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Antibiotic Resistance Mechanisms in Bacteria: A Review.

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ABSTRACT: Antibiotic resistance has been a major cause of morbidity and mortality around the world as a consequence of antibiotic misuse in the medical, veterinary, and agricultural sectors, including improper antibiotic prescribing, overuse in livestock, and inadequate hygiene practices in hospitals.The majority of pathogenic microorganisms are capable of developing resistance to at least certain antibiotics. Antibiotic inactivation, target alteration, altered permeability, and metabolic pathway "bypass" are some of the resistance mechanisms used by bacteria.Knowledge about bacterial cell morphology, antibiotic classification based on mechanism of action, antibiotic resistance mechanisms, and antibiotic resistance prevention strategies will hopefully lead to better treatment options for infective diseases, and development of antibiotics drugs that can withstand the micro-organisms attempts to become resistant.Overall, this article establishes a conceptual framework for comprehending bacterial cell morphology, antibiotic classification based on mechanism of action, antibiotic resistance mechanisms, and antibiotic resistance prevention strategies.

Keywords: Bacterial; antibiotics resistance; resistant mechanisms;bacterial cell wall; mechanism of action;controlling methods.

I. INTRODUCTION

Antibiotics are drugs that are used to cure and prevent bacterial infections. Antibiotics were a big part of the rise in life expectancy in the second half of the twentieth century. Antibiotics revolutionized modern agriculture and livestock industries, with antibiotics being used for prophylaxis, meta-prophylaxis, infection treatment, and as a growth promoter to improve feed production in healthy livestock [1]. Antibiotics are cytotoxic or cytostatic to bacteria, enabling the body's natural defenses, such as the immune system, to kill them. They are low molecular weight compounds produced by microorganisms or derived from natural products that are active against bacteria at low concentrations. Some antibiotics, such as sulfa drugs and oxazolidinones, do not come from natural products [2].

Antibiotic resistance is one of the most pressing public health issues today. Antibiotic resistance mechanisms often arise as a result of overuse of antibiotics in medicine and agriculture, posing a challenge to modern medicine by reducing the effectiveness of clinically applicable antibiotics. Antibiotics resistant have resulted in increased morbidity and mortality as a result of treatment failure[3]. Antibiotics, often act by inhibiting bacterial cell synthesis, protein synthesis, deoxyribonucleic acid (DNA), ribonucleic acid (RNA) synthesis, membrane disorganization, or other unique acts [4].

The aim of this review is to look at how antibiotics work and how resistance develops in commonly used antibiotics. To do so, we'll need to know about bacterial cell morphology, antibiotic classification based on mechanism of action, antibiotic resistance mechanisms, and Antibiotic Resistance Prevention Strategies

II. BASIC BACTERIAL CELL ANATOMY

The cytoplasmic membrane of Gram-positive bacteria is enclosed by a tough and rigid mesh called the cell wall. Gram-negative bacteria, on the other hand, have a thin cell wall that is surrounded by a second lipid membrane called the outer membrane (OM). In Gram-negative bacteria, the OM is an external defensive layer that prevents several compounds from entering the bacterium. This membrane, on the other hand, contains porins, which enable different molecules, such as drugs, to pass through. The bacterium's cell wall is a durable layer that gives it its form and protects it from osmotic and mechanical stress. The cytoplasmic membrane keeps ions out of the cell and keeps cytoplasmic and bacterial components separated in a given area(fig 1)[5].

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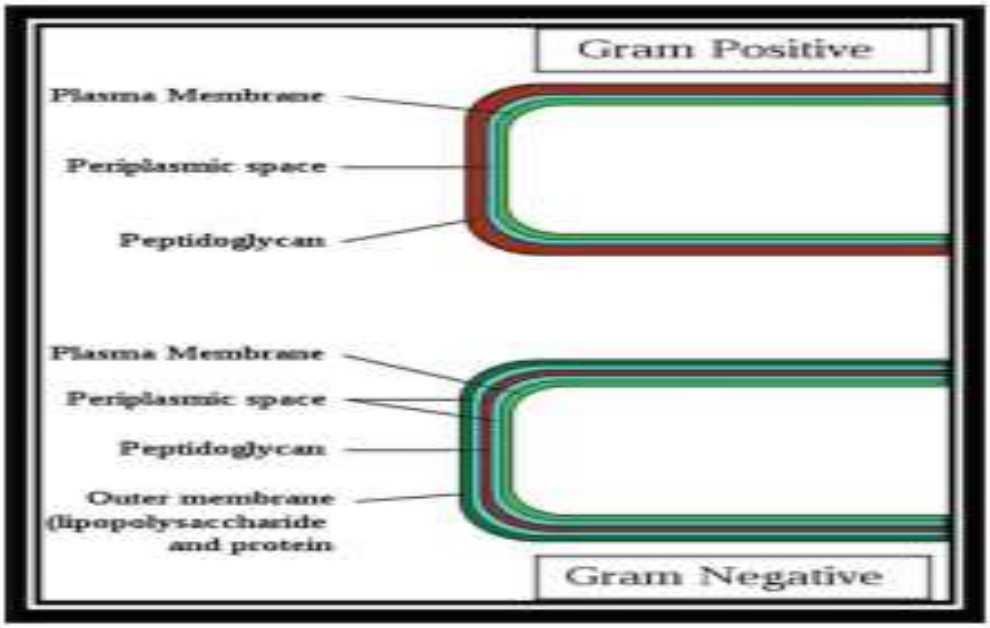

Fig 1. Bacteria cell envelope[6]

III. ANTIBIOTICS CLASSIFICATION

Antibiotics are classified into classes based on their mode of action. The main groups are: agents that inhibit cell wall synthesis, depolarize the cell membrane, inhibit protein synthesis, inhibit nuclei acid synthesis, and inhibit metabolic pathways in bacteria(table 1).

a. Cell wall synthesis inhibitors.

Cell walls are not found in human or animal cells, but they are essential for the life and reproduction of bacterial organisms. As a result, a drug that attacks bacterial cell walls may selectively destroy or inhibit bacteria. Penicllins, cephalosporins, bacitracin, and vancomycin are some examples.

b. Cell membrane function inhibitors.

The intracellular and extracellular flow of substances are separated and controlled by cell membranes. If this structure is disrupted or damaged, important solutes required for the cell's survival can leak out. Since this structure can be present in both eukaryotic and prokaryotic cells, the action of this class of antibiotics is often ineffective and detrimental to the mammalian host when used systemically. As a result, most clinical procedures are limited to topical applications. Polymixin B and colistin are two examples.

c. Protein synthesis inhibitors.

Proteins make up the majority of enzymes and cellular structures. Protein synthesis is a critical step in the multiplication and survival of all bacterial cells. Several antibacterial agents target bacterial protein synthesis by binding to the intracellular ribosome's 30S or 50S subunits. This behavior causes the bacteria's normal cellular metabolism to be disrupted, resulting in the organism's death or inhibition of growth and multiplication. Aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol, and tetracyclines are only a few examples.

d. Nucleic acid synthesis inhibitors.

All living things, including bacteria, rely on DNA and RNA for replication. Some antibiotics function by binding to components involved in DNA or RNA synthesis, interfering with normal cellular processes and, as a result, compromising bacterial replication and survival. Quinolones, metronidazole, and rifampin are some examples.

e. Other metabolic processes are inhibited by inhibitors.

Other antibiotics target specific cellular processes needed for bacterial pathogen survival. Sulfonamides and trimethoprim, for example, disrupt the folic acid pathway, which is needed for bacteria to produce precursors for DNA synthesis. Trimethophrim inhibits dihydrofolatereductase, while sulfonamides target and bind to dihydropteroate synthase; both of these enzymes are needed for the development of folic acid, a vitamin synthesized by bacteria but not by humans.

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Table 1 Major antibiotic categories and mechanisms of action.

Mechanisms of action	Antibiotic categories
Interference with cell synthesis	penicillin, cephalosporins, carbapenems, monobactam, vancomycin, teicoplanin
Protein synthesis inhibition	Tetracyclines, aminoglycosides, Oxazolidonones, streptogramins, ketolides, macrolides, lincosamides
Interference with nucleic acid synthesis	Fluoroquinolones
Inhibition of metabolic pathway	Sulphonamides, trimetrophim
Disruption of bacterial membrane structure	polymyxins, daptomycin

Source [7]

IV. ANTIBIOTIC RESISTANCE

Antibiotic resistance is a complicated problem that affects people all over the world. Antibiotic misuse in the medical, veterinary, and agricultural sectors, such as improper antibiotic prescribing, overuse in the livestock sector, and poor hospital hygiene practices, all contribute to the rise of antibiotic resistance.The spread is also being accelerated by global trade and travel. Simultaneously, the pipeline for new antibiotics has stalled, owing to a lack of incentives, enabling microorganisms to outpace the production of new drugs. Antibiotics enabled the advancement of modern medicine by allowing previously lethal infections to be healed and surgical procedures to be made safer [8]

When microorganisms are no longer inhibited by antibiotics to which they were previously susceptible, they are referred to as "antibiotics-resistant" or "drug-resistant."This form of resistance is known as 'acquired resistance,' and it is encoded by resistance genes in the microbe's DNA. Resistance genes can develop spontaneously in microbial DNA, but some have developed over time as a result of natural selection by antibiotics in the environment[9].

3.1 Antibiotic Resistance Mechanisms in Bacteria

Bacteria have remarkable genetic plasticity, allowing them to adapt to a wide range of environmental threats, including the presence of antibiotic molecules, which could jeopardize their survival. Bacteria, which share the same ecological niche with antibiotics-producing species, have evolved ancient mechanisms to withstand the harmful antibiotic molecule's influence, and as a result, their inherent resistance allows them to survive in its presence [10].Antibiotic resistance is caused by a variety of mechanisms that bacteria use to defend themselves, and understanding these mechanisms will be crucial to resolving the crisis

Active efflux pumps, drug inactivation/alteration, modification of drug binding sites/targets, changes in cell permeability resulting in reduced intracellular drug accumulation, biofilm formation, and others are examples of drug resistance mechanisms (fig 2)[11,12].

3.1.1 Efflux pumps

Efflux pumps are transporter proteins that transport toxic substances from the cell's interior to the outside world. Efflux pumps in bacteria play a big role in drug resistance because they extrude a

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wide range of antibiotics to the outside of the organism, making infections caused by these pathogens difficult to treat [13, 15].The small multidrug regulator subfamily (SMR), the Large Facilitator Superfamily (MFS), the ATP binding cassette (ABC) family, the Resistance Nodulation Cell Division Subfamily (RND), and the Multidrug and Toxic Effects (MATE) family are the five major efflux pump families. Some are designed to transport only a single drug, while others can transport several substrates [14].

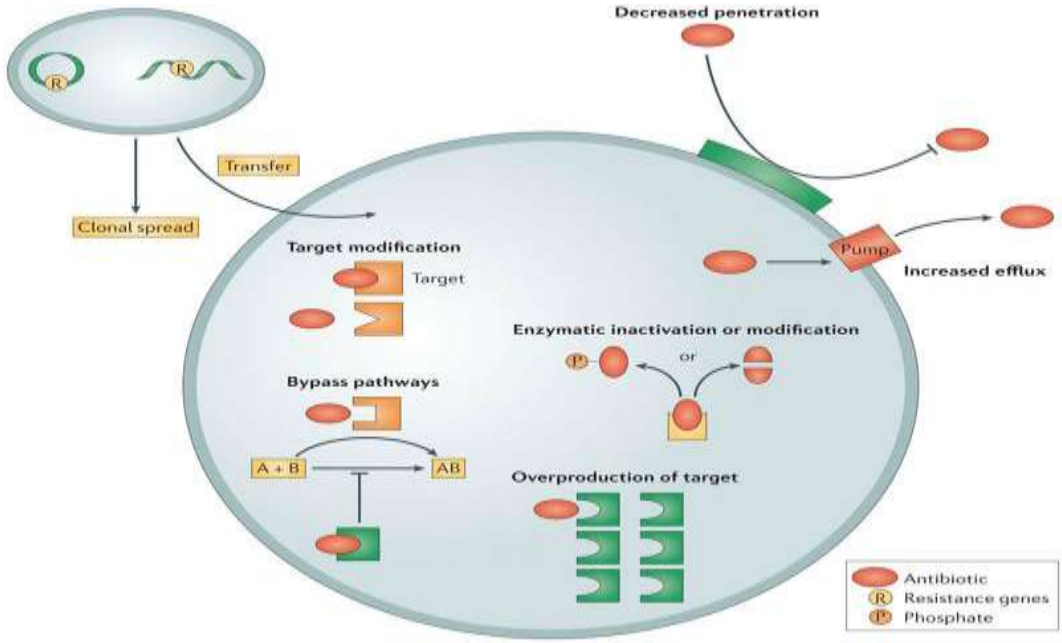

Figure 2 Mechanism of antibiotics resistance in bacteria [16].

3.1.2 Modification of target site

When the antibiotic target site is altered, the antibiotic loses its ability to bind properly. Because of the critical cellular functions of the target sites, microorganisms cannot completely avoid antibiotics action through ignoring them. Bacteria discovered a way to change the targets of antibiotics agents using this mechanism. The staphylococcal mechanism of altering the Penicillin Binding Protein (PBP), which is the target of β-lactam antibiotics, is a classic example of drug target modification [17].

3.1.3 Reduced permeability

In order to reach their target location, most antibiotics compounds need to enter the bacterial cell. Antibiotics usually cross the outer membrane of bacteria via porin channels. Antibiotics compounds are blocked from entering the cell walls of certain bacteria [18].

3.1.4 Mutation

A random change in the DNA sequence within a gene may result in a change in the trait that the gene codes for[10]. A single base pair shift can cause a change in one or more of the aminos for which it codes, altering the enzyme or cell structure and, as a result, altering the affinity or effective activity of the targeted antibiotics. Exogenous agents, DNA polymerase errors, deletions, insertions, and duplications are all common causes of mutations in prokaryotic genomes [19].

3.1.5 Inactivation of Antibiotics

Bacteria use a variety of mechanisms to make antibiotics inactive, including enzymatic hydrolysis, group transfer, and the redox process. Antibiotic inactivation is best illustrated by the development of β-lactamases, which hydrolyze the β-lactam ring of penicillins. The enzymes are often excreted by bacteria, rendering antibiotics ineffective until they meet their intended target within the bacteria. The second mechanism of antibiotic inactivation involves the transfer of a functional group such as an acyl, ribosyl, phosphoryl, or thiol group to the drug by an enzyme.Because of the structural shift, the changed antibiotic is unable to bind to the target, and the reaction is irreversible [20]. The redox reaction is the third mechanism of antibiotic inactivation [21].

3.1.6 Formation of Biofilms

Biofilms are complex microbial species that include bacteria and fungi. Microorganisms produce and secrete a protective matrix that securely adheres the biofilm to a living or nonliving surface. Bacteria trapped in a dense, slimy barrier of sugars and proteins are known as a biofilm. The microorganisms are protected from external threats by the biofilm barrier. Biofilms have a high cell density, which increases the number of resistant mutants available for selection under antibiotics strain. [22]

V. ANTIBIOTIC RESISTANCE PREVENTION STRATEGIES

Antibiotic-resistant bacteria propagate like any other bacteria around the world. This means they can be passed from person to person, animal to animal, and food to food, and they can spread across our world. Because of the inter-connectedness of the different industries, attempts to tackle antibiotic resistance must be approached from a broad perspective[23].

A formalized, functional guideline for proper antibiotic prescribing should be established and supplemented by formulary enforcement of the guidelines contained therein to avoid antibiotic overuse and misuse.It is also critical to reduce antibiotic use in agriculture, especially in food animals.Improvement of current management strategies by the production of fast and efficient molecular diagnostic techniques for identifying and epidemiological surveillance of antibiotic resistance genes in pathogens.Educate the public on the proper use of medicines[24, 25].

VI. CONCLUSION

Antibiotics were discovered, and people breathed a sigh of relief, knowing that bacteria would no longer exist on this planet.Bacterial have evolved over time, and the extensive use of antibiotics in healthcare, animal health, and agricultural settings has resulted in their resistant to various classes of antibiotics.To delay the evolution of resistance and prolong the useful lifetime of successful antibiotics, prudent use of antibiotics in healthcare, animal health, and agricultural settings, better understanding of the mechanisms of antibiotic resistance, production of new antibiotics, and bioactive molecules derived from aromatic and medicinal plants are all essential.

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