International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1509-1514 www.ijprajournal.com ISSN: 2249-7781

"A Comprehensive Review on Causes, Consequences and Strategies to Tackle Antibiotic Resistance"

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Submitted: 25-11-2023 Accepted: 05-12-2023

ABSTRACT:
Antibiotics are a class of medicines that inhibit the growth of or destroy bacteria. Both humans as well as animals bacterial infections are treated with them. Antibiotics prevent bacteria from growing and surviving by interfering with certain bacterial activities, such as the synthesis of proteins or the formation of cell walls. In order to prevent antibiotic resistance and maintain antibiotic efficacy over time, it is important that antibiotics be utilized appropriately. Bacterial resistance to antibiotics is reportedly a result of the increasing use of antibacterial agents in clinical practice and other industries, such as livestock farming. In order to survive, bacteria created their own defense systems.

Antimicrobial agent resistance in bacteria can arise from either acquired or innate features. All antibiotics do not work against every kind of bacteria. A bacterium is said to have intrinsic resistance if it lacks the target for a certain antibiotic. Vancomycin, an antibiotic that is specifically designed to combat gram-positive bacteria, cannot cross through the cell wall of Gram-negative bacteria.

Also, bacteria can become resistant by acquiring resistance genes from other bacteria or by undergoing a mutation that reduces or eliminates the effectiveness of antibiotics. This type of resistance is known as acquired resistance.

People at any stage of life, as well as the veterinary, agricultural, and healthcare sectors, may be impacted by antibiotic resistance. This makes it among the most urgent public health issues facing globally.

Unfortunately, social and economic factors, combined with overuse and misuse of medicines in recent decades, have hastened the growth of antibiotic-resistant bacteria, making medication treatment ineffective. The resistance mechanisms of these bacteria are a key step in the development of new antimicrobial drugs to tackle drug-resistant bacteria.

This study aimed to assess the antibiotic resistance, its causes and consequences, it's clinical and economic burden and Strategies to tackle antibiotic resistance.

Key Words: Antibiotic Resistance, bacteria, infection

I. INTRODUCTION

Antibiotics:

The term "antibiotics," which means "against life," refers to chemical compounds produced by actinomycetes, fungi, or bacteria that interfere with some essential bacterial structure or process with no effects on the eukaryotic host having the infectious agents.[1] Antibiotics have both bactericidal and bacteriostatic effects on bacteria. Bacteriostatic drugs, like the medication chloramphenicol, stop the growth of bacterial cells, while bactericidal medicines, like penicillin, kill bacteria.[2] Although the term ‘‘antibiotic’’ was first introduced by Waksman in 1942 to denote chemical substances produced by a microorganism, semisynthetic modifications of natural products have produced a large variety of antibacterial agents, such as beta-lactam antibiotics and macrolides, that are also called antibiotics.[3] This definition distinguishes antibiotics from antibacterial agents totally synthesized by the chemist. Three kinds of chemically synthesized antibacterial agents are currently being used in clinical settings: quinolones, which were introduced in the 1960s, sulfa medicines, which were introduced in the 1930s, and oxazolidinones, which were licensed in the US in 2000.[3,4]

History of antibiotics:

Antibiotics have a fascinating history. Sir Alexander Fleming made the discovery of penicillin, the first real antibiotic, in 1928. He discovered that a substance produced by the mold

Penicilliumnotatum killed germs.[5] But it wasn't until the 1940s that penicillin was effectively refined and produced in large quantities, which redefined medicine and helped save a great deal of lives in World War II.[6] However, shortly thereafter, penicillin resistance became a substantial clinical problem, so that, by the 1950s, many of the advances of the prior decade were threatened.[7] In response, faith was restored with the discovery, development, and use of novel beta-lactam antibiotics.[6,7] However, during that same decade, the first cases of methicillin-resistant Staphylococcus aureus (MRSA) were discovered in the US in 1968 as well as the UK in 1962.[6,8]

Following penicillin, other antibiotics like streptomycin and tetracycline were discovered in the mid-20th century. These breakthroughs significantly advanced medical treatments, leading to the development of a wide array of antibiotics to combat bacterial infections.[9]

Unfortunately, resistance to almost every antibiotic ever developed has been observed over time.[10]Vancomycin was first used in clinical settings in 1972 to treat methicillin resistance in coagulase-negative staphylococci and S. aureus.[6,10]Vancomycin resistance has proven to be so hard to produce that a clinical environment was thought to be implausible for it to occur.[6] On the other hand, vancomycin-resistant coagulase-negative staphylococci were documented in 1979 and 1983.[6] From the late 1960s through the early 1980s, the pharmaceutical industry introduced many new antibiotics to solve the resistance problem, but after that the antibiotic pipeline began to dry up and fewer new drugs were introduced.[7] As a result, in 2015, many decades after the first patients were treated with antibiotics, bacterial infections have again become a threat.[7]

Benefits of antibiotics:

In addition to saving lives, antibiotics have been essential in attaining significant advancements in surgery and medicine.[11] They have successfully treated or prevented infections that can arise in patients undergoing chemotherapy; in patients suffering from long-term conditions like diabetes, end-stage renal disease, or rheumatoid arthritis; or in patients recovering from difficult surgeries like cardiac surgery, joint replacement, or organ transplants.[11, 12, 13, 14]

Antibiotics provide several benefits in the field of medicine:

- **Treatment of Bacterial Infections**: Antibiotics are highly effective in treating various bacterial infections, ranging from minor ailments like ear or urinary tract infections to severe conditions such as pneumonia, sepsis, and bacterial meningitis.[15]
- **Life-Saving**: Antibiotics have saved countless lives since their discovery, especially in cases where bacterial infections were once fatal. They played a significant role in reducing mortality rates from infectious diseases.[16]
- **Surgical Procedures and Medical Advances**: Antibiotics are essential for preventing and treating infections that can occur after surgeries or medical procedures. They facilitate advanced surgical procedures, organ transplants, and chemotherapy by reducing the risk of post-operative infections.[17]
- **Prevent Spread of Infections**: Antibiotics help prevent the spread of bacterial infections within communities, minimizing the risk of outbreaks and epidemics.[7]
- **Childhood Diseases**: Antibiotics have drastically reduced the mortality and complications associated with childhood diseases like strep throat, whooping cough, and bacterial pneumonia.[18,19]
- **Improvement in Public Health**: Widespread use of antibiotics has contributed to overall improvements in public health by controlling and managing bacterial infections effectively.[20]
- **Increased Life Expectancy**: The advent of antibiotics has extended human life expectancy by addressing and curing a wide range of bacterial illnesses.[21]

Antibiotic resistance:

Antibiotic resistance refers to the ability of bacteria, viruses, and other microorganisms to resist the effects of antibiotics, making the standard treatments ineffective and infections persist and spread.[22]This poses a significant threat to public health globally, requiring careful antibiotic use and development of new strategies to combat resistant strains.

Causes of antibiotic resistance

Antibiotic resistance can occur due to several reasons:

- **Overuse and Misuse of Antibiotics**: Using antibiotics inappropriately, for non-bacterial infections or not completing a full course, can allow bacteria to develop resistance.[23]

- **Incomplete Treatment**: Not finishing a prescribed antibiotic course allows bacteria to survive and develop resistance to that antibiotic.[24]
- **Suboptimal Dosage**: Inadequate dosing or incorrect administration of antibiotics can contribute to the development of resistance.[25]
- **Use in Agriculture**: Antibiotics are often used in livestock for growth promotion and disease prevention, leading to the emergence of resistant bacteria that can be transmitted to humans through consumption of contaminated food.[26]
- **Poor Infection Control**: Inadequate infection control practices in healthcare settings can facilitate the spread of resistant bacteria.[27]
- **Lack of New Antibiotics**: The development of new antibiotics has slowed down, reducing the available options to treat infections and potentially leading to increased reliance on existing ones.[9]
- **Horizontal Gene Transfer**: Bacteria can transfer resistance genes to other bacteria, even of different species, through mechanisms like plasmid exchange, accelerating the spread of resistance.[28]

Addressing antibiotic resistance requires a comprehensive approach, including appropriate antibiotic use, improved sanitation and hygiene, surveillance and monitoring, responsible use in agriculture, and continued research and development of new antibiotics.

Mechanisms of Resistance and Examples

More than one type of bacterial resistance maybe present in a bacterial organism. Common resistance strategies are listed here.

Reducing Intracellular Antibiotic Concentrations

- Increased efflux
- Decreased influx [29,30]

Antibiotic Inactivation

- Enzymatic modification
- Chemical degradation [29,30]

Target Site Alteration

- Mutation of the target site
- Antibiotic modification
- Target site protection
- Elimination of the target site [29,30]

Consequences of antibiotic resistance

Antibiotic resistance can lead to ineffective treatments, increased mortality rates, prolonged illnesses, higher healthcare costs, and a potential for the spread of resistant infections within communities and globally. It also limits treatment options for common infections, making even minor injuries or routine surgeries risky.[31] Preventing and managing this issue is crucial to safeguard public health.

Clinical and economical burden of antibiotic resistance

Antibiotic resistance imposes a significant clinical burden by limiting the effectiveness of antibiotics, leading to prolonged illnesses, more severe infections, and increased mortality rates. Patients may require longer hospital stays, intensive care, and additional medical interventions. Moreover, it hinders the ability to combat infectious diseases effectively, impacting overall healthcare delivery.[32]

Economically, antibiotic resistance escalates healthcare costs due to extended hospitalizations, costly treatments, and the need for specialized care. It strains healthcare systems, reduces productivity, and places a financial burden on individuals, families, and societies. Investments in research, surveillance, and education are essential to mitigate these burdens and preserve the effectiveness of antibiotics.[32]

Emerging strategies to combat antibiotic resistance

Adopting a multi-faceted approach and international collaboration are crucial to effectively address antibiotic resistance and ensure the continued efficacy of antibiotics. These approaches hold promise in addressing antibiotic resistance and improving the arsenal of antibiotics to combat bacterial infections.

- **Targeting Unique Bacterial Structures**: Researchers are exploring antibiotics that target specific bacterial structures or functions not present in human cells, minimizing side effects.[33]
- **Combination Therapies**: Utilizing multiple antibiotics or combining antibiotics with other drugs to enhance effectiveness and reduce the risk of resistance.[34]
- **Bacteriophage Therapy**: Utilizing bacteriophages, viruses that infect and kill bacteria, as a targeted treatment for bacterial infections.[35]

- **Probiotics and Microbiome Restoration**: Using beneficial bacteria to restore a healthy microbiome, which can help prevent infections and reduce the need for antibiotics.[36]
- **Antibiotic Adjuvants**: Developing compounds that can enhance the effectiveness of existing antibiotics or revive their potency against resistant strains.[37]
- **Immunomodulation:** Enhancing the immune system's ability to fight infections by developing drugs that boost the immune response against bacterial pathogens.[38]
- **AI and Machine Learning:** Utilizing artificial intelligence and machine learning to identify new drug candidates and predict their efficacy, streamlining the drug discovery process.[39]
- **Alternative Therapies:** Exploring non-antibiotic treatments such as phage therapy, which uses viruses to target and kill bacteria.[40]
- **Antibiotic Stewardship**: Implementing guidelines to optimize antibiotic use, ensuring they're prescribed appropriately and in the right doses for the right duration.[41]
- **Novel Antibiotics**: Investing in research to develop new classes of antibiotics that are effective against resistant bacteria.[42]
- **Antibiotic Alternatives**: Exploring plant-based compounds, peptides, and nanoparticles with antibacterial properties as potential substitutes for antibiotics.[43]
- **Vaccination Programs**: Developing and promoting vaccines to prevent bacterial infections, reducing the reliance on antibiotics for treatment.[44]
- **CRISPR-Cas Technology**: Utilizing CRISPR-Cas gene editing to target and modify bacterial genes associated with antibiotic resistance, potentially reversing resistance.[45]
- **One Health Approach**: Addressing antibiotic resistance through a holistic approach that considers human, animal, and environmental factors to minimize the spread of resistant bacteria.[46]
- **Diagnostic Innovations**: Rapid and precise diagnostic tools to identify bacterial infections and determine antibiotic susceptibility, guiding appropriate antibiotic use.[47]
- **Public Awareness and Education**: Promoting understanding of antibiotic resistance and the importance of responsible antibiotic use among healthcare professionals, patients, and the general public.[48]

II. CONCLUSION

Antibiotics have helped to extend expected life spans by changing the outcome of bacterial infections. In developing countries where sanitation is still poor, antibiotics decrease the morbidity and mortality caused by food-borne and other poverty-related infections.

The development of new antibiotics faces challenges such as antibiotic resistance, high research and development costs, regulatory hurdles, and a lack of financial incentives for drug companies due to low profitability. Additionally, identifying novel compounds with effective antibacterial properties while minimizing side effects is a significant obstacle.

Hence, it's crucial to use antibiotics responsibly to prevent the development of antibiotic-resistant bacteria and maintain their effectiveness for future generations. Overuse or misuse of antibiotics can lead to antibiotic resistance, rendering these drugs less effective in treating infections.

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