Industrial Engineering Journal
ISSN: 0970-2555
Volume : 53, Issue 2, No. 1, February : 2024

A COMPREHENSIVE LOOK AT ANTIBIOTIC RESISTANCE

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Abstract
Antibiotic resistance has emerged as a global public health concern. It arises when bacteria stop responding to the antibiotics used to check their growth. This means that the antibiotics that were once effective in treating certain infections can no longer do so, leading to increased morbidity and mortality rates. This is a major challenge in modern medicine, as it makes the treatment of numerous bacterial infections more complicated, longer, and more expensive. It is essential to reduce the spread of antibiotic-resistant bacteria by implementing measures such as responsible antibiotic use, infection control, and investment in developing a new class of antibiotics and other alternative treatment methods. The inability to address this emerging threat could lead to a future in which common infections become untreatable, making even minor surgeries and procedures life-threatening. Antibiotic resistance results from natural selection from the overuse and misuse of antibiotics and from the developmental lack of new antibiotics to replace those that are no longer effective. This review provides a summary of antimicrobial resistance and its mechanism and has discussed strategies to overcome this burning problem.

Keywords: antimicrobial resistance, bacteria, antibiotics, multidrug resistance

Introduction

Antibiotics, occasionally called antimicrobial agents, constitute a category of medications employed in the treatment of bacterial infections. Uncovered in the early 20th century, they have since become a fundamental aspect of modern medicine, playing a pivotal role in saving numerous lives through the effective treatment of bacterial infections (Fleming). Antibiotics either kill or prevent bacteria from reproducing and spreading, allowing the immune system to clear the infection. Over the years, numerous antibiotics have been developed to target different types of bacteria and to treat a broad spectrum of infections, ranging from minor to life-threatening conditions. Unfortunately, the widespread use of antibiotics has also led to a major challenge: antibiotic resistance. This happens when bacteria acquire mechanisms to avoid the antibiotic's inhibitory effect, thus making them ineffective in treating infections. Several factors have contributed to this resistance, namely, natural selection, mutations, the excessive and improper application of antibiotics, and insufficient progress in creating new antibiotic options (Rather, Kim et al. 2017, Ribeiro da Cunha, Fonseca et al. 2019). It is being estimated that in 2019, globally, over 4.95 million deaths were linked to antimicrobial resistance, with bacterial antibiotic resistance accounting for 1.27 million of these fatalities (Antimicrobial Resistance 2022). As such, there is a pressing need to address this issue by promoting responsible antibiotic use, investing in new antibiotic development and alternative treatment methods, and implementing measures to control the dissemination of antibiotic-resistant bacteria.

Industrial Engineering Journal
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Acquisition/Development of Antibiotic resistance

Bacteria adopt various strategies to acquire protection against various threatening agents. These have been classified mainly into intrinsic, acquired, and adaptive resistance (Fig.1).

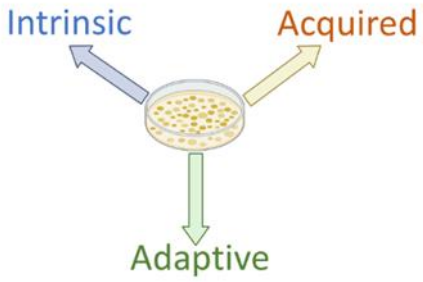

Fig.1 Mode of acquisition of antibiotic resistance

Intrinsic resistance: As the name described, this type of resistance is mainly conferred by the inherent properties of the bacterium. Against a specific antibiotic, bacterial intrinsic resistance can be characterized as its inherent capacity to withstand the effect of that antibiotic due to its inherent structural or functional features (Blair, Webber et al. 2015). These are generally chromosomally encoded and include antibiotic-inactivating enzymes, non-specific efflux pumps, or mechanisms serving as permeability barriers (Fajardo, Martinez-Martin et al. 2008, Cox and Wright 2013); Generally, intrinsic resistance mechanisms do not confer a high level of resistance, but bacteria having intrinsic resistance mechanisms become opportunistic in immunocompromised pathogens (Wright 2007).

Acquired resistance: This form of resistance evolves through two primary mechanisms: genetic mutation and the acquisition of new genetic material from an external source. Genetic mutation involves changes in the DNA sequence, leading to alterations in the bacterial genome that may confer resistance. On the other hand, the acquisition of new genetic material can occur through processes such as horizontal gene transfer, where bacteria obtain genes from other bacteria or external sources. Both genetic mutation and the acquisition of foreign genetic material contribute to the development of this type of resistance, allowing bacteria to adapt and survive in the presence of antimicrobial agents.

Adaptive: Here the bacterium adopts and develops resistance over time. This occurs due to bacterial genetic plasticity and their ability for swift evolutionary changes. Adaptive resistance is transient, unlike intrinsic and acquired resistance. This form of resistance enables bacteria to promptly react to challenges such as sub-inhibitory levels of antibiotics, changes in pH, stress, variations in ion concentrations, and changes in nutrient conditions. Once the inducing signal is removed, bacteria typically revert to their initial state. (Fernandez, Breidenstein et al. 2011, Motta, Cluzel et al. 2015, Kobra Salimiyan Rizi 2018, Lee 2019). This happens because of the modulation of gene expression in response to changes in the environment. Contrary to genetic modifications that usually lead to permanent phenotypes, adaptive resistance in bacteria is often attributed to epigenetic changes.
The variation in *in vitro* and *in vivo* effectiveness resulting in the clinical failure of an antibiotic may be attributed to adaptive resistance. Importantly, the gained resistance due to environmental stimuli may not entirely return to its original state once the stimuli are no longer present. This gradually increases the MIC levels (Fernandez, Breidenstein et al. 2011). It has also been proposed that once the bacteria gain the capability to multiply in the sub-inhibitory concentration of antibiotics through adaptive resistance, the probability of acquiring more potent and enduring resistance mechanisms also rises(Fernandez, Breidenstein et al. 2011, Kobra Salimiyan Rizi 2018).

Mechanisms of antibiotic resistance

Resistance mainly occurs through antibiotic modification/destruction, target alteration, target overproduction, low-affinity target production, target overproduction, or target bypass by altering the

Industrial Engineering Journal
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permeability of the efflux pumps (Fig.2). We will discuss these mechanisms with suitable examples from each category.

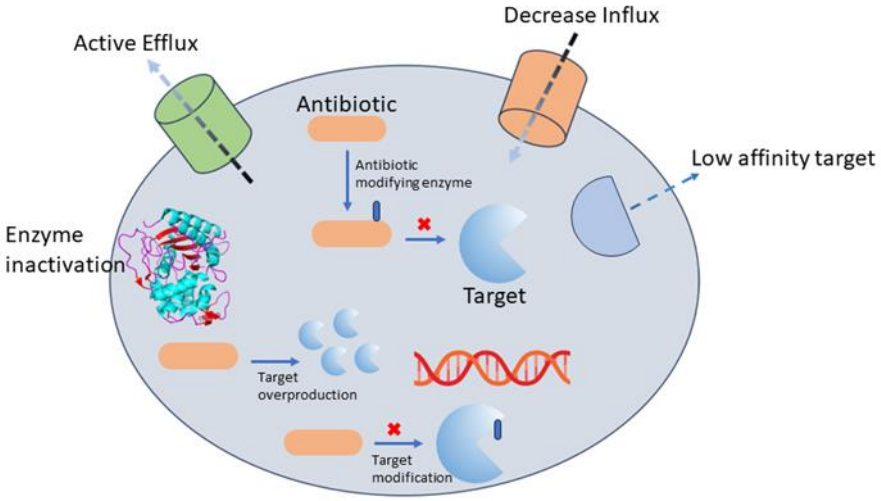

Fig.2 Overview of the mechanisms of antibiotic resistance

Antibiotic modification or destruction: This mechanism involves modifying or destroying the antibiotic molecules before they can exert their deleterious effect on the bacteria. Beta-lactamases represent a classic example of this resistance mechanism (Abraham and Chain 1988). Beta-lactamases are widely distributed among Streptomyces, and along with similar enzymes present in non-pathogenic and pathogenic bacteria, they form the b-lactamase superfamily of proteins (Ogawara, Kawamura et al. 1999, Sattler, Wang et al. 2015). Bacteria generate beta-lactamases to cleave the antibiotic's beta-lactam ring. This ring is a critical component of penicillin and cephalosporin-like antibiotics (Powell, Tomberg et al. 2009, Tomberg, Fedarovich et al. 2017, Singh, Tomberg et al. 2019, Singh, Turner et al. 2020, Turner, Connolly et al. 2021), as it allows them to bind to and inhibit the activity of enzymes of bacterial cell wall synthesis. The antibiotic can also be rendered ineffective by enzymatic modification involves enzymes like acetyltransferases, phosphotransferases, and nucleotidyl transferases, which can add a chemical moiety to the antibiotic molecule, changing its structure and making it ineffective.

Replacement or Bypassing of the Target: *Streptococcus pneumoniae* and *Staphylococcus aureus* demonstrate resistance to β-lactam antibiotics by replacing their Penicillin-Binding Proteins (PBPs). In the case of *Streptococcus pneumoniae*, the formation of mosaic PBPs results from genetic recombination between native and foreign DNA obtained from β-lactam-resistant streptococci, ultimately leading to the emergence of β-lactam resistance. On the other hand, in *Staphylococcus aureus*, the acquisition of methicillin resistance occurs through the integration of the mecA gene. This gene carries the genetic code for a penicillin-binding protein, denoted as PBP2a, which exhibits a notably low affinity for β-lactams. This gene is positioned on a mobile genetic element named staphylococcal chromosomal cassette mec (SCC mec) and plays a crucial role in the acquisition of resistance. The integration takes place within the bacterial chromosomal DNA. Penicillin-Binding Protein 2a (PBP2a) exhibits minimal affinity towards most β-lactams. This characteristic enables the bacterium to maintain cell wall synthesis effectively, even when exposed to β-lactams, leading to methicillin resistance (Moellering 2012, Hiramatsu, Ito et al. 2013).

Modification of Target Sites (Through Mutation or Enzymatic Alteration): Antibiotics bind to their target site specifically and with high affinity resulting in blocking the usual target's function. However, modifications in the target site result in blocking the antibiotic binding, allowing its normal substrate to bind, and this confers resistance against that antibiotic. A prominent example of this type

of resistance is in the Penicillin Binding Protein 2 (PBP2) of *Neisseria gonorrhoeae*. PBP2 enzyme of *N. gonorrhoeae* mutates close to its active site residue and hinders the binding of the cephalosporin class of antibiotics (Singh, Turner et al. 2020). Neisseria gonorrhoeae achieved this feat by acquiring a mosaic form of PBP2. PBP2 mosaicism in *N. gonorrhoeae* occurs through transformation, involving the uptake of foreign DNA followed by homologous recombination.

Target Site Protection and Overproduction: In target site protection method, mutations are not required. Here target sites are protected by enzymatic modification of residues, preventing the bindings of antibiotics. For example, the family of genes known as erythromycin ribosome methylase (erm) can methylate the 16S rRNA, causing a modification in the drug-binding area, thus hindering macrolides, lincosamines, and streptogramins binding. In target overproduction type of mechanism, microbes overproduce the target enzyme, which results in the availability of enough antimicrobial-free enzymes to proceed with the enzymatic reaction. Resistance against trimethoprim in *E. coli* has been linked to overexpression of *DHFR (Di hydrofolate reductase)* (Flensburg and Skold 1987, Huovinen 2001).

Reduced Membrane Permeability: The outer membrane of Gm (-ve) bacteria checks the permeation of antibiotics and various other substances. Its low permeability to specific antibiotic agents results in the development of intrinsic resistance against those particular antibiotics in some Gm (-ve) bacteria. Moreover, any alteration in the permeability of the outer membrane can additionally aid in the emergence of acquired resistance (Nikaido 1989). β-lactams antibiotics which are hydrophilic in nature, such as fluoroquinolones and chloramphenicol, generally enter through porins that are present on the outer membrane of the bacteria. Porins are of various types and are expressed differently in numbers. The expression of types of porins and their numbers influence the penetration of hydrophilic antibiotics and, thus, ultimately, their effectiveness against bacterial cells (Fernandez and Hancock 2012).

Efflux Pumps: These energy-dependent pumps are situated on the bacterial cytoplasmic membrane and possess the ability to actively export undesirable molecules out of the cell. They utilize energy to pump substances against their concentration gradients, contributing to the efflux of various molecules, including antibiotics, and playing a pivotal role in the development of resistance. The majority of these efflux pumps lack specificity, meaning they can expel a wide range of substances, including antibiotics, from the bacterial cell. This non-specific nature of efflux pumps contributes significantly to the development of antibiotic resistance. As these pumps actively remove antibiotics from the bacterial cell, it hinders the effectiveness of the antibiotics and allows bacteria to survive and proliferate even in the presence of these drugs. The broad substrate specificity of these efflux pumps underscores their role in fostering resistance by actively removing diverse antimicrobial agents (Piddock 2006, Piddock 2006, Nikaido and Pages 2012). However, there are also some efflux pumps that have high specificity for a particular antibiotic or drug (Piddock 2006, Piddock 2006).

Ways to deal with emerging antibiotic resistance problem

Although the problem of antibiotic resistance is not trivial and there are no clear-cut ways to address this problem, certain methods have been applied or could further be utilized to minimize or slow down this rising problem. Strategies like diagnostic improvement, proper prescriptions, development of a few new antibiotics have been applied at large (Christaki, Marcou et al. 2020). The use of nanocarriers has been under investigation to enhance the delivery methods of antimicrobials. They can potentially enhance antibiotic bioavailability and reduce treatment duration (Van Giau, An et al. 2019). Utilization of dual therapy, i.e., the use of two antibiotics with different target sites could reduce the rate of potential chances of acquiring resistance as has been adopted in the case of cephalosporin resistance *Neisseria gonorrhoeae* strain H041 (Singh, Turner et al. 2020). Other approaches could be the use of monoclonal antibodies, vaccines or phage therapy could be utilized to reduce the chances of antimicrobial resistance (Rappuoli, Bloom et al. 2017, Christaki, Marcou et al. 2020).

Conclusion

Antibiotic resistance is on the rise. It has become a major global health problem and requires immediate scientific attention. Bacteria and other pathogens tend to adapt to varying conditions, and in doing so, they acquire resistance to currently used antibiotics. Bacterial antibiotic resistance is on the rise with the overuse and misuse of antibiotics and bacterial evolution to changing local environments by either mutating or acquiring foreign DNA. Several bacterial strains have acquired resistance against multiclass antibiotics making infections harder to treat. More alarmingly, since resistant bacterial strains can transfer their resistance capabilities to other pathogens, this makes treatment of even common bacterial infections quite challenging, so strategies must be adopted to tackle this rising problem of antibiotic resistance. Strategies like discovering novel classes of antibiotics, limited use, and precise prescriptions must be made. In addition, the use of alternative treatment plans, like the use of monoclonal antibodies or vaccines, should be investigated.

Conflict of Interest Statement

No conflict of interest.

Funding

None to declare.

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