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ANTIBIOTICS AND ANTIBIOTIC RESISTANCE

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Abstract
The discovery of antibiotic substances was probable the greatest achievement of medicine, because they allow treating many infectious diseases or syndromes and curing them. Only the substances that killed bacteria are called antibiotics, and those against other microorganisms are called antimicrobials. It is very important to understand the role and functions of antibiotics, how they inhibit or kill bacterial cells and their adverse events.
Once the antibiotics were widely used, the resistant bacterial strains appeared. Many bacteria become resistant to such substances and the mechanisms of resistance are not complete understood yet in some cases. Therefore it is necessary to perform the antibiogram and to use the appropriate treatment with efficient antibiotics. Also the scientists search for new substances with antibacterial activity (new antibiotics, synthetic substances, plant extracts) to avoid the induction of antibiotic resistance and to have success in therapy of bacterial infections.

Keywords: antibiotic, antibiotic resistance, microorganism.

1. INTRODUCTION

The human infections are produced by microorganisms (bacteria, fungi, microscopic parasites) and leading to illness and diseases. Antimicrobials are used to treat these infections, but only substances that target bacteria are called antibiotics. In addition to antibiotics, synthesized by microorganisms, synthetic homologues have been used to accomplish the same tasks.
The antibacterial effects of natural products were used from ancient times (for example, mould and warm soil were used to treat infected wound by Greeks and Indians). During times, the scientists observed the antimicrobial effects of some live organisms, especially fungi.
In pre-antibiotic era the three main causes of death in America were tuberculosis, pneumonia and gastrointestinal infections (Fair and Tor, 2014). The discovery of Penicillin in 1928 by Alexander Fleming and the development and usage of antibiotics represented a turning point in human history (Davies and Davies, 2010) and changed the public health hazards, while prior the beginning of the 20th Century morbidity and mortality by infectious diseases were high and the life expectancy was almost 47 years (Adedeji, 2016). A number of antibiotics was discovered and used to cure certain infections produced by microbes in 1970s and 1980s, but there is a constant concern to search for new substances required to decrease the infection rate (Bueno, 2018).
Nowadays the infectious diseases affect worldwide especially children, elderly, surgical patients, transplant patients, patients on immunosuppressive treatment, but other risk factors can contribute.
Simultaneous with antibiotic discovery has been observed a parallel phenomenon, the antibiotic resistance, the capacity of bacteria to resist the effect of antibiotic. This resistance is increasing

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because of inadvertent use of chemotherapeutic agents. In certain bacterial species the antibiotic resistance is a natural parameter, but in other species this resistance due to genetic mutations or acquiring resistance from another strains under antibiotic presence pressure. Some antibiotics are accompanied by adverse effects in human host, including hypersensitivity, and this is one of the reasons to seek other antibacterial agents effective against pathogenic bacteria (Ghosh, 2007).

2. DEFINITION AND CLASSIFICATION

Antibiotics are various organic molecules naturally produced by some microorganisms (moulds from soil, but bacteria, too) with manifest antibacterial effects. In lower concentration they control the bacterial growth or even kill bacteria by specific interactions with targets and they have a low toxicity on human cells. There are many known antibacterial substances with microbial origin, but limited number of them is useful for therapy and they are produced by microorganisms like *Bacillus*, *Streptomyces*, *Micromonospora*, *Penicillium* and *Cephalosporium.*

Synthetic antibiotics have similar effects against bacteria, usually are chemically related to natural antibiotics. Nowadays some of antibacterial therapeutic agents have a semi-synthetic origin (like Amoxycillin, Ampicillin and Doxycycline).

Both natural and synthetic antibiotics are used in treatment of infectious diseases or syndromes to fight against pathogenic microorganisms (Debeleac and Popescu Drânda, 2003).

Antibiotics can be classified based on multiple criteria: origin (bacterial, actinomycetes or fungal origin), type and spectrum of activity, route of administration (parenteral or oral route), mode of action etc.

For instance, antibiotics with bacterial origin are Polymyxin (produced by *Bacillus polymyxa*), Bacitracin (produced by *Bacillus subtilis*), with actinomycetes origin are Streptomycin, Erythromycin, Tetracycline, Chloramphenicol, Vancomycin (produced by different species of genus *Streptomyces*), and antibiotics with fungal origin are Penicillin (produced by *Penicillium chrysogenum*) or Cephalosporin (produced by fungus A*cremonium*, previously called *Cephalosporium*).

Based on type of action, they are bacteriostatic antibiotics (those inhibit the bacterial growth, by interfering with bacterial protein synthesis or DNA replication, such as Tetracycline and Chloramphenicol) or bactericidal antibiotics (they kill bacteria, generally by interfering with the cell wall synthesis, such as Vancomycin). Based on their bacterial spectrum of action, they can be narrow-spectrum antibiotics (such as Vancomycin, active only on Gram positive bacteria) or broad-spectrum antibiotics (for instance Tetracycline).

The most important classification of antibiotic is based on chemical structure and the mode of action against bacteria depends on it. Each class of antibiotics contains several antibiotics with similar action, level of toxicity or adverse effects. The chemical classes of antibiotics include the Beta-lactams (Penicillins, Cephalosporins, Carbapenems), Aminoglycosides, Macrolides, Tetracyclines, Quinolones and Fluoroquinolones, Sulfonamides. The chemical composition are various, from carbohydrates, saccharides (eg. aminoglycosides), macrocyclic lactones, quinolones, to peptide and heterocyclic antibiotics.

The action mechanisms of antibiotics are the biochemical ways to affect the bacterial target (enzymes, receptors) at a molecular level. The knowledge of these mechanisms allows understanding how antibiotics selectively act on vital functions of bacteria, without affect the host functions (Dowling et al., 2017). There are four main mechanisms, one of them involves the destruction processes of cellular membrane, and three of them involve the inhibition of some cellular synthesis (cell wall, nucleic acids and proteins) by inhibition of caretaker enzymes.

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Some antibiotics, like Polymixin B and Colistin, disrupt the cellular membrane of the Gram negative bacteria because they bind the membrane phospholipids. Other antibiotics due to monovalent ion channels in the cell wall of Gram positive bacteria and the transport of ions through membrane and the permeability of this are altered.

Beta-lactams (Penicillins, Cephalosporins) and Vancomycin inhibit the bacterial cell wall assembly by interfering with peptidoglycan polymerization at different stages of cell wall construction. These antibiotics selectively target the bacteria with no important negative effect on the eukaryotic cells, because the lack of the peptidoglycan wall in eukaryotic host. Beta-lactams bind and inhibit Penicillin Binding Proteins (PBPs), which are different in various bacteria (Debeleac and Popescu Drânda, 2003). Penicillins are effective especially against Gram positive bacteria. Cephalosporins are similar to Penicillins and have the beta-lactam ring, less susceptible to beta-lactamases; they can be prescribed for penicillin-allergic patients.

Other mechanisms of antibiotic action consist of inhibition of nucleic acids synthesis (DNA or RNA) or prevent the proper reading of genetic messages and the growth of bacterial cells. Quinolones (especially Fluoroquinolones like Levofloxacin, Norfloxacin and Ciprofloxacin) interfere with bacterial topoisomerase II (DNA gyrase enzyme), which is essential for DNA replication. Some Quinolones are useful in treatment of infections with intracellular parasites (Todar, 2006). Rifampicin inhibits the bacterial RNA polymerase by binding to the beta subunits of enzyme and blocks the mRNA synthesis.

Some antibiotics inhibit the bacterial protein synthesis. Aminoglycosides, Macrolides, Tetracyclines and Chloramphenicol are binding to 30S subunit or 50S subunit of the bacterial ribosome. The protein synthesis is a very complex multi-step process and many antibiotics act at one of the events occurring on the bacterial ribosome, for instance during elongation, to inhibit factor binding or peptide bond development; there are no antibiotics that target the termination phase of translation (Arenz and Wilson, 2016). The affinity of some antibiotics for 70S ribosome contributes to their selective toxicity (Todar, 2006).

Aminoglycosides are represented by Streptomycin, Kanamycin, Tobramycin and Gentamycin. They obstruct the initiation of protein synthesis after they bind to 30S subunit of ribosome.

Among Macrolides, Erythromycin acts on 23S rRNA molecule and inhibits the assembly of 50S ribosomal subunit.

Tetracyclines block the A site of the 30S subunit of ribosome and inhibit both prokaryotic and eukaryotic protein synthesis.

Chloramphenicol binds to 50S ribosomal subunit and inhibits the peptidyl transferases implicated in peptide bond formation.

3. ANTIBIOTIC RESISTANCE OF BACTERIA

Antibiotic resistance of bacteria are the capacity of these microorganisms to survive in the presence of antibiotic. This is a major inevitably public health and scientific issue, because the antibiotics become ineffective and the control of severe bacterial infections fails. The therapeutic failures increase the time and costs of hospitalization, because the resistant bacteria are difficult to treat and demand higher doses or more toxic and expensive drugs (Adedeji, 2016).

The specialists discover more than 20,000 potential resistance genes in about 400 different species of bacteria, but not all of them are functionally (Davies and Davies, 2010). Because of these, the resistant bacteria are capable to resist in inappropriate condition, especially in living human hosts.

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The profound knowledge of action mechanisms of antibacterial agents it is necessary to understand the mechanisms of bacterial resistance to common antibiotics. It is also necessary to prevent the dissemination of multiresistant bacterial strains in the environment.

The antibiotic resistance is a natural process (even if not all scientists thought that), but it can be amplified and accelerated by certain factors (some of them socioeconomic or behavioural factors). For example the persistent irrational usage of antibiotics in treatment of various infectious diseases and human applications increases the antibiotic pressure on bacteria. Because some antibacterial treatments are not based on rational and precise data and type of antibiotic, doses (especially suboptimal doses) or treatment period are not appropriate is increased the antibiotic stress on bacteria and the resistance genes transfer between strains. The self-medication, the inadequate usage of broad-spectrum antibiotic and the misuse of antibiotics used by unskilled practitioners or laypersons are factors that contribute to occurrence of antibiotic resistance of bacteria. Other factors could be unhygienic standard of living, poverty, lack of resources, inappropriate hospital infection control and surveillance practices (Adedeji, 2016).

Multiresistant bacterial strains spread all over the world due to facility to travel and the resistance factors also disseminate within bacterial populations. Some antibiotic resistance events occur quickly after the usage of respective antibiotic, like resistance to Benzylpenicillin and Methicillin in *S. aureus*, resistance to Imipenem in *Pseudomonas aeruginosa*, resistance to Extended Spectrum Cephalosporins in Gram negative bacilli after just one year.

Many bacterial strains implicated in different infections develop resistance mechanisms to antibiotics under pressure of antimicrobial agents. Some examples of significant resistant bacteria are Methicillin Resistant *Staphylococcus aureus* (MRSA), Vancomycin Resistant *Enterococcus faecium* (VRE), Penicillin Resistant *Streptococcus pneumoniae* (PRSP) and Multiple Drug Resistant Gram negative Bacilli (MDR GNB), especially Extended Spectrum Beta-lactamases (ESBL)-producing Enterobacteriaceae. Often the nosocomial (hospital-linked) bacterial agents present the multiple antibiotic resistances, such as *Acinetobacter baumannii*, *Clostridium difficile*, *Pseudomonas aeruginosa* and other.

The antibiotic resistance can be described like microbiologic resistance or clinical resistance. The absolute microbial resistance is the *in vitro* phenomenon of bacterial resistance determined by resistance genes and it can be illustrated by minimal inhibitory concentration (MIC) of antibiotic (Mărculescu et al., 2007). The clinical resistance is linked by certain response to antimicrobial treatment that is established based on laboratory tests (antibiogram methods). It is very important to establish the antibiotic susceptibility of bacterial strains *in vitro*, because the success of therapy depends on it.

An accurate diagnosis and treatment for infectious diseases depend on the microbial cause of illness, the site of infection, the health status of the host and the exposure history of host to microbial agents (Leekha et al., 2011).

The antibiotic resistance of bacteria can be natural or acquired by mutations or by genetic transfer.

The natural resistance in bacteria most likely preceded the discovery of antibiotics, given the fact that some resistance elements have been found in bacterial DNA from permafrost; bacteria had a very long time to develop the resistance mechanisms to many natural product antibiotics (Fair and Tor, 2014). It is characteristic for all members of certain bacterial species and it is genetically conditioned resistance (for example, the strains of *Salmonella* are resistant to Penicillin G and the species of *Proteus* are resistant to Tetracyclines).

The acquired antibiotic resistance can occur by spontaneous mutations or by transfer from other bacterial strains that hold resistance genes. It is common to those species that previously were

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natural susceptible to antibiotic and it is manifest itself in decrease or absence of sensitivity to antimicrobial agent.

This kind of antibiotic resistance can be classified into a few types, depend on speed and moment of resistance setting, number of antibiotics and presence of antibacterial substances. It is possible to see primary or secondary resistance, monoresistance or multiresistance, inducible or constitutive antibiotic resistance (Mărculescu et al., 2007).

In the most cases, acquired antibiotic resistance is determined by plasmid-mediated transfer of antibiotic resistance factors by bacterial conjugation. Other cases involve the transposons or integrons. Many resistant bacteria can be limited growth under laboratory conditions because the cells consume important energy for that, so they are unstable in the absence of antibiotic, but pathogens with combinations of resistance genes successfully survive *in vivo* (Davies and Davies, 2010).

The scientist revealed the molecular mechanisms of antibiotic resistance both in pathogenic and commensally bacteria. Bacteria found some important ways to defend themselves against antimicrobial effects of antibiotics. Antibiotic resistances can occur through three general mechanisms: modification of compounds (for example enzymatic inactivation of antibiotic), efflux of the antibiotic from the cell and prevention the interaction between the bacterial target and the drug (Wright, 2005).

In the case of enzymatic inactivation of antibiotic by hydrolysis, group transfer (phosphorylation, glycosilation, nucleotidylation, ribosylation, acyltransfer or thiol transfer) and redox mechanisms, the genes responsible for the specific enzymes are usually plasmidial ones. This mechanism is effective for Beta-lactams, Aminoglycosides, Chloramphenicol. Beta-lactamases are various and they depend of bacteria: beta-lactamases from *Staphylococcus aureus* are effective against Penicillins and they are plasmid encoded or chromosomal encoded; those produced by Gram negative bacteria are effective against Cephalosporins and metallo-beta-lactamases are effective against the most of the Beta-lactams, inclusive Carbapenems. Some beta-lactamases are plasmid encoded; they are frequently in Enterobacteriaceae (penicillinases, oxacilinases and carbenicillinases).

Aminoglycosides are inactivated by different enzymes which act against amino and hydroxyl groups and Chloramphenicol is inactivated through acetylation by an enzyme that is plasmid encoded.

There are hundreds of different Beta-lactams and there are different mechanisms to acquire resistance to these; the inactivation by beta-lactamases is the most important way, but the efflux and altered transpeptidases are occur, too (Palzkill, 2013).

Many antibiotics have a bacterial target on the inner membrane level and Gram negative bacteria develop some resistance mechanisms by decreasing the uptake of the antimicrobial molecules because the decrease of porins (in the case of Beta-lactams and Quinolones), the loss of certain outer membrane protein (in the case of Chloramphenicol) or decrease of membrane permeability. The antibiotic resistance can be realised by an active efflux of antibiotic from cells (for example Tetracyclines and Fluoroquinolones).

The alteration of the target for antibiotic is one of the most common mechanisms of antibiotic resistance in bacterial pathogens, by point mutations, enzymatic modification of the binding site (for example Penicillin Binding Proteins) or replacement of the original target (Munita and Arias, 2016). Fluoroquinolones resistance is produced by mutations in a small section of the genes encoding DNA gyrase and the antibiotic become inefficient. Bacteria are capable to produce new targets that have similar functions but are not affected by antibiotic. That is the resistance

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mechanism for *S. aureus* resistant to Methicillin because the bacteria acquire an exogenous Penicillin Binding Proteins.

Given the fact that the antibiotic resistance increases and the new classes of antibiotics were not discovered, some infectious diseases can emerge or re-emerge and can be a threat worldwide.

Nowadays are few novel antibiotics under development and pharmaceutical companies are obtaining new chemical derivates of existing antibiotics. Because of antibiotic resistance phenomenon, the scientists try to discover new antibacterial agents from natural products, with a broad-spectrum of activity and no side effects or adverse reactions in human hosts (Bueno, 2018). The bioactive products from folk medicines are known today and the demand for plant-based therapeutics is increasing, because the natural compounds with useful activity against bacteria have the advantages of lower prices, availability and no side effects (Ghosh, 2007).

4. CONCLUSIONS

The antibiotics have different ways to affect bacteria and the antibiotic resistance mechanisms are various and complex. The efficiency of antimicrobial agents depends on their chemical structure and affinity to target sites of bacterial cells. Unfortunately, more strains of bacteria become resistant to common antibiotics, but not all bacterial pathogens are resistant all of the time.

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