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Bacterial resistance to antimicrobial agents: A comprehensive review

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Abstract

Antimicrobial resistance (AMR) poses a significant global threat to public health. The increasing prevalence of bacteria resistant to antimicrobial agents necessitates a thorough understanding of the underlying mechanisms, contributing factors, and potential mitigation strategies. This review provides a comprehensive overview of bacterial resistance mechanisms, focusing on the biochemical and genetic basis of resistance to various classes of antimicrobials. It explores the factors driving the emergence and spread of AMR, including antibiotic overuse, horizontal gene transfer, and selective pressures. Finally, the review delves into strategies for combating AMR, encompassing antimicrobial stewardship, development of novel antimicrobials, and alternative therapeutic approaches.

Keywords: Antimicrobial resistance; Antibiotic resistance; Bacteria; Resistance mechanisms; Antimicrobial stewardship; Horizontal gene transfer

1. Introduction

The discovery and widespread use of antimicrobial agents, particularly antibiotics, revolutionized the treatment of infectious diseases in the 20th century (Aminov, 2010). These agents, targeting essential bacterial processes, significantly reduced morbidity and mortality associated with bacterial infections. However, the remarkable adaptability of bacteria has led to the emergence and spread of antimicrobial resistance (AMR), an escalating global health crisis (WHO, 2014). AMR occurs when bacteria evolve mechanisms that allow them to survive exposure to antimicrobials that would normally inhibit their growth or kill them. This renders treatment of infections ineffective, leading to prolonged illness, increased healthcare costs, and higher mortality rates (O'Neill, 2016).

The complexity of bacterial resistance necessitates a comprehensive understanding of the underlying mechanisms. This review aims to provide an in-depth exploration of the diverse mechanisms employed by bacteria to resist antimicrobial agents, the factors contributing to the rise and dissemination of AMR, and the strategies being developed to combat this growing threat.

2. Mechanisms of Antimicrobial Resistance

Bacteria have developed a variety of sophisticated mechanisms to counteract the effects of antimicrobial agents. These mechanisms can be broadly categorized into enzymatic inactivation of the antimicrobial, alteration of the antimicrobial target site, decreased antimicrobial accumulation, and activation of efflux pumps (Blair et al., 2015).

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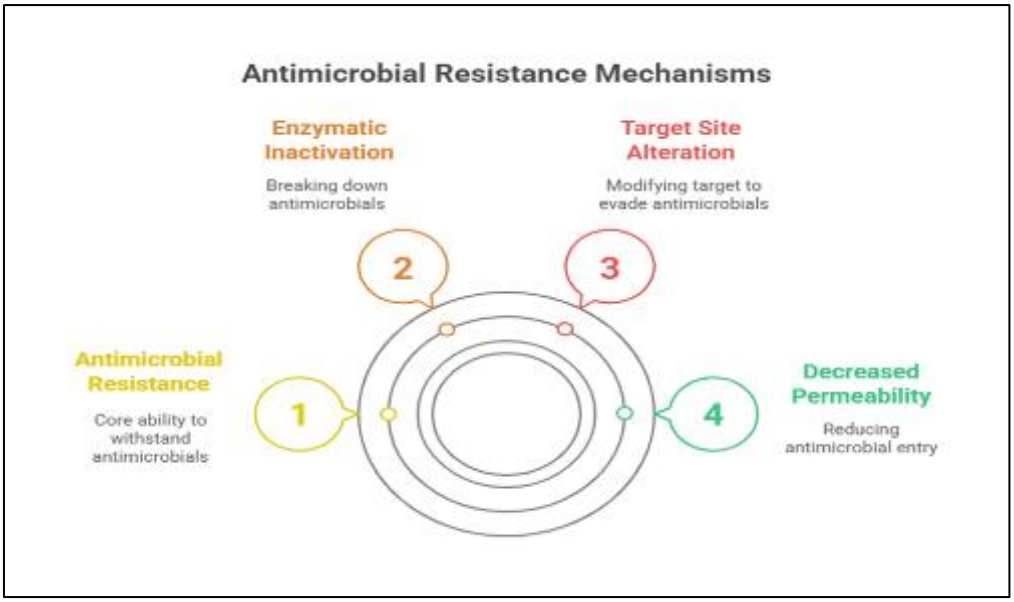

Figure 1 Mechanisms of antimicrobial resistance through enzymatic inactivation of antimicrobial agents

Enzymatic Inactivation: One of the most prevalent mechanisms of AMR involves the production of enzymes that inactivate or modify the antimicrobial agent, preventing it from reaching its target. A classic example is the production of β-lactamases, enzymes that hydrolyze the β-lactam ring of penicillin and cephalosporin antibiotics (Bush, 2018). Different classes of β-lactamases exist, each with varying substrate specificities, contributing to resistance against a wide range of β-lactam antibiotics. For example, extended-spectrum β-lactamases (ESBLs) confer resistance to cephalosporins like ceftriaxone and cefotaxime (Rawat & Nair, 2010). Carbapenemases, another class of β-lactamases, hydrolyze carbapenems, considered last-resort antibiotics for treating severe infections (Queenan & Bush, 2007). Similarly, aminoglycoside-modifying enzymes (AMEs) modify aminoglycoside antibiotics, such as gentamicin and tobramycin, by acetylation, phosphorylation, or adenylation, rendering them inactive (Ramirez & Tolmasky, 2017). Some bacteria produce enzymes that modify chloramphenicol, like chloramphenicol acetyltransferases (CATs) (Shaw, 1983, p.161).

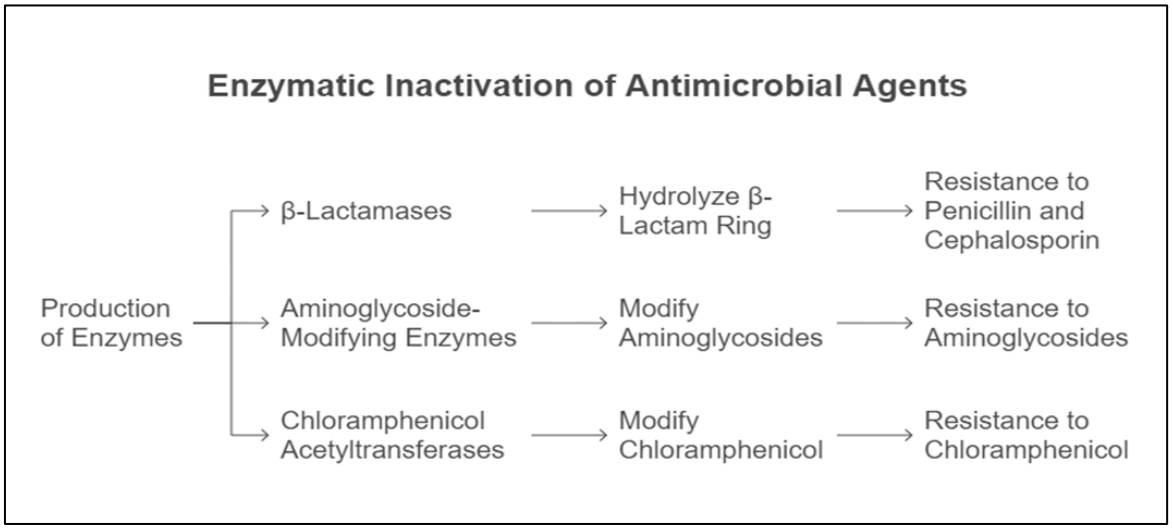

Figure 2 Mechanisms of antimicrobial resistance via alteration of antimicrobial target sites

Alteration of the Antimicrobial Target Site: Bacteria can also develop resistance by altering the target site of the antimicrobial agent, reducing its binding affinity and effectiveness. For instance, resistance to macrolide antibiotics, such as erythromycin and azithromycin, can arise from mutations in the 23S rRNA of the bacterial ribosome, the target of these drugs (Vester & Douthwaite, 2001). These mutations alter the ribosome structure, preventing macrolide binding. Resistance to quinolone antibiotics, such as ciprofloxacin and levofloxacin, can result from mutations in

the *gyrA* and *parC* genes, which encode subunits of DNA gyrase and topoisomerase IV, respectively (Hooper & Jacoby, 2016). These mutations alter the binding sites of quinolones, reducing their ability to inhibit DNA replication. Similarly, resistance to vancomycin, a glycopeptide antibiotic that inhibits cell wall synthesis, can occur through modification of the peptidoglycan precursor terminating with D-Ala-D-Ala to D-Ala-D-Lac (vancomycin resistance operon), which reduces vancomycin binding (Courvalin, 2006).

Decreased Antimicrobial Accumulation: Another mechanism of AMR involves reducing the intracellular concentration of the antimicrobial agent, either by decreasing its influx or increasing its efflux. Porins are channel proteins located in the outer membrane of Gram-negative bacteria that allow diffusion of small hydrophilic molecules, including some antibiotics. Loss or mutation of porins can reduce the uptake of antimicrobials into the cell, leading to resistance (Pages et al., 2008). For example, decreased expression of OprD, a porin in *Pseudomonas aeruginosa*, can lead to resistance to carbapenems (Ochs et al., 1999).

Efflux Pumps: Efflux pumps are transmembrane proteins that actively transport antimicrobial agents out of the bacterial cell, reducing their intracellular concentration and preventing them from reaching their targets (Blair et al., 2015). Bacteria can possess multiple efflux pumps with broad substrate specificities, contributing to multidrug resistance. The AcrAB-TolC efflux pump in *Escherichia coli* is a well-characterized example, conferring resistance to a wide range of antibiotics, including tetracycline, chloramphenicol, and fluoroquinolones (Nikaido, 2009). Overexpression of efflux pumps can play a significant role in AMR, particularly in Gram-negative bacteria.

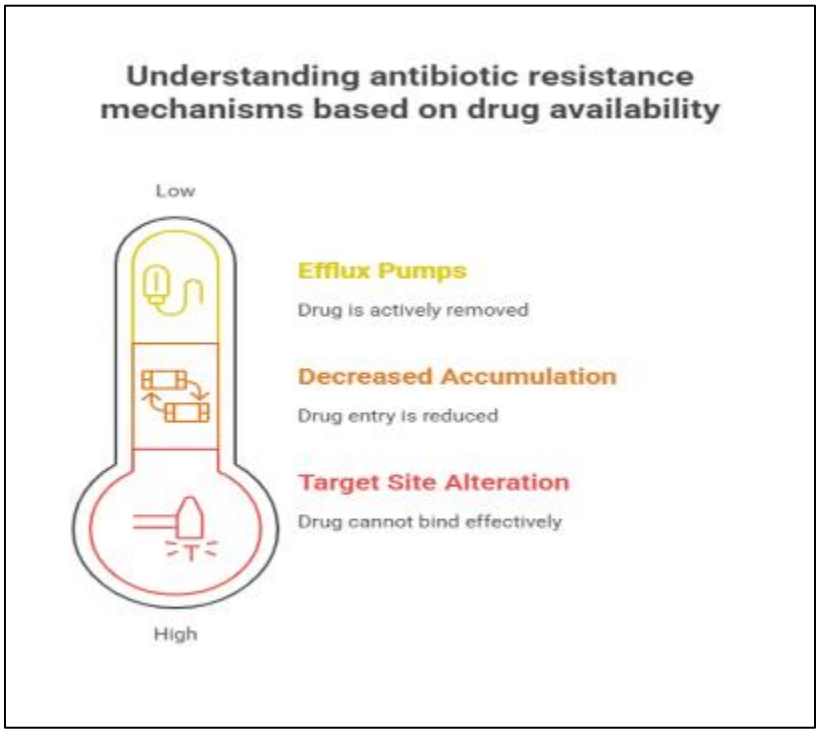

Figure 3 Role of efflux pumps and decreased antimicrobial accumulation in bacterial resistance

3. Factors Contributing to the Emergence and Spread of AMR

The escalating problem of AMR is driven by a complex interplay of factors, including antibiotic overuse, horizontal gene transfer, and selective pressures. Understanding these factors is crucial for developing effective strategies to combat AMR.

- **Antibiotic Overuse and Misuse:** The inappropriate and excessive use of antibiotics, both in human medicine and agriculture, is a major driver of AMR (Goossens et al., 2005). Unnecessary antibiotic prescriptions for viral infections, over-the-counter availability of antibiotics in some countries, and prophylactic use of antibiotics in livestock contribute to this problem. Exposure to sublethal concentrations of antibiotics can promote the selection and survival of resistant bacteria (Andersson & Hughes, 2017). This selective pressure favors the proliferation of resistant strains, leading to their dominance in bacterial populations.

- **Horizontal Gene Transfer:** Horizontal gene transfer (HGT) is a crucial mechanism for the rapid spread of AMR genes among bacteria. HGT involves the transfer of genetic material between bacteria that are not directly related, allowing resistance genes to disseminate across species and genera (Bennett, 2008). The three main mechanisms of HGT are transformation, transduction, and conjugation. Transformation involves the uptake of naked DNA from the environment by competent bacteria (Chen & Dubnau, 2004). Transduction involves the transfer of DNA from one bacterium to another via bacteriophages (viruses that infect bacteria) (Weinbauer, 2004). Conjugation involves the transfer of DNA between bacteria through direct cell-to-cell contact, often mediated by plasmids (Lederberg & Tatum, 1946). Plasmids are extrachromosomal DNA molecules that can carry multiple resistance genes, facilitating the rapid spread of multidrug resistance (Carattoli, 2011). Integrons are genetic elements that can capture and express gene cassettes, including antibiotic resistance genes, further contributing to the dissemination of AMR (Cambray et al., 2010).
- **Selective Pressure:** The presence of antimicrobial agents in the environment, including hospitals, farms, and wastewater treatment plants, exerts selective pressure on bacterial populations, favoring the survival and proliferation of resistant strains (Baquero et al., 2008). Resistant bacteria have a competitive advantage in the presence of antibiotics, allowing them to outcompete susceptible bacteria. The higher the concentration of antimicrobial agent, the stronger the selective pressure becomes, leading to the rapid enrichment of resistant bacteria in the bacterial population.
- **Globalization and Travel:** International travel and trade contribute to the global spread of AMR. Individuals carrying resistant bacteria can travel to different countries, introducing these bacteria into new environments (Huijsdens et al., 2006). The international trade of food products, particularly meat, can also contribute to the spread of AMR, as resistant bacteria can be transferred from livestock to humans through the food chain.
- **Poor Infection Control Practices:** Inadequate infection control practices in healthcare settings, such as poor hand hygiene and inadequate sterilization of equipment, can facilitate the transmission of resistant bacteria between patients and healthcare workers (Pittet et al., 2000). This can lead to outbreaks of healthcare-associated infections caused by multidrug-resistant organisms.

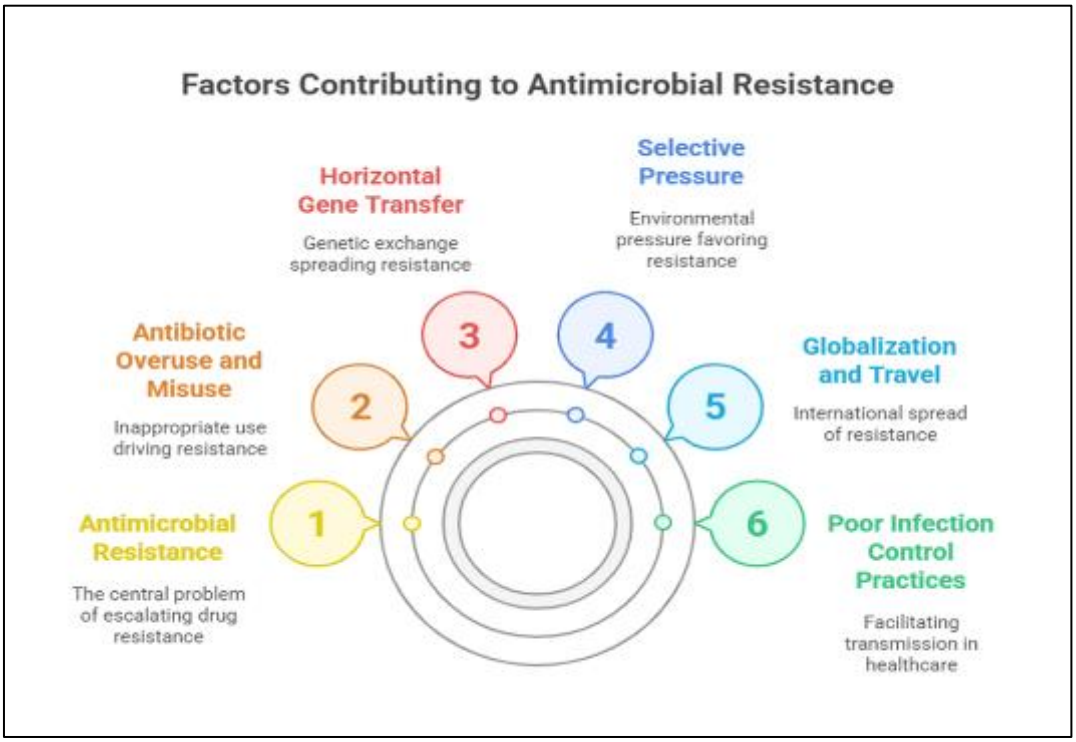

Figure 4 Key factors contributing to the emergence and global spread of antimicrobial resistance

4. Strategies for Combating Antimicrobial Resistance

Addressing the challenge of AMR requires a multifaceted approach that encompasses antimicrobial stewardship, development of novel antimicrobials, and alternative therapeutic strategies.

- **Antimicrobial Stewardship:** Antimicrobial stewardship programs aim to optimize antimicrobial use to improve patient outcomes, reduce the development of AMR, and decrease healthcare costs (Barlam et al., 2016). These programs typically involve implementing guidelines for appropriate antimicrobial prescribing, monitoring antimicrobial use, and providing education to healthcare professionals and patients. Key elements of antimicrobial stewardship include promoting the use of narrow-spectrum antibiotics when possible, avoiding unnecessary antibiotic use for viral infections, and ensuring appropriate dosing and duration of therapy.
- **Development of Novel Antimicrobials:** The development of new antimicrobial agents is crucial for overcoming AMR. However, the pipeline of new antibiotics has been drying up in recent years, due to economic and regulatory challenges (Spellberg et al., 2004). There is a need for increased investment in antimicrobial research and development, as well as innovative approaches to drug discovery. New strategies include exploring novel targets in bacteria, developing antimicrobials that circumvent existing resistance mechanisms, and utilizing natural products as a source of new drugs.
- **Alternative Therapeutic Strategies:** In addition to developing new antibiotics, alternative therapeutic strategies are being explored to combat AMR. These strategies include phage therapy, antimicrobial peptides, antibodies, and vaccines. Phage therapy involves using bacteriophages to infect and kill bacteria (Salmond & Fineran, 2015). Phages are highly specific to their bacterial hosts, making them a potentially attractive alternative to antibiotics. Antimicrobial peptides are naturally occurring peptides with broad-spectrum antimicrobial activity (Hancock & Sahl, 2006). Antibodies can be used to neutralize bacterial toxins or enhance the immune response to infection (Casadevall & Pirofski, 2015). Vaccines can prevent bacterial infections, reducing the need for antibiotic use.
- **Improved Diagnostics:** Rapid and accurate diagnostic tests are essential for guiding antimicrobial therapy and preventing the inappropriate use of antibiotics. These tests can identify the causative pathogen and determine its antimicrobial susceptibility profile, allowing for targeted treatment with the most effective antibiotic (Landry & Bernard, 2017). Point-of-care diagnostics, which can be performed at the patient's bedside, can provide rapid results, enabling timely treatment decisions.
- **Infection Prevention and Control:** Effective infection prevention and control measures in healthcare settings are crucial for preventing the spread of resistant bacteria. These measures include hand hygiene, environmental cleaning, isolation of infected patients, and judicious use of medical devices (Boyce & Pittet, 2002). Implementing strict infection control protocols can significantly reduce the incidence of healthcare-associated infections caused by multidrug-resistant organisms.
- **Public Awareness and Education:** Raising public awareness about AMR and promoting responsible antibiotic use is essential for changing behaviors and reducing the selective pressure driving resistance. Educational campaigns can inform the public about the importance of using antibiotics only when necessary, completing the full course of antibiotics as prescribed, and practicing good hygiene to prevent the spread of infections.

5. Conclusion

Antimicrobial resistance represents a serious and growing threat to global public health. The multifaceted mechanisms of AMR, coupled with the factors driving its emergence and spread, necessitate a comprehensive and coordinated response. Strategies to combat AMR must include antimicrobial stewardship programs to optimize antibiotic use, continued investment in the development of novel antimicrobials, exploration of alternative therapeutic approaches, improved diagnostics, enhanced infection prevention and control measures, and public awareness campaigns. A concerted effort involving healthcare professionals, researchers, policymakers, and the public is essential to mitigate the threat of AMR and preserve the effectiveness of antimicrobial agents for future generations.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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