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Antibiotic Resistance- A Comprehensive Review

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Kaveri. A*, Hyma P, Jyothi.V

Sarojini Naidu Vanita Pharmacy Mahavidyalaya, Hyderabad, Telangana, India.

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ABSTRACT

Antibiotic resistance has become a worldwide challenge. Multidrug resistance patterns in gram +ve and gram -ve are becoming a major problem and it cannot be controlled by conventional therapies. So, there is a need for the development of new antibiotics to treat multidrug resistance. Various ways through which bacteria develop resistance are Biofilm formation, efflux-mediated antibiotic resistance, decreased uptake, modifications of the antibiotic resistance, changes in the target site. Another means by which resistance is developed by mutational resistance and horizontal gene transfer. Now that there is a shortage of effective treatment for antimicrobial resistance there is an urge in implementing new strategies for development and research in new antimicrobials.

INTRODUCTION

Antibiotics are drug substances that contain bacteria that are used to kill other bacteria and fungi. The ability of bacteria to mutate so that antibiotic doesn't show their effect is called antibiotic resistance. It has become a challenge to overcome resistance for the past few years. So, there is a necessity for developing techniques to reduce antibiotic resistance. Many ways have been adopted by these pathogens to develop resistance. Some of those are Biofilm formation, Efflux-mediated antibiotic resistance, Decreased uptake of antibiotics, Modifications of antibiotic resistance, Changes in target sites. Antibiotic resistance can also be due to mutation or a gene transfer from one bacteria to another bacteria i.e. horizontal gene transfer. Other methods by which bacteria resist antibiotics are: By producing proteins that destroy antibiotics and by changing bacteria's cellular structure by either blocking the binding site or inhibiting the function of antibiotics and by making the cell wall a barrier to drugs. Challenges that are interconnected with bacterial infection and other diseases are due to lack of proper preventive measures, dearth of effective therapies, and lack of new antibiotics, which requires the development of new strategies and alternative antimicrobial therapies for control of antibiotic resistance.

MUTATIONAL RESISTANCE

The mutation is considered the primary reason for antibiotic resistance. In this method bacteria, cells formed from other bacteria develop mutations that are effective against antibiotics. These mutations cause changes in bacterial genetic structure resulting in producing a difference in genotype and phenotype. Mutations results against antibiotic action through various ways like 1) modifications of the antimicrobial target 2) a decrease in the drug uptake 3) activation of efflux mechanisms to extrude toxic molecules 4) global changes in important metabolic pathways.

HORIZONTAL GENE TRANSFER

Acquiring foreign genes through HGT is one of the most common methods for acquiring resistance. Bacteria can obtain foreign genes by three main mechanisms they are

1) Transduction

2) Transformation

3) Conjugation

Among these conjugation is the most common and reliable method for gene transfer. In this conjugation mobile genetic elements are used as carriers to share the genetic information. The most important MGE's are plasmids and transposons.

One final mechanism is integrons, which reads the gene to be transferred and passes the information to another bacterium.

BIOFILM FORMATION:

It is considered a worldwide challenge because of its inherent antibiotic resistance acquired by its lifestyle. Biofilm formation is a process in which bacteria attach irreversibly to the surface and produce extracellular polymer which helps in attachment and matrix formation, resulting in an alteration in the phenotype of organisms concerning growth rate and gene transcription. These extracellular polymeric substances consist mostly of polysaccharides which can be detected microscopically and by chemical analysis. A layer of biofilm is heterogeneous in terms of both space and over time with water channels that promote the exchange of oxygen and nutrients for cell growth. Cells get separated from biofilm due to either overload or cell division and growth. These separated cells cause systemic infection. Polymerase chain reaction provides a sensitive and precise method for the timely diagnosis of microbial infection associated with biofilm formation.

EFFLUX-MEDIATED ANTIBIOTIC RESISTANCE

It plays an important part in drug resistance and also provides other functions in bacteria. Many classes of efflux pumps are categorized in gram +ve and gram –ve pathogens. This mechanism may be substrate-specific or can be broad substrate specificity. This kind of resistance mechanism affects a wide range of antimicrobial classes.

There are 5 major classes of efflux pumps:

1. The major facilitator superfamily (MFS)
2. The small multidrug resistance family (SMR)
3. The resistance nodulation cell division family (RND)
4. ATP binding cassette family (ABC)

5. Multidrug resistance and toxic compound extrusion family (MATE)

These pumps are characterized by structural conformation, energy source, substrates range, and types of bacteria in which they are distributed. Phytochemicals are found as an alternative for resistance modifying agents. They act either by killing bacteria or by interrupting the pathway that causes resistance thereby decreasing the chance of developing resistance.

DECREASED UPTAKE OF ANTIBIOTIC

Pathogens have developed a mechanism to inhibit the uptake of antibiotics to reach their target sites which are mostly intracellular target sites. In general, the outer membrane works as the first-line defense mechanism against the absorption of multiple toxic compounds including antimicrobial agents. Many types of porins have been described and are classified based on their structure, selectivity, and regulation of their expression.

Porins are altered by 3 basic processes:

1. The shift in the type of porins expressed
2. A change in the level of porin expression
3. Impairment of the porin function

Example: Clinical isolates of K. pneumonia were recovered before and after antimicrobial therapy. Post therapy was found to exhibit a shift in porin expression from Ompk35 to Ompk36. This alteration in porin expressed correlated with a 4-8 fold decrease in susceptibility to a wide range of β-lactam antimicrobials.

MODIFICATIONS OF THE ANTIBIOTIC MOLECULE

Chemical alterations of the antibiotics: some of the enzymes have the ability to introduce chemical changes to the antimicrobial molecule. It is well known and adopted by gram +ve and gram -ve bacteria. Mostly, the drugs which inhibit protein synthesis at ribosomes levels are being inhibited by these enzymatic modifications. There are several types of modifying enzymes and the most common biochemical reactions they catalyze are 1) acetylation 2) phosphorylation 3) adenylation.

The resulting effect depends on steric hindrance that decreases the affinity of the drug for its target regardless of a biochemical reaction.

Destruction of the antibiotic molecule: In β-lactam resistance, it is due to the destruction of these compounds by β-lactamases. These enzymes destroy the amide bond of the β-lactam ring and prevent it from its action. So, new β-lactam compounds have been developed with a wider spectrum of activity and less sensitive to penicillinases were manufactured. The development of newer generations of β-lactams has been followed by the rapid appearance of enzymes that are capable of destroying any compound in the market. It is one of the major examples of antibiotic-driven adaptive bacterial evolution.

CHANGES IN TARGET SITES

In this mechanism, antimicrobial resistance is acquired either by protecting the target or by modification of the target site that causes a decrease in the affinity of the antibiotic molecule.

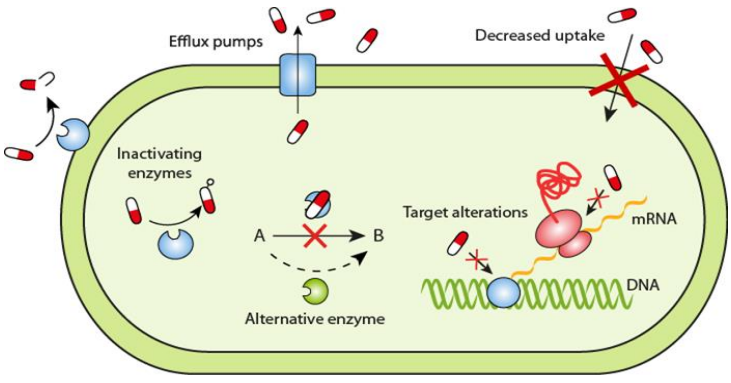
Target protection: Some genetic determinants coding for a protein that helps in target protection have been found in the bacterial chromosomes. But most of the genes involved in this mechanism are carried by MGE's.

Modification of target site: Modification of target site is the most common mechanism of antibiotic resistance. This modification can be due to

1) Point mutations in genes encoding target site

2) Enzymatic alterations of the binding site

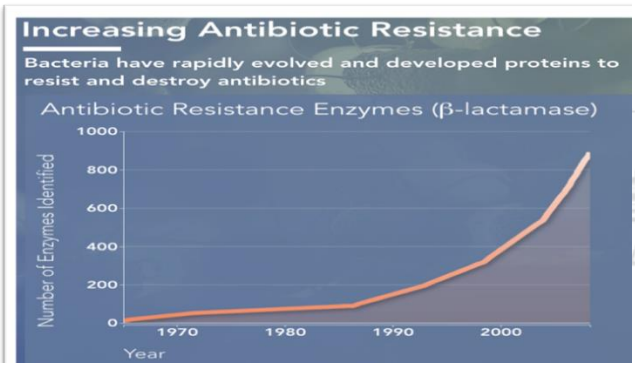
3) Replacement (or) bypass of the original target

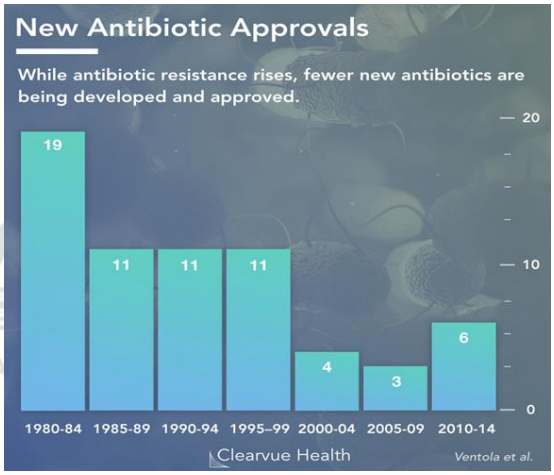


Resistance takes place mainly due to cellular changes that also effects the biocide accumulation. Target site modifications can also lead to biocide resistance. Many multidrug efflux systems also cause the accumulation of biocides and bacteria to become resistant to both biocide and antibiotics.

CONCLUSION

Antibiotics are playing a great role to control many bacterial infections. According to CDC's Antibiotic Resistance Threats in the United States, in 2019 more than 2.8 million antibiotic-resistant infections occur in the U.S each year and more than 35,000 people die as a result. So, there should be an increase in the development of new antibiotic agents against various death-causing infections. Over the past few decades research on antibiotics has been declined due to multidrug resistance and it has become more complicated and rare to find out new antibiotics. If we have to solve this problem there should be an increase in efforts for development and research in new antibiotics and they must be supported. Therefore, attempts on developing new antibiotics and research on the mechanism of resistance should be persistent, steady, and resilient.





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