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REVIEW ON ANTIBIOTIC RESISTANCE

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ABSTRACT

Antibiotics are widely used most effective medication since the twentieth century against bacterial infections (Tetanus, Strep Throat, Urinary Tract Infections, etc.) and thus save one's life. Before 20th-century infectious disease played the main role in the death. Thus, antibiotics opened a revolutionary era in the field of medication. These cannot fight against viral infections. Antibiotics are also known as an antibacterial that kill or slow down bacterial growth and prohibit the bacteria to harm. Resistance comes as a curse with antibiotics that occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals or other agents designed to cure or prevent infections. It is now a significant threat to public health that is affecting humans worldwide outside the environment of the hospital. When a bacterium once become resistant to antibiotic then the bacterial infections cannot be cured with that antibiotic. Thus, the emergence of antibiotic resistance among the most important bacterial pathogens causing more harm. In this context, the classification of antibiotics, mode of action of antibiotics, and mechanism of resistance and the process of overcoming antibiotic resistance are discussed broadly.

KEYWORDS: antibiotics resistance, bacterial infection, revolutionary era, mechanism of action.

1. INTRODUCTION

Antibiotics are used for treatment and prevention of bacterial Infection. Antibiotics played a significant role in increasing life Expectancy witnessed in the second half of the 20th century. Antibiotics transformed modern agriculture and livestock Industries, the latter of which used antibiotics for prophylaxis, metaprophylaxis, treatment for infection, and as a growth promoter To enhance feed efficiency in healthy livestock.[1] Antibiotics are Either cytotoxic or cytostatic to the micro-organisms, allowing the Body's natural defenses, such as the immune system, to eliminate Them. They are low molecular weight compounds and most of Our natural products made by microorganisms or derived from Natural products, which are active at low concentrations against Other microorganisms but some antibiotics such as sulfa drugs and Oxazolidinones do not originate from natural products.[2] Often, They act by inhibiting the synthesis of a bacterial cell, synthesis Of proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), By a membrane disorganizing agent, or other specific actions.[3] Antibiotic resistance is among the leading global health concerns to Date. Due to an overuse of antibiotics in medicine and agriculture, Antibiotic resistance mechanisms commonly emerge and threaten Modern medicine by diminishing the utility of clinically relevant Antibiotics. Resistance to antimicrobial agents (AMR) has resulted In morbidity and mortality from treatment failures and increased Health care costs.[4]

2. Mechanism of antibiotic resistance

The three fundamental mechanisms of antibiotic resistance are.

1) Enzymatic degradation of antibacterial drugs.

2) Alteration of bacterial proteins that are antimicrobial targets.

3) Change in the membrane permeability to Antibiotics.[5]

Bacteria commonly use a mechanism to minimize the effects of antibiotics, which is the expression of drug efflux pumps. Efflux pumps have been reported as one of the mechanisms responsible for the antimicrobial resistance in biofilm structures. Efflux pumps are transport proteins involved in the extrusion of toxic substrates (including virtually all classes of clinically relevant antibiotics) from within cells into the external environment. These proteins are found in both Gram-positive and -negative bacteria and in eukaryotic organisms.[6] Few conceptions are closely connected with antibiotic resistance. First, the environment plays a role in the spread of clinically relevant antibiotic resistance. The pathways which are responsible for the release of resistance-driving chemicals into the environment are controlled by environmental regulators. Hence, environmental regulators contribute significantly to developing global and national antimicrobial resistance (AMR) action plans.[7] Antimicrobial resistance is an expected result of the interaction of many organisms with their environment. As antibiotics are naturally produced, so cohabiting bacteria have evolved mechanisms to overcome their actions to survive. Thus, these organisms are often considered to be "intrinsically" resistant to one or more antimicrobials.

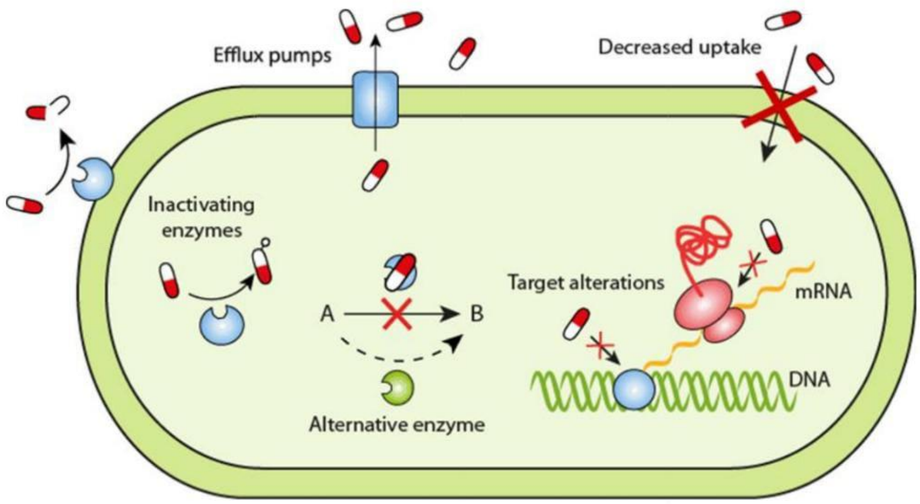

Figure 1: Mechanism of Antibiotics Resistance.

3. Detecting Methods of Antimicrobial Resistance

Antimicrobial susceptibility testing methods are in vitro Procedures used to detect antimicrobial resistance in individual Bacterial isolates. Those laboratory-based detection methods Can determine the resistance or susceptibility of an isolate against Any therapeutic candidates.

- Disk-diffusion method

The application of commercially available drug-impregnated Filter paper disks to the surface of an agar plate that has been Inoculated to confluence with the organism of interest is called Disk diffusion.[8] Disk diffusion is also known as Kirby-Bauer Antibiotic testing. The drug diffuses radially through the agar, the Concentration of the drug decreasing logarithmically as the distance From the disk increases and results in a circular zone of growth inhibition around the disk, the diameter of which is inversely proportional to the MIC. The zone diameters are interpreted based on guidelines published by CLSI, and the organisms are reported As susceptible, intermediate, or resistant. Disk diffusion can only Be used to test rapidly growing organisms, for which criteria for Interpretation of zone sizes are available.[9] The diameter of the zone Of inhibition around the antimicrobial disk is related to the minimum Inhibitory concentration (MIC) for that particular bacterial isolate; The zone of inhibition correlates inversely with the MIC of the test Bacterium. Generally, having larger the zone of inhibition, the lower The concentration of antimicrobial required to inhibit the growth of The organisms.[10] Disk diffusion test is performed by applying a bacterial inoculum Of approximately 1–2×108 CFU/ml to the surface of a large (150 mm Diameter) Mueller-Hinton agar plate. The results of the disk diffusion test are "qualitative," In that a category of susceptibility (i.e., susceptible, intermediate, Or resistant) is derived from the test rather than an MIC.[11] The Test is straightforward to perform, reproducible, and does not Require expensive equipment. The diameter of the zone of growth Inhibition is measured with calipers or a ruler and recorded in Millimeters.[12]

- Dilution Method

Agar dilution and broth dilution are the most commonly used Methods to determine the minimal concentration of antimicrobial Agents that kill (bactericidal activity, MBC) or inhibit the growth (bacteriostatic activity, MIC) of microorganisms. Dilution methods Are performed when quantitative methods are required for Microorganisms with a variable growth rate.

- Broth Dilution Technique

The Broth dilution method involves Subjecting the isolate to a series of concentrations of antimicrobial Agents in a broth environment. Micro dilution testing uses About 0.05 to 0.1 ml total broth volume and can be conveniently Performed in a microtiter format. Macro dilution testing uses Broth volumes at about 1.0 ml in standard test tubes. For both Broth dilution methods, the lowest concentration at which the Isolate is completely inhibited is recorded as the minimal inhibitory Concentration or MIC.[13] The MIC is thus the minimum Concentration of the antibiotic that will inhibit this isolate. The Broth dilution technique of antibiotic susceptibility testing is also known as the minimal inhibitory concentration (MIC) technique. Test tubes or wells containing increasing concentrations of each Antibiotic to be tested, from 0.0312 to 512 µg/ml, are inoculated With a fixed volume of nutrient broth containing a standard Concentration of bacteria. The concentration of the antibiotic in Each tube is double that in the previous tube. In the broth Dilution assay, an antimicrobial is added to a culture tube of non selective broth medium at different concentrations.[14] Tubes are Incubated under optimum conditions for the test microorganism From 16 to 24 hours. Antimicrobial effect could be determined by Spectro-photometry or by plating counting.[15]

- The Agar Dilution Method

Agar dilutions are most often Prepared in petri dishes and have advantage that it is possible to test Several organisms on each plate.[16] In the agar dilution method, The antimicrobial agent is incorporated into the agar medium with Each plate containing a different concentration of the agent. The Inoculum can be applied rapidly and simultaneously to the agar Surfaces using an inoculum replicating apparatus. Mueller-Hinton Agar is prepared from a dehydrated base. The advantages of agar Dilution testing include the reproducible results and satisfactory Growth of most nonfastidious organisms. Agar dilution testing Generally is not performed in routine clinical laboratories but can Be ideal for regional reference laboratories or research laboratories That must test large numbers of isolates.[17]

4. Mode of action of antibiotics

An antibiotic becomes functional by killing the bacteria. Antibiotics block the fundamental functions that took place in bacteria or stop them from multiplying which helps the immune system to fight against the bacterial infection. The antibiotics that affect a wide range of bacteria are known as broad-spectrum antibiotics. Some affect only a few types of bacteria known as narrow- spectrum antibiotics.

The mechanism of action of antibiotics,

- bacterial cell wall synthesis inhibition,
- Antibiotics cell membrane structure and function breakdown
- Disrupts the structure and function of nucleic acids
- Disrupts protein synthesis
- Key metabolic pathways blockage.[18]

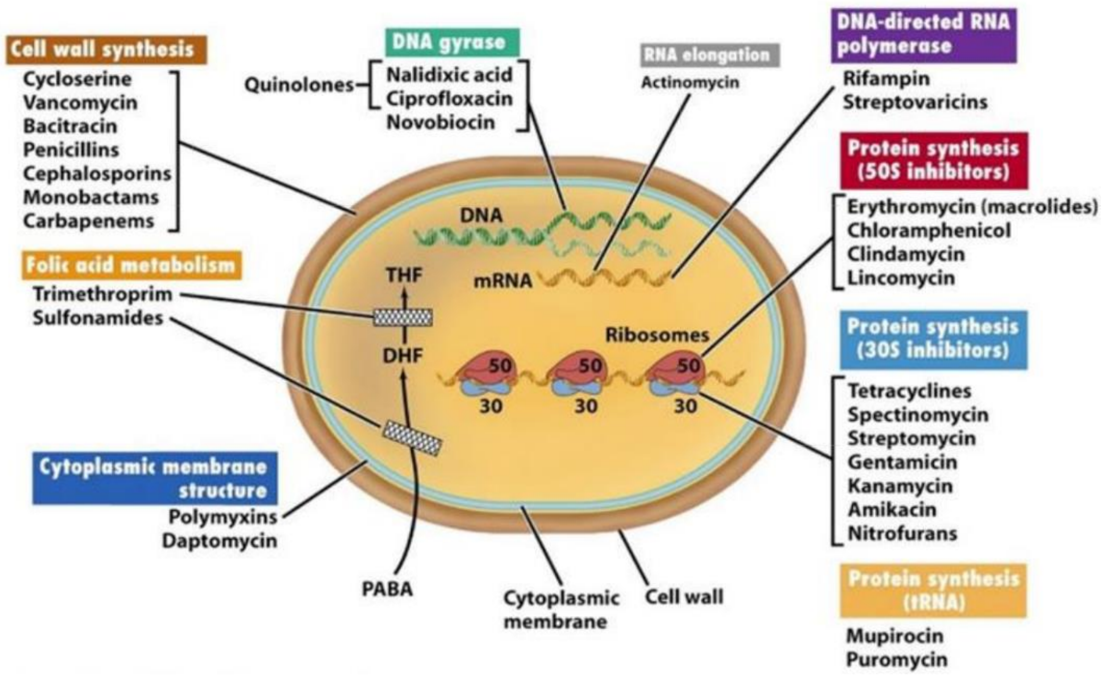

Figure 2: Major Target Sites of Antimicrobial Agents.

4.1. Inhibition of cell wall synthesis

Humans and animals do not have cell walls in their cells while the bacterial cells are surrounded by a rigid layer of peptidoglycan (PG), this structure is critical for the life and survival of bacterial species. The antibiotics (e.g., penicillins, cephalosporins, bacitracin, and vancomycin) target the cell walls of bacteria and can selectively kill or inhibit bacterial organisms.[19]

4.2. Inhibition of cell membrane function

Intra- and extracellular flow of substances are regulated and segregated through the cell membrane. If somehow this important barrier becomes disrupted or damaged, then the essential solutes leaked which helps in cell survival. Because this structure is found in both eukaryotic and prokaryotic cells, the action of this class of antibiotic are often poorlyselective and can often be toxic for systemic use in the mammalian host. Most clinical usage is therefore limited to topical applications. Examples: polymixin B and colistin.

4.3. Inhibition of protein synthesis

Protein synthesis is a fundamental process for the multiplication and survival of all bacterial cells as enzymes and cellular structures are primarily made of proteins. Proteins are responsible for structuralcomposition, metabolic and physiological processes, and response to adverse conditions. Several types of antibacterial agents target bacterial protein synthesis by binding to either the 30S or 50S subunits of the intracellular ribosomes. This activity then results in the disruption of the normal cellular metabolism of the bacteria and consequently leads to the death of the organism or the inhibition of its growth and multiplication. Examples: Aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol, tetracyclines.[20]

4.4. Inhibition of nucleic acid synthesis

Nucleic acid (DNA and RNA) synthesis is an essential process for all living organisms including bacteria. Some antibiotics work by binding to components involved in the process of DNA or RNA synthesis, which causes interference of the normal cellular processes which will ultimately compromise bacterial multiplication and survival. Examples: quinolones, metronidazole, and rifampin.

4.5. Inhibitors of other metabolic processes

Other antibiotics act on selected cellular processes essential for the survival of the bacterial pathogens. For example, both sulfonamides and trimethoprim disrupt the folic acid pathway, which is a necessary step for bacteria to produce precursors important for DNA synthesis. Sulfonamides target and bind to dihydropteroate synthase, trimethophrim inhibit dihydrofolate reductase.[6]

5. Strategies to Minimize Antibiotic Resistance

Antibiotic-resistant bacteria are spread globally in the same way as other bacteria. This means they can be transferred between people, animals and foodstuffs, and they can spread in our environment. These links between the various sectors mean that efforts to combat antibiotic resistance must be made from a broad perspective. Prudent use of antibiotics in healthcare, animal health and agricultural settings is essential to slow the emergence of resistance and extend the useful lifetime of effective antibiotics. Treatment conditions of antibiotics for bacterial infections have gradually worsened, because of antibiotic resistance and the lack of new drugs. Apparently, it is now clear that antibiotic use can increase the emergence of antibiotic-resistant bacteria, and reducing prescribing is one of the effective ways to reduce selection pressure.[21] Resistant bacteria can spread quickly and represent a reservoir of bacteria that can spread further to both people and animals. Animals can get infections that are difficult to treat as a result of resistant bacteria and causes suffering for the animals and economic losses. To prevent overuse and misuse of antibiotics, a formalized, practical guideline for appropriate antibiotic prescribing should be developed and followed by formulary implementation of the guidelines contained therein. The development of quick and effective molecular diagnostic techniques for identification and epidemiological surveillance of resistance genes of antibiotic resistant pathogens can improve current control strategies. Reducing use of antibiotic in agriculture, especially in food animals, is also important. Changing policies to use of antibiotics in livestock can include ban or restriction on using veterinary important antibiotics, promising financial incentives for developing livestockspecific antibiotics, making drug licensing rules more stringent and imposing penalties. Effective strategies are required to address the problem of antibiotic resistance. Therefore, appropriate use of antibiotics, vaccination, education, research, development of novel antibiotics, policy, regulations, surveillance of antimicrobial resistance and antibiotic use have a great role in minimization of antibiotic resistance.[22]

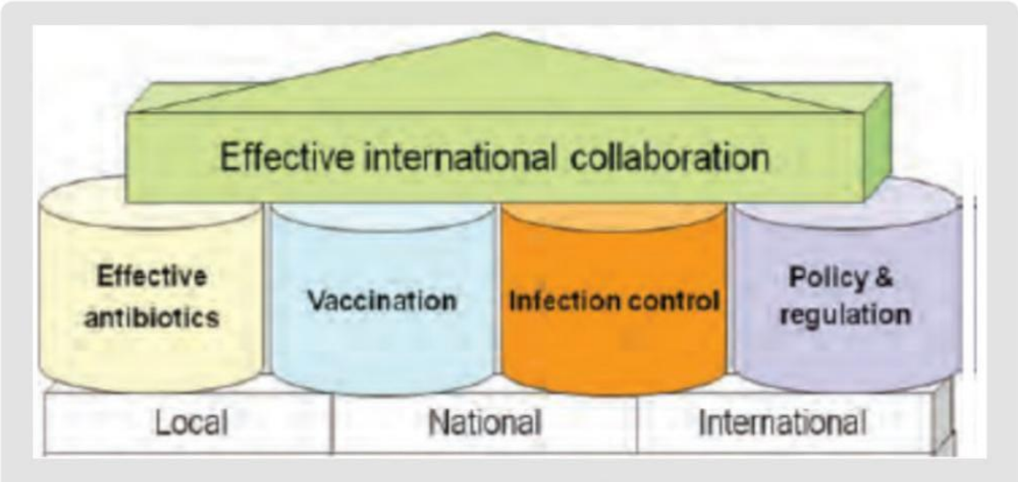

Figure 3: major components of strategies to minimize antibiotic resistance.

6. CONCLUSION

This review analyzes the importance of antibiotics, their classification, and mode of action, resistance mechanism and way to get rid of the current problem of antibiotic resistance. The antibiotics can be classified based on their molecular structures, mode of action, route of administration (injectable, oral, and topical), and spectrum of activity. Antibiotics help us to fight against infectious diseases. However, the improper use or over use of antibiotics helps to develop the emergence of bacterial resistance to all known antibiotics, which is an alarming concern now-a-days. If the bacteria oncebecome resistant to the antibiotic, it is hard to cure the infectious disease using the antibiotic. Proper uses of antibiotics play an important role to minimize the antibiotic resistance. This review is delivering the knowledge about antibiotics, the proper use, and mode of action and resistance mechanism.

Antibiotic resistance is rising to dangerously high levels in All parts of the world. New resistance mechanisms are emerging And spreading globally, threatening our ability to treat common Infectious diseases. Infections caused antibiotic-resistant germs Are difficult, and sometimes impossible, to treat. Therefore, prudent Use of antibiotics in healthcare, animal health and agricultural Settings is essential to slow the emergence of resistance and extend The useful lifetime of effective antibiotics.

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