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An Overview of Antimicrobial Resistance

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ABSTRACT

All living organisms have developed intricate mechanisms to ensure their existence, driven by the natural instincts of their survival. Humans have developed antimicrobial drugs as a response to infections, while microorganisms have concurrently adapted to survive in the presence of these antimicrobials. So, a significant challenge we face today is antimicrobial resistance (AMR). This article explores the origins, emergence and factors leading to AMR, as well as potential solutions, including alternative therapies, antimicrobial stewardship programs and use of Artificial intelligence to combat this issue and ensure the future of healthcare

Introduction

Antimicrobial drugs have undoubtedly played a key role in mitigating the human and animal sufferings, considerably reducing the risks associated with infectious diseases [1]. However, an alarming trend emerged a few years after the discovery of antibiotics: microorganisms demonstrated resilience and persist even after the administration of antimicrobial drugs. This marked the beginning of the Antimicrobial Resistance (AMR) era. Antimicrobial resistance (AMR) is a phenomenon wherein bacteria acquire the capacity to withstand the effects of antibiotics, resulting in their sustained survival or diminished susceptibility to these antimicrobial agents [2]. The consequences of AMR are profound and can include clinical treatment failures, the requirement for increased antibiotic concentrations to achieve efficacy, unique bacterial resistance mechanisms, or deviations from conventional susceptibility patterns within populations. AMR represents a significant global health challenge, limiting the effectiveness of antimicrobials in combatting bacterial infections [10]. The fact that infectious diseases may no longer respond to available antibiotics, if not managed, depicts an uncertain future for healthcare [4]. The global burden of AMR is steadily increasing and is closely associated with elevated morbidity and mortality rates within clinical and community settings [9]. Current estimates suggest that AMR will contribute to approximately 10 million deaths annually [11].

Emergence of AMR

The emergence of Antimicrobial Resistance (AMR) represents a natural evolutionary response of microorganisms to the exposure of antimicrobial agents, according to the principles mentioned in Darwin's theory of natural selection. Over time, microorganisms have developed complex mechanisms to evade destruction by these toxic substances. The realization that antibiotics, previously called as 'magical bullets,' were losing strength in their efficacy marked the beginning of antimicrobial resistance [1]. This decline in effectiveness was a direct result of the selective pressure exerted by the extensive use of antimicrobial drugs. Initially, it was hypothesized that microorganisms released antimicrobial agents to inhibit the growth of others. However, this phenomenon proved to be more complex, as the concentrations produced were insufficient to kill other microorganisms. Paradoxically, these antimicrobial agents seemed to accelerate the process of microbial adaptive evolution, making them resistant to these chemicals [3]. Interestingly, the genes responsible for AMR may have originated from antibiotic producing microorganisms, which employ similar mechanisms to combat against their own antibiotic production [2]. These genes can then be transferred to other bacteria of the same or different species, continuing the cycle of resistance. Before the 1990s, this issue was not perceived as a serious threat [2]. But gradual treatment failures led to the development of first, second, and third generations of antimicrobial drugs which emphasized the growing urgency of the AMR challenge.

Factors leading to AMR

Misuse or Overuse of Antibiotics

In many developing countries, the use of poor-quality antibiotics worsens the issue of AMR [11]. Additionally, antibiotics are inappropriately used to combat viral diseases, such as the flu. The absence of strong regulatory frameworks and diagnostic tools often leads to excessive antibiotic usage, characterized by a trial-and-error approach that undoubtedly contributes to the spread of AMR. Also there is a growing trend of public demand for antibiotics, often for self-medication purposes, even when they are not needed. In the healthcare sector, the influence of financial incentives offered by some pharmaceutical companies to physicians can sometimes lead to the prescription of antibiotics when they are not the most appropriate course of treatment. All these malpractices contribute to the emergence and spread of AMR.

Agricultural Use of Antibiotics

The agricultural use of antibiotics, particularly in animal and livestock feed for growth promotion, is a common practice in food animal production [4]. This approach aims to enhance growth rates and productivity of animals in form of milk and meat. However, it raises concerns about the development of antibiotic resistance and the potential transmission of resistant bacteria from animals to humans through the food chain.

Biological Factors

Many biological factors drive the development of antibiotic resistance in bacteria. First, bacteria have the innate ability to undergo natural mutations, potentially leading to the emergence of antibiotic resistance [4]. These genetic changes can result in modifications to essential cellular components, making antibiotics less effective or ineffective. Additionally, bacteria have the capacity to acquire foreign DNA containing genes that cause resistance to antibiotics. Horizontal gene transfer is a vital phenomenon in the context of antimicrobial resistance which occur through three basic processes i.e. Transduction, Transformation and Conjugation. Transduction involves the transfer of genes between bacterial cells via bacteriophages, which are viruses that specifically infect bacteria. Transformation enables bacteria to directly uptake genes from their external environment, often originating from lysed bacterial cells and may include resistance genes. Conjugation, most occuring process in the spread of antibiotic resistance, involves the direct sharing of small DNA segments between bacterial cells [5]. These factors collectively contribute to the emergence and spread of AMR, posing significant challenges to public health and healthcare systems all over the world.

Mechanisms of Antimicrobial Resistance

Understanding the scientific basis of AMR is essential for addressing this significant public health concern and developing more effective antimicrobial drugs that can bypass both known and unknown mechanisms of resistance. Two types of resistance are present in microorganisms [1].

1. **Intrinsic Resistance**

Intrinsic resistance is a naturally occurring phenomenon that exists independently of exposure to antimicrobial drugs. It is chromosomally mediated and universally present in bacteria [6]. This type of resistance is predictable based on an organism's identity and is not influenced by previous exposure to antimicrobial drugs or horizontal gene transfer. For example, klebsiella pneumoniae is intrinsically resistant to Ampicillin.

Mechanisms

Common mechanisms of intrinsic resistance include reduced permeability of outer membrane, making it difficult for antimicrobial drugs to enter the cell. Bacteria may naturally possess non specific efflux pumps that can actively pump out a wide range of substances, including antimicrobial drugs, reducing their effectiveness [5]. Certain bacteria lack receptor or specific target sites required for the action of antimicrobial drugs.

2. **Acquired Resistance**:

Acquired resistance differs from intrinsic resistance in that it develops as a response to exposure to antimicrobial drugs [5]. It is frequently facilitated by genetic changes and horizontal gene transfer. The most common route for the acquisition of foreign genetic material is through plasmid mediated transmission of resistance genes.

Mechanisms

Decreased Accumulation of Drug

Bacteria may use one or both of these processes to reduce the accumulation of antimicrobial drugs in their cells. One of which is decrease in permeability of outer membrane. This process differs between gram positive and gram negative bacteria. Gram negative bacteria often employ this mechanism to reduce the entry of drugs. Gram positive bacteria, which lack an outer membrane, use alternative mechanisms to resist Antimicrobials like formation

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of biofilms. Bacteria often form biofilms to protect themselves from the immune system and antimicrobial drugs. Biofilms provide a suitable environment for the transfer of resistance genes. Porin channels are used for chemical transfers, and bacteria may decrease the number of these channels (e.g., in Enterobacteriaceae) or change their selectivity (e.g., in E. Aerogenes) to reduce permeability [6]. The other process to reduce accumulation of drug is increased efflux of drug. Bacteria can actively pump out antimicrobial drugs using efflux pumps. Bacteria possess encoded genes for efflux pumps, some of which are expressed constitutively, while others are induced under specific stimuli [7]. These pumps are classified into some major families based on structure and energy source, such as the ATP binding cassette (ABC) family and the Small Multidrug Resistance (SMR) family. They actively remove drugs from bacterial cells.

Drug Inactivation/Modifications

Some bacteria produce enzymes that can degrade antimicrobial drugs, rendering them ineffective.

Another mechanism involves transferring chemical groups, such as acetyl or adenyl, to the drug [8]. This modification prevents the drug from performing its intended action on bacteria.

Alteration of Drug Target

Bacteria have multiple components that serve as targets for antimicrobial drugs. Resistance can occur through mutations that alter the structure of the binding site or receptor. Examples include ribosomal mutations that affect antibiotics targeting protein synthesis and modifications to DNA gyrase for drugs that target nucleic acid synthesis. These alterations reduce the drug's ability to exert its effect on bacteria [9].

Some bacteria may possess alternative enzyme for the enzyme which is targeted by Antimicrobial drugs or some can over produce their target sites which reduce the efficiency of antimicrobial drugs. Understanding these diverse mechanisms of acquired resistance is crucial for developing strategies to combat antimicrobial resistance and design more effective antimicrobial drugs.

Multidrug Resistance (MDR)

Multidrug resistance (MDR) is a significant concern in the context of antimicrobial resistance (AMR). It occurs when bacteria possess not only intrinsic and acquired resistance but also multiple mechanisms of resistance making them resistant to a wide range of antimicrobial agents. In MDR bacteria, these mechanisms can collectively cause resistance to multiple classes of antibiotics. A commonly used definition of MDR is when bacteria exhibit resistance to at least one antibiotic in three or more different classes of antibiotics [5]. This broad resistance makes treatment of infections more challenging and often requires the use of more potent or less commonly used antibiotics, which can have greater side effects or limited effectiveness [7]. Example of this is MRSA known as methicillin resistant staphylococcus aureus. It caused many deaths due to resistance against many antibiotics in previous years. MDR bacteria are a serious public health concern because they limit the available treatment options for infectious diseases, increasing the risk of treatment failures and the spread of drug resistant infections.

Management and Strategies to Combat AMR

Efforts to manage and combat AMR involve a multifaceted approach at both national and international levels. Here's an overview of various strategies:

Regulatory Measures for Antibiotics

Use of antibiotics in combination with different mechanisms of action to treat infections can reduce the risk of resistance development. Antimicrobial Stewardship Programs (ASPs) should be implemented to promote the rational and responsible use of antibiotics ensuring that antibiotics are prescribed only when they are needed and used effectively [5]. Antibiotics sensitivity test should be done which can prevent the wrong treatment course of antibiotics. Healthcare professionals should have access to standard treatment guidelines based on the latest scientific evidence and follow them. Regulation of the sale and distribution of antibiotics to prevent their misuse and overuse. Antimicrobial surveillance should be done to monitor antimicrobial use and resistance patterns, identifying the emerging resistance and inform treatment guidelines.

Alternative Therapies

There should be research and practical application of alternative treatment options, such as phage therapy, vaccination, immune stimulants, and probiotics, can reduce reliance on antibiotics and mitigate resistance [10]. Alternative medicines like homeopathy should be considered and research should be done to understand its mechanism and approaches to use it effectively. Prophylactic measures can also decrease the risk of infections.

National and International Approaches

Comprehensive National Policies and action plans are essential on a domestic level to combat antimicrobial resistance (AMR). These policies, when developed and implemented, serve as a foundation in addressing the multifaceted challenge of AMR. Simultaneously, Public Education campaigns play a vital role in raising awareness among the general population regarding the proper use of antibiotics, the severe consequences of AMR, and the critical importance of completing prescribed antibiotic courses.

On international level, compliance to the World Health Organization's (WHO) Recommended Approaches for addressing AMR is of significant importance. These guidelines and recommendations, developed through thorough scientific studies, provide a unified framework for nations to combat AMR collectively [9]. Moreover promoting collaboration is essential not only among government agencies but also with non-governmental organizations, international agencies, and research institutions.

Conclusion and Future Directions

In conclusion, the global challenge of antimicrobial resistance (AMR) needs a comprehensive and collaborative approach. Implementation of regulatory measures, educating the public, and fostering international cooperation are important steps in combating AMR. Developing new antimicrobial drugs and using alternative therapies, along with surveillance, are crucial for the future. Our collective efforts are necessary to preserve the effectiveness of Antimicrobial drugs and ensure continued success in treatment of infectious diseases. Artificial intelligence can play a crucial role in addressing antimicrobial resistance (AMR). Sequencing-based AI applications analyze genomic data, assisting us to understand AMR and early detection of resistant strains [12]. AI also collects and analyzes clinical data to build real-time clinical support systems which can enpower the clinical decisions and reduce unnecessary antibiotic use in the fight against AMR.

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