

Strategies to overcome antibiotic resistance: An overview



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1. Introduction

Modern medicine's remarkable advancements have saved countless lives and enhanced the quality of human existence. Antibiotics have been especially beneficial in treating infections and preventing severe complications. However, an alarming threat lurks in the future: the rise of antibiotic resistance. Antibiotic resistance is a significant and rising global danger to human, animal, and environmental health. Antibiotic resistance is the ability of microorganisms, mainly bacteria, to resist the effects of antibiotic drugs, making it more challenging to treat infections and presenting a grave threat to global health. The global resistome, made up of genes that cause antibiotic resistance, is affected by factors such as population growth, rising migration, excessive antibiotic use in medical and agricultural sectors, poor sanitation, wildlife transmission, and inadequate wastewater treatment (1). This alarming problem presents a plethora of issues, most notably affecting patient care and public health. As the efficacy of antibiotics declines, the treatment of once-easily curable infections becomes difficult, resulting in prolonged illnesses, increased medical costs, and increased mortality.

Particularly worrisome are "superbugs" or multidrug-resistant bacteria immune to all known antibiotics that can proliferate, posing treatment barriers. The UN estimates by 2050, superbugs and associated forms of antimicrobial resistance could be responsible for up to 10 million deaths, equaling the 2020 annual global mortality toll from cancer (2). The World Health Organization estimates that antimicrobial resistance (AMR) is responsible for approximately 4.9 million deaths annually, while a 2022 Lancet study revealed that 1.27 million deaths in 2019, including 860,000 in Africa, were the direct result of drug-resistant bacterial

bacterial infections (3, 4). While it is true that the risks associated with infectious diseases are a concern for all nations, it is essential to acknowledge that Low-Income Countries (LICs) and Lower-Middle-Income Countries (LMICs) shoulder a substantial portion of this burden, particularly those in Asia and Africa. As we face this imminent crisis, there is an urgent need to explore effective strategies to battle antibiotic resistance.

2. Understanding the development of antibiotic resistance: Molecular mechanisms

Antibiotic resistance is associated with various molecular and enzymatic processes through eliminating or modifying the drug. Primarily, four mechanisms are discussed here: modification of the binding target, membrane efflux protein, enzymatic inactivation, and molecular bypass (Figure 1).

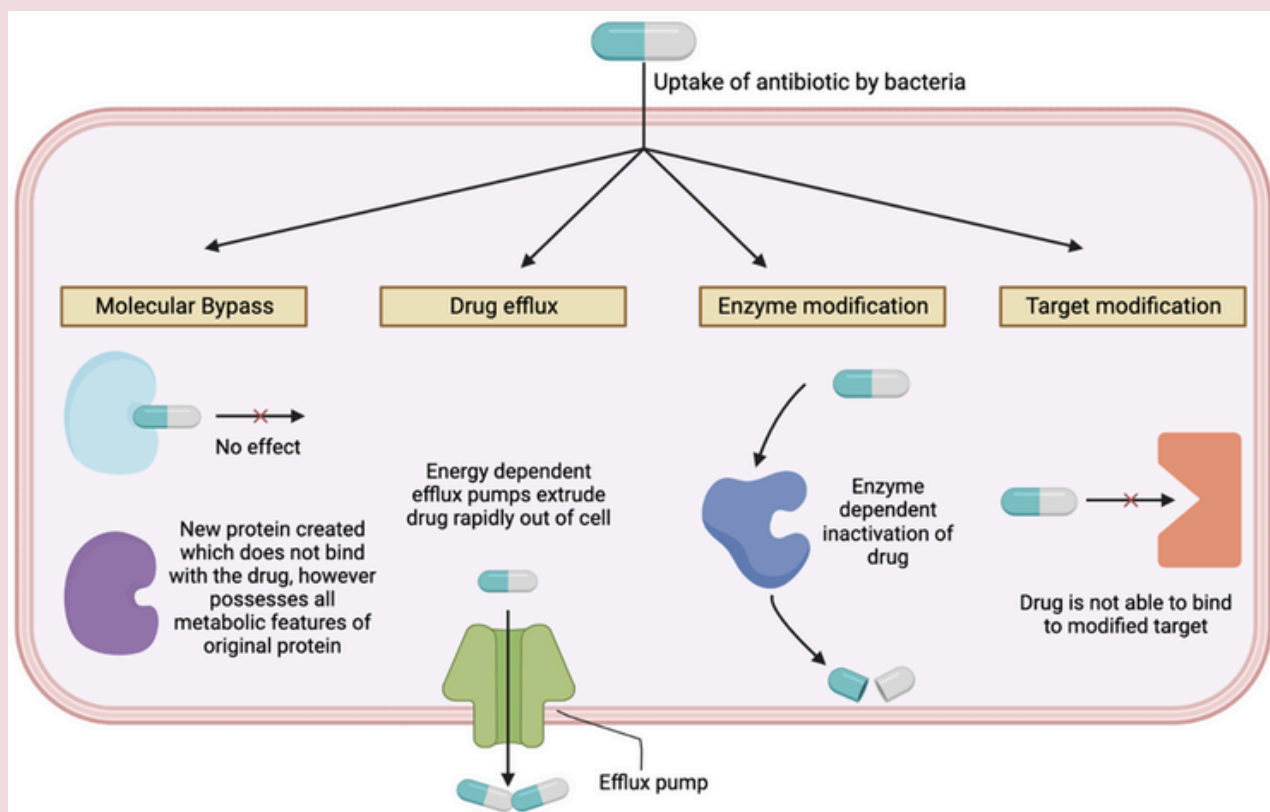


Figure 1. Molecular Mechanisms of Antibiotic Resistance.

2.1 Target modification: Modification of target binding is one of the most significant mechanism occurring due to point mutations in plasmid genes. The mutation of Serine in the GyrA gene with the bulkier group causes resistance to fluoroquinolones. The process can also involve the role of enzymes, as seen by Erm enzymes, which modify the 23sRNA ribosome, causing resistance to three classes of antibiotics: macrolides, lincosamide, and type B streptogramin in *Escherichia coli* (5).

2.2 Membrane efflux protein: Membrane efflux proteins are transporters involved in removing toxic substances from cells to the outside. Generally, it is the overexpression of these transporters that leads to resistance to antibiotics, as seen in Gram-negative bacteria, where the MFS (Major Facilitator Super-transporter) inhibits phenothiazines, and the RND family (Resistance Nodulation Division) inhibits quinolones. In Gram-positive bacteria, the overexpression of the MATE family inhibits Verapamil (6).

2.3 Enzyme inactivation: It can occur through the formation of a covalent enzyme intermediate followed by hydrolysis. The most important example is the Beta-lactamase enzyme, which causes the hydrolysis of beta-lactam by attacking the carbonyl carbon of B-lactam using the hydroxyl group of reactive Serine, further inhibiting the enzyme's action. Other antibiotics include fosfomycin, where the epoxide-containing ring is destroyed by a thiol-containing substrate followed by hydrolysis.

2.4 Molecular bypass: Certain bacteria can produce alternative proteins that might be ineffective against antibiotic action. The most famous example is found in Vancomycin (5). When acyl-D-Alanyl-D-Alanine is changed to acyl-D-Alanyl-D-Lactate, the amide bond is altered to an ester bond. As a result, an H donor deficiency is created, resulting in the non-productive binding of antibiotics.

3. Strategies for combating antibiotic resistance

3.1 Rational use of antibiotics

The irrational use of antibiotics has emerged as a pressing global concern, as many individuals are not adhering to the standard treatment guidelines set forth by the World Health Organization (WHO). Both the public and private sectors must be educated effectively to ensure the rational use of antibiotics. Shockingly, less than 30% of people in the private sector and only 40% in the public sector currently follow the proper guidelines for treatment, leading to the development of antibiotic resistance. A major contributing factor is the rampant use of over-the-counter (OTC) antibiotics, where individuals obtain and use these drugs without a prescription, often neglecting to complete the full course of treatment. To combat this problem, stringent measures and regulatory controls must be implemented to prevent the use of antibiotics without a prescription (7). Proper use of antibiotics should consider critical factors, such as the patient's clinical condition, the specific pathogen causing the disease, and the resistance pattern of the drug. Making decisions regarding the change of antibiotics based on microbial sensitivity and the patient's condition falls under the responsibility of registered medical practitioners. Therefore, antibiotic guidelines must be regularly updated to optimize the use of appropriate antibiotics, including considerations for the proper route of administration, treatment duration, and dosing frequency. By promoting a greater understanding of the significance of rational antibiotic use, we can safeguard the efficacy of these vital medications and combat the rise of antibiotic resistance effectively (8).

3.2 Discovery of new antibiotics

The decline in the efficacy of readily accessible antibiotics is a significant worldwide healthcare issue in the context of treating bacterial infections since these medications are susceptible to the development of resistance (9). There exists a pressing need to replace the currently available antibiotics in the market with novel drugs and pharmacological classes to sustain their efficacy for the treatment of bacterial illnesses. One potential strategy is the development of analogues of already available medications that possess the ability to combat bacterial species that have developed resistance (10).

Another potential strategy that has recently emerged involves the alteration of naturally occurring peptides, which exhibit both non-resistance to bacteria and comparable efficacy to

other categories of antibiotics. The researchers have made modifications to the naturally occurring peptide known as “thanatin” to augment its efficacy and mitigate bacterial resistance. This intervention has generated very promising outcomes. The identification of new peptides has the potential to considerably decelerate the development of antibiotic resistance.

Nevertheless, it is recommended by experts in the field of infectious diseases that the utilization of novel antibiotics be limited and reserved as a final resort for the management of the ailment. These medications are specifically designated for instances of severe resistance and should only be administered when patients have developed resistance to currently available antibiotics. As a result of this factor, the rate of discovery and advancement of novel antibiotics has diminished due to insufficient return on investments (9).

3.3 Adjuvant therapy

Antibiotic adjuvants are compounds that lack direct antimicrobial activity. Instead, they are co-administered with antibiotics to combat bacterial resistance and preserve their efficacy. Consequently, antibiotic adjuvants are classified into two groups: Class I agents that target the pathogen include - β -lactamase inhibitors, and efflux pump inhibitors (EPIs), whereas membrane permeabilizing are class II agents that act on the host.

3.3.1 β -lactamase inhibitors: β -lactam antibiotics (penicillins, cephalosporins, and carbapenems) disrupt the proteins necessary for peptidoglycan biosynthesis leading to bacterial cell lysis. However, β -lactamases, bacteria’s defense enzymes, inactivate them by hydrolyzing the β -lactam ring in their structure and developing a resistant phenotype. β -lactamases inhibitors block this enzyme's active site, boosting the potency of co-administered antibiotics. Clavulanic acid, sulbactam, tazobactam, avibactam, vaborbactam, and relebactam are approved β -lactamases inhibitors used with specific antibiotics.

3.3.2 Efflux pump inhibitors: Efflux pumps in bacterial membranes expel antibiotics, lowering intracellular concentrations and causing resistance. Adjuvants called EPIs physically hinder these pumps, increasing the intracellular antibiotic concentration and restoring sensitivity.

3.3.3 Membrane Permeabilizer: Antibiotics must penetrate the bacterial membrane to work. For Gram-negative bacteria protected by an outer membrane, antibiotic adjuvants promote membrane permeability (permeabilizer). These cationic and amphiphilic compounds destabilize the outer membrane by interacting with lipopolysaccharides or capturing cations, facilitating antibiotic passage. Substances such as polymyxin B, colistin, aminoglycosides, cationic peptide, and polyamines act as permeabilizers (11).

4. Novel drug delivery system

The emergence of novel drug delivery systems (DDS) represents a promising and innovative strategy to enhance antibiotic treatment regimens while reducing the development of antibiotic resistance. By formulating single or combinations of multiple antibiotics into diverse nano-formulations, including metal-based (e.g., gold, silver nanoparticles), lipid-based (e.g., liposomes, solid lipid nanoparticles), carbon-based (e.g., Carbon nanotubes, graphene sheets), and polymeric nanoparticles (derived from both natural and synthetic polymers), these advanced DDS offer viable alternatives to conventional antibiotics as efficient drug-delivery vehicles (12).

An essential advantage of nanoparticle-based DDS is their ability to protect antibiotics from enzymatic degradation, prolonging drug release and increasing drug half-life and bioavailability. Furthermore, these DDS can be engineered to facilitate antibiotic bacterial binding, resulting in higher antibiotic concentrations at the site of infection. Upon penetrating the microbial cell membrane, the nanomaterials induce structural alterations, disrupting the size and configuration of the bacterial membrane and altering metabolic pathways. Subsequently, when the nanoparticles enter the intracellular environment, they engage with biological pathways, impeding enzymes, deactivating proteins, instigating oxidative stress, causing electrolyte imbalances, and inducing genetic variations (13). These orchestrated interactions result in the primary eradication of microorganisms.

By optimizing drug delivery, inhibiting bacterial defense mechanisms, and fostering synergistic effects, nanoparticle-based DDS demonstrate unparalleled potential in revolutionizing the management and control of antibiotic-resistant infections (Figure 2).

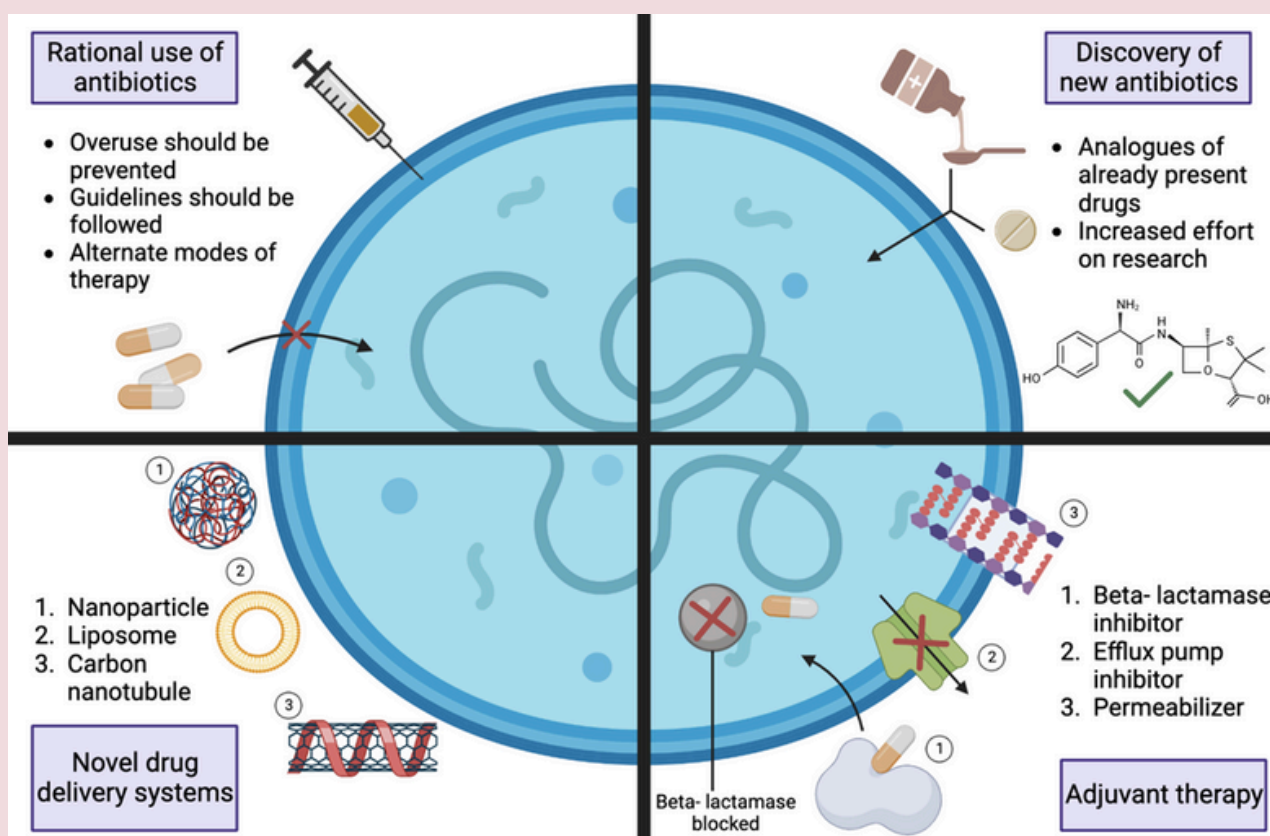


Figure 2. Strategies to combat Antimicrobial Resistance

5. Conclusion

The current problem of antibiotic resistance is a serious challenge to global health and demands immediate action. An increase in multidrug-resistant pathogens and the lack of efficient existing antibiotics requires innovative solutions. Rational antibiotic use, the discovery of new antibiotics and adjuvant therapies, and novel drug delivery systems offer promising avenues to combat this crisis. Urgent collaboration between healthcare providers, policymakers, researchers, and the public is essential to preserve the effectiveness of antibiotics and treat disease. We can pave the way for a healthier and more sustainable future for future generations with concrete efforts.

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Fun & frolic – Crossword

Solution on page 89

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Across

1. First drug against which resistance was identified
5. Hospital-Acquired Infections
6. Drug cleaved by beta lactamase
7. Antimetabolite
8.Resistant K. pneumoniae is the pathogen on the CDC threat list
9. Antibiotic against cell wall synthesis
10. Drug affected by mutation in RNA polymerase

Down

2. E of ESKAPE
3. Responsible for antimicrobial resistance
4. Recent bacterial secondary metabolite drug against gram negative superbugs