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Review Article

The Evaluation of Antibiotic Resistance: Mechanisms, Challenges, and Future Directions

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ABSTRACT

An antibiotic is a type of medication designed to kill or inhibit the growth of bacteria, helping to treat bacterial infections in humans, animals, and sometimes plants. Antibiotics work by targeting specific components of bacterial cells, such as cell walls, protein synthesis, or DNA replication, thereby preventing bacteria from growing or killing them directly. Antibiotics are not effective against viruses, so they should not be used to treat viral infections like the flu or common cold. Antibiotic resistance has become a major global health concern that threatens the efficacy of treatments for a variety of bacterial infections. This review looks at the mechanisms by which bacteria develop resistance, the main causes, such as the overuse of antibiotics in agriculture and healthcare, and the current status of resistant infections globally. It also highlights the implications for public health, from increased mortality to the financial burden on healthcare systems. Finally, the review looks at creative solutions, such as alternative therapies, novel antibiotic discovery, and policy interventions aimed at reducing antibiotic misuse. A multidisciplinary approach, involving scientific research, public awareness, and policy reform, is necessary to stop the spread of antibiotic resistance and maintain the efficacy of current treatments.In order to ensure a sustainable future in the fight against infectious diseases, it is imperative that the world take immediate action to tackle antibiotic resistance.

INTRODUCTION

At first, antibiotics were considered "wonder drugs" mainly because they were developed when the only ways to treat severe bacterial infections were surgical drainage or spontaneous cures. Sulfonamides and trimethoprim, penicillins, cephalosporins, chloramphenicol, tetracyclines, colimycins, macrolides, lincosamides, streptogramins, rifamycins, glycopeptides, aminoglycosides, fluoroquinolones, oxazolidinones, glycylglycines, lipoglycopeptides, and variations on these themes have all become available in the five or six decades since their introduction[1].Antibiotics are

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a class of drugs specifically designed to treat bacterial infections by either killing the bacteria or inhibiting their growth. They target various aspects of bacterial cells, such as cell wall synthesis, protein synthesis, DNA replication, or metabolic pathways, without affecting human cells. Antibiotics are ineffective against viruses and are typically prescribed for bacterial infections like strep throat, urinary tract infections, and pneumonia. Their discovery transformed medicine by providing an effective way to combat bacterial diseases. Plants, microbes, soil, and aquatic habitats are the sources of antibiotics. These medications are among the biological weapons that the producers employ to stay alive in their crowded, multispecies habitats where resources may be limited. As a result, since the beginning of time, microbes have developed the ability to evade the effects of antibiotics. However, because of the overuse, misuse, or usage of antibiotics, antibiotic resistance is currently a concern to world health. These days, resistance to every antibiotic class has surfaced, leading to 700,000 drug-resistant disease-related deaths annually, with dire predictions for the years ahead [2]. The problem posed by antibiotic resistance has been widely acknowledged, and it is easily detectable using common microbiological techniques [3].This holds true for substances used to treat viral, bacterial, fungal, and parasitic infections as well as chronic illnesses like diabetes and cancer; it also applies to conditions that affect or are caused by any living thing, including people, animals, fish, plants, insects, and so on. Resistance may be caused by a variety of physiological and biochemical processes .[Initially put forth by Selman Waksman, the discoverer of streptomycin and a pioneer in screening soils for biologicals, the term "antibiotic" has been greatly overinterpreted; it simply refers to a chemical compound's use, laboratory effect, or activity[4].

Antibiotic resistance is the ability of bacteria to survive and multiply despite the presence of antibiotics that would normally kill them or inhibit their growth. This resistance occurs when bacteria evolve mechanisms to withstand the effects of an antibiotic, often due to genetic mutations or the acquisition of resistance genes from other bacteria. The overuse or misuse of antibiotics—such as not completing a prescribed course or using them for viral infections—accelerates the spread of resistant bacteria. Antibiotic resistance makes bacterial infections harder to treat, requiring alternative medications or higher doses, and poses a significant threat to public health globally. According to the US and WHO, the percentage of mortality from infectious diseases has decreased from slightly less than half of all deaths over the 20th century to less than 10%. Advanced microbial resistance to antibiotics started to emerge during the end of the 20th century and the start of the 21st, and the new use of antibiotics as growth boosters for food animals in the human diet occurred in the second part of the 20th century [5

Intrinsic Resistance: By altering their structure or constituent parts over time, bacteria may develop intrinsic resistance to antibiotics. For instance, bacteria without a cell wall are immune to antibiotics like penicillin that interfere with the bacteria's ability to form walls.]. The four groups listed below are typically used to classify the mechanisms of antibiotic resistance:

Acquired Resistance: Bacteria can develop the capacity to withstand an antimicrobial agent's action to which they were previously vulnerable. A new genetic mutation that aids in the bacterium's survival or the acquisition of DNA from an existing resistant bacterium are two ways that bacteria can develop resistance. Rifamycin-resistant Mycobacterium tuberculosis is one example.

Genetic affect: The DNA of bacteria may mutate and affect how proteins are produced, which could lead to several bacterial components and receptors that prevent the antibiotic from identifying the bacteria. The genomics of bacteria that share an environment may be changed by intrinsic genetic factors of resistance. Trimethoprim-resistant Haemophilus influenza and Escherichia coli (E. coli) are two examples.

DNA Transfer: Through a horizontal gene transfer, bacteria can exchange genetic components with one another and spread the resistant DNA. Bacteria typically go through three primary processes to acquire exogenous genetic material:

Transformation (by incorporating naked DNA)

Transduction (by the phagocytosis process)[6].

Antibiotic resistance effects on populations of humans and animals Antibiotic resistance has emerged as a complex problem that affects both human and animal health. Drug-resistant strains of bacteria have emerged more quickly as a result of the overuse and misuse of antibiotics in a variety of fields, including veterinary medicine, agriculture, and healthcare facilities. Antibiotic-resistant bacteria, or "superbugs," have emerged as a result of an over-reliance on antibiotics. These germs can cause serious infections and provide serious obstacles to the effectiveness of therapy.[7].

MECHANISM OF ANTIBIOTIC RESISTANCE-

The Antimicrobial Resistance Genetic Basis

Because of their exceptional genetic flexibility, bacteria can adapt to a variety of environmental dangers, such as the presence of antibiotic compounds that could endanger their life. As previously stated, bacteria that occupy the same biological niche as organisms that produce antibiotics have developed long-standing defenses against the damaging effects of the antibiotic molecule; as a result, their inherent resistance enables them to flourish in its presence. From an evolutionary standpoint, bacteria employ two main genetic strategies to adjust to the antibiotic "attack": i) mutations in the gene or genes frequently linked to the compound's mechanism of action, and ii) horizontal gene transfer (HGT) to acquire foreign DNA coding for resistance determinants [8].

Antibiotic resistance occurs by following mechanisms-

1]Enzyme production

2]Alteration of target sites

3]Efflux pumps

4]Reduced permeability

5]Biofilm formation

6]Horizontal gene transfer

Mutations in native PBPs, their overproduction, and the synthesis of novel PBPs that are resistant to β-lactam inhibition are the primary causes of Gram-positive bacteria becoming resistant to β-lactam antibiotics. A worry nowadays is the spread of methicillin- and other semi-synthetic penicillin and cephalosporin-resistant forms of Staphylococcus aureus. The resistance mechanism is depicted in the figure: Both domains of a high-molecular-weight PBP participate in peptidoglycan biosynthesis (A) in the absence of an antibiotic; in a high-molecular-weight PBP, the transpeptidase domain is acylated and does not form crosslinks, whereas only the glycosyltransferase domain is active in the presence of an antibiotic. Transpeptidase activity is demonstrated by the acquired low-molecular-weight PBP2a (B) in the resistant strain. Cell viability is subsequently restored. Enzymes for PBP2a are encoded by the gene mecA[9].

Efflux pump-

variety of antimicrobial classes, such as protein synthesis inhibitors, fluoroquinolones, β-lactams, carbapenems, and polymyxins, are impacted by the efflux pump mechanism of resistance.The

major facilitator superfamily (MFS), the small multidrug resistance family (SMR), the resistance-nodulation-cell-division family (RND), the ATP-binding cassette family (ABC), and the multidrug and toxic compound extrusion family (MATE) are the five main families of efflux pumps. These families vary in the kinds of bacterial species they are found in, their energy source, the range of substrates they can extrude, and their structural conformation [8,10]. Bacterial cytoplasmic membranes have efflux pumps, which actively transport harmful materials out of the cell. Drug efflux is the term for this mechanism [11].Bacteria have time to adjust and develop antibiotic resistance due to the gradual process of antibiotic efflux. Either mutations or changes to the antibiotic targets may cause this [12].The five main families of efflux pumps are distinguished by the energy source they employ:

1. The main organizer (MF).
2. MATE (multidrug and toxic efflux) and RND (resistance-nodulation-division)
3. ATP binding cassette for small multidrug resistance (SMR) (ABC)[12].

Decreased Permeability:

Gram-negative bacteria use decreased permeability as a defense mechanism against antibiotics. This process lowers the quantity of antibiotics that can enter the cell by changing the bacteria's outer membrane [13].Several antibiotic families may develop cross-resistance as a result of decreased permeability. Additionally, it may make other resistance mechanisms more effective at producing resistance. The cytoplasmic membrane, often known as the inner membrane, is home to intracellular bacterial targets for many of the antibiotics used in modern practice. Therefore, for the chemical to have an antibacterial action, it needs to pass through the cytoplasmic and/or outer membrane. In order to stop the antibiotic from getting to its intracellular or periplasmic target, bacteria have evolved defense mechanisms that reduce the antibacterial molecule's absorption. This mechanism, which restricts the inflow of chemicals from the external environment, is especially significant in gram-negative bacteria (for the reasons mentioned above). Actually, the outer membrane serves as the initial line of defense against the entry of many harmful substances, such as antibacterial agents. Since they frequently use water-filled diffusion channels called porins to pass across this barrier, hydrophilic compounds including β-lactams, tetracyclines, and some fluoroquinolones are most impacted by changes in the outer membrane's permeability [8,14].

Biofilm Formation-

The creation of biofilms has attracted a lot of attention because of issues in a number of fields, including public health, medicine, and the pharmaceutical sector. Bacteria that produce biofilms exhibit a remarkable capacity for drug resistance, which raises morbidity and mortality. The healthcare industry is under tremendous financial strain as a result. Biofilm formation is a complicated process that is influenced by a number of variables. Numerous attempts have been undertaken to decipher the processes involved in the creation of biofilms; these endeavors have yielded valuable information regarding the mechanisms that the therapy should target. Targeting infections within biofilm is a profitable endeavor because the biofilm-state renders the bacterial pathogens considerably resistant to medications. The pathogen can be eliminated by repurposing the available medications, so lessen the burden of antimicrobial therapy. Infections caused by biofilm formers have also been discovered in people, animals, and plants. Much focus has been paid to the development of innovative approaches, such as bioinformatics tools, for both treating and preventing the formation of biofilms. Due to their increased resistance to antibiotics

and disinfectants, bacterial biofilms are a major contributor to chronic infections: they can interfere with phagocytosis and other immune system functions. Biofilms face an imminent therapeutic dilemma as a result of the microorganisms within them being less vulnerable to various antimicrobial medicines [15, 16].Antibiotic tolerance or resistance might be a result of biofilm resistance. Through genetic mutation or horizontal gene transfer (HGT) in biofilm EPS, microorganisms acquire foreign genetic material coding for resistance determinants, which enables them to develop defenses against antimicrobials. AMR is caused by a number of mechanisms, including enzymatic degradation of the antimicrobials through hydrolysis or chemical change, mutational alterations in antibiotic targets, and reduced permeability or restriction of access to antimicrobials. Since antibiotics work against bacteria, yet the bacteria develop resistance to them, antibiotic resistance (ABR) is a subset of antimicrobial resistance (AMR).[15, 16, 18] .

Horizontal Gene Transfer-

One of the main causes of the spread of antibiotic resistance is horizontal gene transfer. HGT can entail a variety of pathways can happen between bacteria of the same or different species. HGT contributes to antibiotic resistance in the following ways:

Resistance Gene Transfer:

A bacterium can use horizontal gene transfer (HGT) to spread its antibiotic resistance to other bacteria. PlasmidsBacteria frequently transfer genes using tiny, circular DNA fragments known as plasmids. The conjugation a method by which genes, like plasmids, are transferred between bacteria through physical touch. Biofilms are linked to severe infections and illnesses and are a hotspot for HGT [19].Numerous variables influence antibiotic resistance, including:

1. Human behavior: prescribing too many antibiotics, using them when unnecessary, and not taking them as prescribed.
2. Hygiene: A lack of infection prevention and control combined with poor hygiene.
3. Travel: Antibiotics and resistant bacteria can be released into soil, water bodies, and waste systems by people traversing the world. 3. Environmental considerations.
4. Practices involving animals: widespread use of antibiotics in aquaculture and cattle.
5. Wildlife: Spread via interaction with wildlife and encroachment on their habitat.
6. Properties of the soil: temperature, nutritional content, depth, and loam.
7. Sociodemographic characteristics: urban residency, low income, and migrant status.
8. Clinical data on the patient: Status of the disease and specific lab findings
9. Hospitalization duration upon admission to healthcare facilities

Impact Of Antibiotic Resistance:

The hospital, a third-party payer, the patient, and society can all be included when evaluating the effects of antibiotic resistance.

1. **Hospital Perspective**: Research on the effects of resistance has mostly focused on the hospital perspective. Hospitals are most likely to make adjustments in response to information evaluated at the hospital level, and data regarding in-hospital morbidity, mortality, and the expenses related to antibiotic resistance are comparatively straightforward to get.

2. **Patient Perspective**: The short-term direct impact of resistance on the afflicted patient is measured by mortality and hospitalization duration measurements. On the other hand, resistant illnesses may have significant long-term and indirect effects.

3. The viewpoint of society: There is currently little knowledge about how antibiotic resistance affects society overall. The Office of Technology

Assessment calculated that the annual national cost of antibiotic resistance in the US was $4 billion in 1995 dollars. However, this estimate would probably be multiplied by several times because it only considered patients who were directly impacted by the resistance. To help decision-makers, more research on the effects of resistance outside of the patient and hospital levels is crucial [19].

Future strategies-

Scientists are investigating a number of innovative strategies that are predicated on a rethinking of the dynamics of resistance, sickness, and prevention. One technique that has proven essential for drug discovery is whole genome sequencing (WGS), which enables the quick identification of resistance pathways and the control of bacterial resistance. The recently identified quorum-quenching (QQ) approach is another promising strategy that prevents bacterial infections by engaging with microbial cell-to-cell interaction. Since bacteriophages, often referred to as viral phage treatment, are more efficient than antibiotics and do not harm host organisms, including gut flora, they have recently acquired favor as a way to reduce the risk of opportunistic infections [20, 21].the face of growing worries about antibiotic development resistance, therapeutic therapy approaches including a single medication might not be sufficient to address the issue. Beyond only filling the new medicine pipeline, there are a number of techniques to address resistance. Combination techniques are more effective in combating multidrug resistance, according to scholarly research, clinically established guidelines, and treatments [22].

Public awareness and education-World Antimicrobial Resistance Awareness Week (WAAW) is a global campaign run by the World Health Organization (WHO) to increase awareness of antibiotic resistance (AMR). Every year, from November 18–24, WAAW is held. In order to slow the development of AMR, the campaign aims to inform the public and promote better practices. AMR happens when parasites, fungi, viruses, and bacteria evolve over time and develop drug resistance. This raises the danger of disease transmission, serious sickness, and death and makes infections more difficult to treat. AMR is a danger to global public health that impacts nations of all economic levels.

Here are a few strategies to fight AMR:

Follow your doctor's instructions when taking antibiotics. Avoid sharing unneeded prescription drugs or stopping antibiotics too soon.

Safely prepare food[23].

CONCLUSION-

Antibiotic resistance poses a severe threat to global health, with rising incidences of resistant infections undermining decades of medical progress. The review underscores the need for an integrated approach, involving enhanced surveillance, prudent antibiotic use, research into alternative therapies, and strong policy frameworks to curb the misuse of antibiotics in healthcare and agriculture. Without immediate and concerted efforts to mitigate antibiotic resistance, the world risks a return to an era where common infections could once again become untreatable. Addressing this crisis requires collaboration across scientific, medical, and policy-making sectors to preserve the efficacy of current antibiotics and develop new solutions for future generations.

REFERENCES

1. Zinner SH. Antibiotic use: present and future. New Microbiol. 2007 Jul;30(3):321-5. PMID: 17802919.
2. Barreiro C, Barredo JL. Worldwide Clinical Demand for Antibiotics: Is It a Real Countdown? Methods Mol Biol. 2021;2296:3-15. doi: 10.1007/978-1-0716-1358-0_1. PMID: 33977439.

3. Huemer M, Mairpady Shambat S, Brugger SD, Zinkernagel AS. Antibiotic resistance and persistence-Implications for human health and treatment perspectives. EMBO Rep. 2020 Dec 3;21(12):e51034. doi: 10.15252/embr.202051034. Epub 2020 Dec 8. PMID: 33400359; PMCID: PMC7726816.
4. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev. 2010 Sep;74(3):417-33. doi: 10.1128/MMBR.00016-10. PMID: 20805405; PMCID: PMC2937522.
5. Dodds DR. Antibiotic resistance: A current epilogue. Biochem Pharmacol. 2017 Jun 15;134:139-146. doi: 10.1016/j.bcp.2016.12.005. Epub 2016 Dec 10. PMID: 27956111.
6. Habboush Y, Guzman N. Antibiotic Resistance. [Updated 2023 Jun 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513277/
7. Ahmed, Sirwan & Hussein, Safin & Qurbani, Karzan & Ibrahim, Radhwan & Saber, Abdulmalik & Mahmood, Kochr & Mohamed, Mona. (2024). Antimicrobial resistance: Impacts, challenges, and future prospects. Journal of Medicine Surgery and Public Health. 2. 100081. 10.1016/j.glmedi.2024.100081.
8. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr. 2016 Apr;4(2):10.1128/microbiolspec.VMBF-0016-2015. doi: 10.1128/microbiolspec.VMBF-0016-2015. PMID: 27227291; PMCID: PMC4888801.
9. Egorov A.M., Ulyashova M.M., & Rubtsova M. Yu. (2018). Bacterial enzymes and antibiotic resistance. Acta Naturae (англоязычная версия), 10 (4 (39)), 33-48.
10. Piddock LJ. Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. Clin Microbiol Rev. 2006 Apr;19(2):382-402. doi: 10.1128/CMR.19.2.382-402.2006. PMID: 16614254; PMCID: PMC1471989.
11. Gaurav A, Bakht P, Saini M, Pandey S, Pathania R. Role of bacterial efflux pumps in antibiotic resistance, virulence, and strategies to discover novel efflux pump inhibitors. Microbiology (Reading). 2023 May;169(5):001333. doi: 10.1099/mic.0.001333. PMID: 37224055; PMCID: PMC10268834.
12. Kumar S, Varela MF. Biochemistry of bacterial multidrug efflux pumps. Int J Mol Sci. 2012;13(4):4484-4495. doi: 10.3390/ijms13044484. Epub 2012 Apr 10. PMID: 22605991; PMCID: PMC3344227.
13. Nguyen Van JC, Gutmann L. Résistance aux antibiotiques par diminution de la perméabilité chez les bactéries à gram négatif [Resistance to antibiotics caused by decrease of the permeability in gram-negative bacteria]. Presse Med. 1994 Mar 19;23(11):522, 527-31. French. PMID: 8022741.
14. Pagès JM, James CE, Winterhalter M. The porin and the permeating antibiotic: a selective diffusion barrier in Gram-negative bacteria. Nat Rev Microbiol. 2008 Dec;6(12):893-903. doi: 10.1038/nrmicro1994. Epub 2008 Nov 10. PMID: 18997824.
15. Dutt Y, Dhiman R, Singh T, Vibhuti A, Gupta A, Pandey RP, Raj VS, Chang CM, Priyadarshini A. The Association between Biofilm Formation and Antimicrobial Resistance with Possible Ingenious Bio-Remedial Approaches. Antibiotics (Basel).

2022 Jul 11;11(7):930. doi: 10.3390/antibiotics11070930. PMID: 35884186; PMCID: PMC9312340.

16. Amato SM, Fazen CH, Henry TC, Mok WW, Orman MA, Sandvik EL, Volzing KG, Brynildsen MP. The role of metabolism in bacterial persistence. Front Microbiol. 2014 Mar 3;5:70. doi: 10.3389/fmicb.2014.00070. PMID: 24624123; PMCID: PMC3939429.
17. Brauner A, Fridman O, Gefen O, Balaban NQ. Distinguishing between resistance, tolerance and persistence to antibiotic treatment. Nat Rev Microbiol. 2016 Apr;14(5):320-30. doi: 10.1038/nrmicro.2016.34. PMID: 27080241.
18. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol. 2015 Jan;13(1):42-51. doi: 10.1038/nrmicro3380. Epub 2014 Dec 1. PMID: 25435309.
19. George M. Eliopoulos, Sara E. Cosgrove, Yehuda Carmeli, The Impact of Antimicrobial Resistance on Health and Economic Outcomes, Clinical Infectious Diseases, Volume 36, Issue 11, 1 June 2003, Pages 1433–1437.
20. Uddin TM, Chakraborty AJ, Khusro A, Zidan BRM, Mitra S, Emran TB, Dhama K, Ripon MKH, Gajdács M, Sahibzada MUK, Hossain MJ, Koirala N. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. J Infect Public Health. 2021 Dec;14(12):1750-1766. doi: 10.1016/j.jiph.2021.10.020. Epub 2021 Oct 23. PMID: 34756812.
21. F. Hemmati, R. Salehi, R. Ghotaslou, H.S. Kafil, A. Hasani, P. Gholizadeh, et al. Quorum quenching: a potential target for antipseudomonal therapyInfect Drug Resist, 13 (2020), pp. 2989-3005, 10.2147/IDR.S263196
22. Brooks BD, Brooks AE. Therapeutic strategies to combat antibiotic resistance. Adv Drug Deliv Rev. 2014 Nov 30;78:14-27. doi: 10.1016/j.addr.2014.10.027. Epub 2014 Oct 28. PMID: 25450262
23. World Health Organisation.

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