intrinsic, acquired, or adaptive (18, 19).

### INTRINSIC RESISTANCE

Intrinsic resistance is mediated by the chromosomal genes and is usually due to the intrinsic physiological or anatomical characteristics of the bacteria (20). The related examples include the resistance to glycopeptides exhibited by gram-negative bacteria, which is due to the impermeability of the outer membrane of the gram-negative bacterial cell, and the natural resistance to vancomycin in all gram-negative bacteria due to their cell wall structure, which is different from the gram-positive bacteria cell wall (21). However, this intrinsic resistance mechanism is not a major concern for human and animal health (22).

### ACQUIRED RESISTANCE

alterations in the genetic material of a given microorganism via mutations in the chromosomal DNA or acquiring exogenous DNA via horizontal gene transfer, which is usually obtained from the intrinsically resistant organisms present in the environment (20, 23, 24, 25).

Acquiring exogenous genetic material via HGT is one of the most important drivers of bacterial evolution. The phenomenon is frequently responsible for developing antimicrobial resistance and includes bacterial transformation, bacterial transduction, and bacterial conjugation (26).

I. Transformation: the uptake of free DNA by a “competent” bacterial cell

II. Transduction: the transfer of genetic material from the donor bacteria to the recipient ones mediated by a bacteriophage

III. Conjugation: the transfer of genetic material from one bacterial cell to another via direct physical contact. This is probably the most important mechanism of horizontal gene transfer.

### ADAPTIVE RESISTANCE

It adaptive resistance is defined as the resistance to one or more antibiotics that is induced by a specific environmental signal. It seems that adaptive resistance is due to gene expression regulations as a response to environmental changes (27).

## BACTERIAL MECHANISMS OF ANTIBIOTIC RESISTANCE

It is not surprising that bacteria have evolved sophisticated mechanisms of drug resistance to avoid being eliminated by antimicrobial chemicals. This process has likely occurred over millions of years of evolution. Here we discuss the main antibiotic resistance mechanisms with their clinically relevant impact (28).

### GENETIC BASIS OF BACTERIAL RESISTANCE

Bacteria have remarkable genetic plasticity, allowing them to respond to a wide range of environmental threats, including the antibiotic molecules that can jeopardize their existence (22, 29). From an evolutionary perspective, bacteria use two major genetic strategies for adapting to the antibiotic “attack.” These mechanisms include mutations in the gene(s) often associated with the mechanism of action of the antibiotic agent and acquiring the exogenous DNA that codes for the resistance determinants through HGT (30).

### MUTATIONAL RESISTANCE

In this case, a subset of bacterial cells derived from a susceptible population undergoes mutations in genes effective on the antibiotic activity, resulting in the survival of the preserved cells in the presence of a certain antimicrobial agent (25). In general, mutations leading to antimicrobial resistance alter the antibiotic action via one of the following mechanisms: 1) modifying the antimicrobial target leading to a decreased affinity for the drug, 2) decreasing the drug uptake, 3) activating the efflux mechanisms to extrude the harmful chemicals, or 4) global changes in important metabolic pathways via modifying the regulatory networks. Thus, resistance due to acquired mutational changes is diverse and varies in complexity. This chapter will give

several examples of antimicrobial resistance due to mutational changes (31).

### HORIZONTAL GENE TRANSFER

As explained above, horizontal gene transfer is defined as transferring genes from a given bacterial cell to another, regardless of the reproductive event (31).

### MECHANISTIC BASIS OF ANTIMICROBIAL RESISTANCE IN BACTERIA

Resistance According to the biochemical route involved, resistance to antibiotics is due to the following mechanisms:

IBacteria have become resistant to antimicrobials through a Number ofHere are the mechanisms used by the bacteria to create resistance to the antimicrobial agents (13):

I. Permeability changes of the bacterial cell wall that restrict the access of antimicrobial agent to its target sites

II. Active efflux of the antibiotic out of the microbial cell

III. Enzymatic modification of the antibiotic

IV. Degradation of the antimicrobial agent

V. Acquisition Development of metabolic pathways alternative to those inhibited by the antibiotic

VI. Modification of antibiotic targets

VII. Over production of the target enzyme

#### Modifications of the antimicrobial molecule

Some bacteria produce enzymes that inactivate the antibiotics by destructing them or adding specific chemical moieties to their structures, thereby making them unable to interact with their targets. This is one of the most successful bacterial strategies for fighting against antibiotics. For example, Aminoglycoside Modifying Enzymes (AMEs) lead to acetylation, phosphorylation, or adenylation of the aminoglycoside, resulting in a modified antibiotic with a decreased affinity for its target. The genes encoding AMEs are usually located in MGEs, enabling them to efficiently disseminate among the bacterial populations (29, 30, 31).

Activation the antimicrobial activity of nitrofurantoin is due to the activation of its molecule by the bacterial reductases, resulting in toxic intermediate compounds. Mutations in the nitroreductase genes, nfsA and nfsB, comprise the principal mechanism of nitrofurantoin resistance. Mutations in the ribE gene have also been implicated in nitrofurantoin resistance. This gene encodes a lumazine synthase, an enzyme required for riboflavin biosynthesis, an essential co-factor of nfsA and nfsB (34).

Enzymatic inactivation of chloramphenicol through acetylation by different types of Chloramphenicol Acetyl Transferases (CATs) is the first and still most frequently encountered mechanism of bacterial resistance to chloramphenicol (33). CATs can inactivate chloramphenicol, thiamphenicol, and azidamfenicol; however, florfenicol is resistant to inactivation by these enzymes due to its structural modification (35).

### ANTIBIOTIC DEGRADATION

The main mechanism of β-lactam resistance is destructing the related molecule by β-lactamases. These enzymes break the amide bond of the β-lactam ring, rendering the antimicrobial agent ineffective. The first β-lactamase was described in 1940, one year before the introduction of penicillin into clinical practice. Over 1,150 chromosomal, plasmid, and transposon located β-lactamases are currently known. After penicillin became widely available, infections caused by penicillin-resistant S. aureus became clinically relevant as well. The causative agent is a plasmid-encoded penicillinase readily transmitted between S. aureus strains, resulting in rapid dissemination of the resistance trait. In order to overcome this problem, new β-lactam compounds, such as ampicillin, were manufactured with wider-spectrum activities and less susceptibility to penicillinases (36).

### DECREASED ANTIBIOTIC PENETRATION AND EFFLUX

#### DECREASED PERMEABILITY

Many antibiotics used in clinical practice have intracellular bacterial targets. If the bacteria are gram-negative, these targets are located inside the inner membrane of the bacteria (36). Therefore, the antibiotic must penetrate the cytoplasmic membrane (or outer membrane in the gram-negative bacteria) to exert its antimicrobial effects. Several mechanisms have been developed by the bacteria to prevent the antibiotic from reaching its intracellular or periplasmic target by decreasing its uptake. Changes in the permeability of the outer membrane can also contribute to the development of acquired resistance. Porins are the major route for the entry of hydrophilic antibiotics, such as β-lactams, fluoroquinolones, tetracyclines, and chloramphenicol, through the bacterial outer membrane. This natural barrier can inhibit the entry of some antibiotics. For example, vancomycin, a glycopeptide antibiotic, is not active against gram-negative bacteria because it cannot penetrate through the outer membrane (37). In essence, the reduced uptake of the antibiotic due to porin expression changes improves the effect of co-existent resistance mechanisms, such as efflux pumps along with antibiotic degrading enzymes, resulting in organisms with a high level of resistance (36, 37).

### EFFLUX PUMPS

Efflux pumps are the main mechanism of

resistance. They decrease the cellular accumulation of the antibiotic by pumping these compounds out of the inner membrane to the periplasmic space or directly to the external environment. The first efflux pump identified, which was plasmid-encoded and pumped tetracycline out of the bacterial cell, was described in Escherichia Coli in 1980. Since then, numerous examples of efflux systems involved in antibiotic resistance have been identified in gram-positive and gram-negative bacteria (38). This mechanism of resistance affects a wide range of antimicrobial classes, including protein synthesis inhibitors, fluoroquinolones, β-lactams, carbapenems, and polymyxins. There are 5 major families of efflux pumps as follows: 1) the Major Facilitator Superfamily (MFS), 2) the Small Multidrug Resistance (SMR) family, 3) the Resistance-Nodulation-Division (RND) family, 4) the ATP-Binding Cassette (ABC) family, and 5) the Multidrug And Toxic compound Extrusion family (MATE). These families differ in structural conformation, energy source, range of substrates for extrusion, and the type of bacterial organisms (38, 39).

## CHANGES IN TARGET SITES

A common strategy of antimicrobial resistance development in bacteria is to prevent antibiotic activity by interfering with its target site. To achieve this, bacteria have evolved different tactics, including target protection, which prevents the antibiotic from reaching its binding site, and target modification, resulting in its decreased affinity for the antibiotic molecule (40).

## TARGET SITE PROTECTION

Ribosomal protection proteins (RPPs) areAs an example of antimicrobial resistance through target site protection, Ribosomal Protection Proteins (RPPs) have been described in gram-positive and gram-negative bacteria (41). A group of these proteins, Qnr proteins that can be chromosomal or plasmid-coded, create resistance to quinolones by acting as a DNA analogue, reducing the interaction between DNA and the bacterial gyrase and topoisomerase IV. Therefore, they reduce the available binding sites for quinolones (40, 41).

## MODIFICATION OF THE TARGET SITE

Introducing modifications to the modifying target sites is one of the most common mechanisms of antibiotic resistance in bacterial pathogens, affecting almost all families of antimicrobial compounds. These target modifications include: 1) point mutations in the genes encoding the target site, 2) enzymatic alterations of the binding site, such as methylation, and 3) replacement or bypass of the original target. As mentioned, the final effect is always the same, a decrease in the antibiotic affinity for the target site, regardless of the modification type (42).

## CONTROLS OF ANTIBIOTIC RESISTANCE

controls of antibiotic resistance can be used against antimicrobial resistance. They include improving the hygiene and sanitation, taking infection control measures to prevent the spread of resistant bacteria, developing new antimicrobials against which bacteria are not resistant, improving the conservation efforts to maintain the effectiveness of new and pre-existed antimicrobials (43,44), prudent use of antimicrobials, promoting new and rapid diagnostics to reduce unnecessary and empiric antimicrobial therapy, and promote vaccines and their alternatives (45).

## CONCLUSION

Antimicrobial resistance the emergence of antimicrobial resistance may be inevitable in the evolutionary process because the mechanisms safeguarding its persistence, even in the absence of selective pressure by antibiotic use, are not fully elucidated. Veterinary services, including veterinarians and veterinary paraprofessionals, have a key role in fighting against antimicrobial resistance by regulating and supervising antimicrobial use, offering professional advice to farmers and animal owners, and collaborating with the human healthcare sector (45, 46,). A complete understanding of the resistance mechanisms is of paramount importance for developing novel strategies to cope with this threat. We need to know that microorganisms will respond to the new and pre-existed antibiotics by developing resistance. It is an evolutionary fact. Therefore, efforts for antibiotic development and studies on the mechanisms of resistance should be continuous and resilient. This is probably a long haul “war” against living entities with a major ability in adaptation and survival (47).

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