The Battle Against Antimicrobial Resistance: causes, consequences and control

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Abstract— Globally, the fight against infectious diseases and the reduction of morbidity and death have been greatly aided by antimicrobial agents. However, the effectiveness of current treatments is under jeopardy due to the advent and rapid spread of antimicrobial resistance (AMR), a serious worldwide health concern. AMR is the result of microorganisms such as bacteria, viruses, fungi, and parasites developing defense mechanisms against antimicrobial medications. The overuse of antibiotics in human medicine, agriculture, and animal husbandry, poor infection control procedures, poor sanitation, and a lack of public awareness are some of the elements that accelerate the emergence of antibiotic resistance. Self -medication and the improper use of antibiotics in medical settings exacerbate the issue and guarantee the long-term control of infectious diseases. A comprehensive strategy is needed to combat AMR, including the prudent use of antibiotics, the establishment of antimicrobial stewardship programs, the creation of innovative therapeutic agents, the reinforcement of infection prevention and control measures, and the advancement of international surveillance systems. Additionally crucial are policy enforcement, public education, and research into alternative therapies including probiotics, vaccinations, and bacteriophages. To maintain the effectiveness of antimicrobial drugs and guarantee sustainable management of infectious diseases for future generations, a concerted international effort is essential.

Index Terms— Antimicrobial resistance, factors accelerating rate antimicrobial resistance, mechanism of AMR, strategies to overcome AMR

I.INTRODUCTION

Antimicrobials are drugs that either eradicate bacteria, fungi, viruses, or other microorganisms or stop their growth. Infections in humans, animals, and plants are prevented or treated with these compounds. The Greek terms anti (against), mikros (small), and bios (life) are the sources of the word antimicrobial. It describes compounds that either destroy bacteria or stop them from growing. The invention and discovery of antimicrobials has completely changed how infectious diseases are treated. The many kinds of antimicrobials are 1) Antibiotics: These substances, such as tetracycline and penicillin, either kill or stop the growth of germs. 2) Antiviral substances that stop viruses from replicating Oseltamivir (tamiflu) and acyclovir are two examples. 3) Antifungals are substances that stop fungus from growing. Examples are amphotericin B and fluconazole (diclofenac). 4) Antiparasitic substances, which prevent the multiplication of parasites. Chloroquine is one example. [1] Antimicrobials are work by targeting specific process or structures essential for Microbial growth and survival. for exemplification inhibiting cell wall conflation, inhibiting protein conflation, intruding with DNA replication. Ehrlich created salvarsan, a syphilis treatment, in 1910, making it the world's first antimicrobial agent. Penicillin was discovered by Fleming in 1928. He describes how the growth of Staphylococcus aureus was suppressed in a zone surrounding a contami-blue earth (a fungus from the Penicillium genus) on culture dishes, which led to the discovery that a microbe would create compounds that could prevent the growth of other microorganisms. The 1940s saw the introduction of the antibiotic, known as penicillin, into therapeutic usage. During World War II, penicillin, an exceptional medication in terms of safety and effectiveness, led the way in antimicrobial chemotherapy by saving the lives of many injured soldier. [2]

After six decades of wide antibiotic use, bacterial pathogens of mortal and beast origin are getting decreasingly resistant to numerous antimicrobial agents. Antimicrobial resistance develops through a limited number of mechanisms(a) permeability Variations in the structure of the bacterial cell wall/ membrane, which restrict antimicrobial access to target spots;(b) The antimicrobial agent is actively transported out of the cell;(c) mutation in the target point;(d) enzymatic revision or declination of the antimicrobial; and(e) accession of indispensable metabolic pathways to those inhibited by the medicine. many bacterial antimicrobial resistance phenotypes affect from the accession of external genes that may give Persistence to an entire class of antimicrobials. [3]

II.ANTIMICROBIAL RESISTANCE

Globally, a single among the biggest concerns for both human and animal health is antimicrobial resistance (AMR). Antimicrobial medication use in humans or animals causes resistant microorganisms to arise and spread, and misuse or overuse exacerbates this issue. So, It is crucial to both maintain the use of effective antimicrobials for as long as feasible and to keep using them to enhance the health of people and animals. Antimicrobial Resistance (AMR) is the result of microorganisms, such as bacteria, viruses, fungi, and parasites, developing the ability to grow and adapt when exposed to drugs that used to affect them.[1]. Antimicrobial resistance (AMR) poses a serious threat to health systems worldwide not just in developing countries. That many antibiotics no longer reliably treat infections signals a precarious future for healthcare. Serious infections and extended hospital stays, greater healthcare expenses, higher costs for second-line medications, and treatment failures are all consequences of AMR infection.[2] The human immune system's ability to combat infectious infections is weakened by antibiotic resistance, which also increases the risk of many problems for susceptible individuals receiving chemotherapy, dialysis, surgery, and joint replacement.[1] AMR, sometimes known as the "Silent Pandemic," Immediate action is needed regarding this issue, better management, and should not be viewed as a potential future crisis.[3] The creation of novel antibiotics has drastically decreased in the last few decades. Additionally, AMR reduces the effectiveness of current antibiotic.

A recent threat to public health around the world is the corona virus disease, or COVID-19. Azithromycin is one of the antibiotics that many COVID-19 Individuals experiencing mild symptoms without signs of pneumonia or moderate illness with pneumonia take, despite Health authorities advise against this practice. The World Health Organization has warned that “increased use of antibiotics during the COVID-19 pandemic will intensify bacterial resistance and result in more deaths during the crisis and beyond.” In the 1940s, Sir Alexander Fleming advised about antibiotic resistance, and his vaticination came true within ten times due to the abuse of the medicines. Since also, educational programs, quality operation protocols, and clinical guidelines were developed by contagious- complaint professional associations to help and control the problem still, these were set up substantially ineffective.[4]

III.MECHANISM OF AMR

Antimicrobial resistance (AMR) arises when microorganisms gain the ability to survive exposure to drugs that are designed to kill them or stop their growth. They achieve this through mechanisms such as genetic mutations, gene transfer, changes in the drug target, drug inactivation, active efflux pumps, and formation of biofilms. [5]

1. Genetic mutations

Microorganisms have the ability to develop resistance against antimicrobial agents through inheritable changes, known as mutations, in their DNA sequences. These mutations can occur spontaneously or be triggered by exposure to antimicrobial substances. [6]

2. Genetic transfer

Microorganisms can acquire antimicrobial resistance by inheritable gene transfer, which enables the acquisition of resistance traits. This process occurs via two main routes vertical gene transfer, where resistance genes pass from parent to offspring during cell division; and horizontal gene transfer, where elements like plasmids or transposons act as carriers to convey resistance genes between organisms. [7]

3. Alteration of drug target, drug inactivation, and efflux pumps

Microorganisms can develop antimicrobial resistance by altering the medication's target site that is, the precise structure in the organism that the drug is meant to attack making it less vulnerable to treatment. Some bacteria generate enzymes that deactivate antimicrobial agents, thereby reducing their effectiveness. Others possess efflux pumps proteins that actively expel these drugs from within the cell preventing the medication from accumulating in sufficient concentration to destroy the organism. [8]

4. Formation of biofilms

Some microbes are able to form biofilms thin layers of microorganisms adhering to a surface and encased in an extracellular matrix. These biofilms can protect the microbes against antimicrobial treatments, making it far harder to eliminate the organisms.[9]

IV.FACTORS ACCELERATING THE RATE OF ANTIMICROBIAL RESISTANCE

1) Misuse and excessive use of antibiotics

Since antibiotics were first discovered in the 1940s, Sir Alexander Fleming advised the public about the There is growing demand for antibiotics in the future, which may result in their excessive use.[10] Different checks across the globe indicate that numerous cases forcefully believe antibacterial agents would help with viral conditions like the common cold wave or flu. likewise, in numerous developing countries where there are scarcities in proper individual tools, patient operation is generally contingent upon the tradition of drug, particularly antibiotics. Administering antibiotics when they're actually not demanded for the treatment is another illustration of common abuse of them. also, numerous antibiotics are of poor quality and vended over the athwart in the developing countries. also, antibacterial resistance can develop because unnecessarily define lengthy courses of antibiotics. fiscal impulses play an important factor in overprescribing antibiotics. For illustration, Chinese hospitals incentivize croakers to define antibiotics; as a result, they will admit further plutocrat from pharmaceutical companies.[11]

2) Agriculture use of antibiotics

The use of antibiotics in agriculture is a major factor driving antimicrobial resistance in humans.[12] In addition to the operation of antibiotics to treat sick brutes, antibiotics are largely added to healthy beast feed and drinking water in order to help sickness (prophylaxis) among brutes to a large extent, to further grow herds at sub therapeutic situations, and to elevate feed effectiveness. For case, one of the considerably used antibiotics in beast husbandry worldwide to further promote the growth of beast, particularly stuffers, is colistin, a critical last- line antibiotic to treat severe infections in humans.[13]

3) Failures in Implementing Infection Control Measures

Infection control involves a series of practices aimed at preventing the spread of infectious diseases.[14] Failing to follow proper infection-control procedures can lead to the spread of infectious diseases and result in serious consequences, such as outbreaks and other harmful impacts on the overall quality and safety of healthcare facilities.[15] To prevent failures in infection-control efforts, it is essential to follow established protocols, maintain clean and sterile environments, and uphold high standards of hygiene. This includes regular handwashing, using appropriate protective measures, and properly handling and disposing of infectious materials. It is also crucial that all healthcare personnel receive thorough training in infection-control practices and are held accountable for applying these measures consistently and correctly.[16]

4) Biological Factors

Antibiotic resistance may be spontaneously through mutation and bacterial elaboration.[17] likewise, plasmids, small indirect fractions of DNA in bacteria, can gain a great variety of resistance genes through transposons and insertion sequences. These plasmids can be transferred to bacteria from other species and spread the antibacterial resistance in the bacterial population. In addition, swapping resistance inheritable factors between bacteria through vertical gene transfer further accelerates the spread of antibiotic resistance.[18]

V.STRATEGIES TO OVERCOME AMR

1. Alternative therapies

A. Antimicrobial peptides

Gramicidin was the first antimicrobial peptide to be identified. Discovered in 1939 from *Bacillus brevis* isolated from soil, it was found to be effective against bacterial pathogens.[19] AMPs interact with bacterial membranes mainly through electrostatic forces, which makes it difficult for bacteria to develop resistance against them. Some AMPs act directly on the membrane, while others operate without damaging it. Membrane-active AMPs are typically cationic and disrupt the bacterial membrane upon contact. In contrast, certain AMPs can pass through the membrane without causing structural harm. Some types even form pores that span the membrane. Other AMPs affect the cell after entering it by interfering with vital processes such as protein synthesis, enzyme activity, cell signeling, and other essential intracellular functions Certain AMPs can break down or alter biofilm formation. During their interaction with bacterial membranes, some AMPs undergo structural or conformational changes. Currently, three main models are used to explain how AMPs act on bacterial membranes. In the barrel-stave model, AMPs aggregate and insert into the lipid bilayer, aligning themselves with the phospholipids to form a channel-like structure. In the toroidal pore model, AMPs embed within the membrane, and their accumulation induces curvature of the lipids, creating a ring-shaped pore. In the carpet model, AMPs cover the membrane surface like a "carpet," disrupting it in a detergent-like manner and ultimately damaging the membrane. [19,20]

B. CRISPR-Cas System

In prokaryotes, the CRISPR-Cas system comprising CRISPR sequences and CRISPR-associated (Cas) proteins acts as an RNA-guided adaptive immune mechanism that detects and defends against invading genetic elements such as phages and plasmids. This system has also emerged as a promising gene-editing tool for combating bacterial drug resistance, as it can precisely target and cut DNA sequences responsible for antibiotic resistance genes. Potential applications of CRISPR-Cas include limiting the spread of antibiotic resistance and controlling horizontal gene transfer.[21]

The CRISPR-Cas system is broadly categorized into two classes based on the proteins involved and their mechanisms of action. Class 1 employs multi-protein effector complexes to degrade nucleic acids and includes types I, III, and IV. Class 2 uses single-protein effector complexes for nucleic acid degradation and includes types II, V, and VI. Among these, type II CRISPR-Cas systems are the most studied and widely used for targeting and removing resistance genes due to their relatively simple structure. Recently, Type I CRISPR-Cas systems have been developed as inheritable tools for removing antibiotic resistance genes. The CRISPR-Cas defense mechanism in bacteria occurs in three stages: adaptation, where spacer sequences from invading genetic elements are acquired; expression, involving the production of crRNA and Cas proteins; and interference, in which the crRNA-Cas complex recognizes complementary nucleic acid sequences and uses endonuclease activity to degrade them. This precise targeting enables the CRISPR system to selectively eliminate specific resistance genes, thereby controlling vertical gene transfer and helping to limit the spread of antibiotic resistance.[22]

2. Improving antibiotic use

A. Antimicrobial stewardship

Antimicrobial stewardship (AMS) is defined as "an organizational or healthcare- system-wide approach for fostering and covering judicious use of antimicrobials to save their effectiveness. It was firstly defined as organized interpositions with the premise of enhancing antimicrobial use when choosing the applicable agents, the correct dosage, route of administration, and the duration of remedy without biasing patient results. AMS refers to a set of coordinated strategies to (i) enhance patient care, and results by optimal remedy; (ii) reduce collateral damage by reducing antimicrobial use (lower resistance), and (iii) reduce the cost for antibiotics. These strategies can be used widely to help control AMR by raising mindfulness of the public and educating healthcare professionals on the prudent use of antimicrobials as part of an ASP. Overall, AMR should be considered a global precedence, and all countries and associations should make coordinated sweats to apply new programs and exploration concerning ASP.[23]

B. Stricter control in agriculture

Antibiotic use for basically non-medical or non-therapeutic purposes in agrarian settings that are at subtherapeutic situations over an extended period is observed as a major route for the arrival of antibiotic resistance and antibiotic- resistant bacteria, and The presence of resistance genes has been observed. to be transferred to humans. so regulate antibiotics use in agriculture to reduce resistance spread. Monitoring antibiotic use and promoting alternate styles similar as probiotics or prebiotics to reduce antibiotic reliance [24]

3. Research and development

A. New antibiotics development

The global rise of multidrug-resistant bacterial pathogens has created an urgent need for new antimicrobials to treat life-threatening infections. This demand contrasts sharply with the limited investment in developing new drugs, especially those derived from natural products or synthetic small molecules. There is a critical worldwide need for novel agents with innovative chemical structures and unique mechanisms of action to combat the growing public health threat of antimicrobial resistance. Developing new antibiotic molecules is essential to stay ahead of emerging resistance.[25]

B. Combination therapy

Combination therapy involves the simultaneous use of two or more antibiotics or adjuvants. Such combinations are important because they can reduce the required dosage, minimize adverse side effects, and improve the overall effectiveness of the treatment. Additionally, combining antimicrobials can enhance the activity of an existing antibiotic, slow the development of resistance, and restore the effectiveness of drugs that have been compromised by resistance. The use of multiple antimicrobials together is a common practice in clinical settings to manage infections more effectively.[26]

VI.CONCLUSION

Antimicrobial agents remain crucial in modern medicine, but their effectiveness is increasingly threatened by antimicrobial resistance (AMR). The rapid spread of resistance is driven by the overuse and misuse of these drugs, poor infection control practices, and a lack of awareness. A comprehensive approach that incorporates sensible medication usage, stringent antimicrobial stewardship, better cleanliness, surveillance, and continuous research into novel treatments is needed to combat AMR. The effectiveness of antimicrobial drugs must be safeguarded for future generations through responsible use and coordinated global efforts.

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