Review Article
Pharmacology

ANTIBIOTICS AND THE MECHANISMS OF RESISTANCE TO ANTIBIOTICS

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SUMMARY: Microorganisms can develop resistance to antibiotics used in the treatment with a variety of mechanisms.

In this article, the general mechanisms of resistance to antibiotics and resistance mechanisms that are frequently encountered in antibiotic groups were summarized.

Key words: Antibiotics, antibiotic resistance, mechanisms.

Resistance is the ability of a bacteria against the antogonizing effect of an antibacterial agent upon reproduction prevention or bactericidal. The development of resistance to antibiotics in bacteria often develop as a result of unnecessary and inappropriate use of antibiotics.

Through the intense use of antibiotics, resistant microorganisms have emerged over the years, and problems were started to be experienced for the treatrment of these infections emerged with these resistant microorganisms. Today, on the one hand trying to develop new drugs, on the other hand, there are difficulties in treatment as a result of development of resistance to these drugs rapidly. The development of resistance to antibiotics is a major public health problem in all over the world (1-3).

The main four types of resistance to antibiotics develops;

1. Natural (Intrensic) resistance
2. Acquired resistance
3. Cross-resistance
4. Multi-drug resistance and pan-resistance

1. Natural (Intrensic, Structural) resistance: This kind of resistance is caused by the structural characteristics of bacteria and it is not associated with the use of antibiotics. It has no hereditary property. It develops as result of the natural resistance, or the microorganisms not including the structure of the target antibiotic, or antibiotics not reaching to its target due to its characteristics. For example, Gram-negative bacteria vancomycin does not pass in the outer membrane so Gram-negative bacteria is naturally resistant to vancomycin. Similarly, L-form shape of bacteria which are wall-less forms of the bacteria, and the bacteria such as cell wall-less cell Mycoplasma and Ureaplasma are naturally resistant to beta-lactam antibiotics that inhibit the cell wall synthesis (1,4-6).

2. Acquired resistance: As result of the changes in the genetic characteristics of bacteria, an acquired resistance occurs due to its not being affected from the antibiotics it has been responsive before. This kind of resistance occurs due to mainly structures of chromosome or extrachromosomal (plasmid, transposon, etc.).

a. Chromosomal resistance arise from mutations in developing in spontaneous bacterial chromosome (spontaneous). Such mutations may occur according to some physical (ultraviolet, etc.) and chemical factors. This can be a result of structural changes in bacterial cells. The result may be reduced permeability of bacterial drug or changes of the target of the drug may be in the cell. Streptomycin, aminoglycosides, erythromycin, lincomycin can develop resistance against these types.

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Spontaneous chromosomal mutations are 10-7-10-12. Therefore such resistance in the clinic are less and often does not cause a problem (1,4).

b. Extrachromosomal resistance, depends extrachromosomal genetic elements that can be transferred in various ways like plasmids, transposons and integro.

Plasmids are extrachromosomal DNA fragments that can replicate independently from chromosome. Plasmid genes are usually responsible for the generation of enzymes which inactive antibiotics. Resistance genes and plasmids carrying the genetic material from a bacterium in three ways those are transduction, transformation, conjugation, and transposition mechanism.

Transduction by bacteriophage resistance genes, transformation via DNA binding protein called competence factor, conjugation via sex pilus between two live bacteria through transfer of resistance genes. Antibiotic resistance genes on the chromosome or plasmid is interconnected with each other and located near the start of specific units of integration is called integrons. Integrons are in warm regions where recombination (re-edited) is very common (1,4,5).

3. Cross resistance: Some microorganisms which are resistant to a certain drug, that acts with the same or similar mechanism and also resistant to other drugs. This condition is usually observed in antibiotics whose structures are similar: such as resistance between erythromycin, neomycin-kanamycin or resistance between cephalosporins and penicillins. However, sometimes it can also be seen in a completely unrelated drug groups. There is an example of cross-resistance between erythromycin-lincomycin. This may be chromosomal or extrachromosomal origin (4,5).

4. Multi-drug resistance and pan-resistance: Multidrug-resistant organisms are usually bacteria that have become resistant to the antibiotics used to treat them. This means that a particular drug is no longer able to kill or control the bacteria. Inapropriate use of antibiotics for therapy resulted in the selection of pathogenic bacteria resistant to multiple drugs. Multidrug resistance in bacteria can be occured by one of two mechanisms. First, these bacteria may accumulate multiple genes, each coding for resistance to a single drug. This type of resistance occurs typically on resistance (R) plasmids. Second type of resistance, namely multidrug resistance may also occur by the increased expression of genes that code for multidrug efflux pumps, enzymatic inactivation, changes in the structure of the target etc. If the bacterial strains resistant to three or more classes of antimicrobials, it is considered as multi-drug resistant. If the strains, resistant to all but one or two antibiotic gruops, they are considered as extensively-drug-resistant, if the strains resistant to all available antibiotic, they are classified as pan-drug-resistant. For example, multidrug resistance (MDR) Acinetobacter species (spp.) can be defined as the isolate resistant to at least three classes of antimicrobial agents (namely, all penicillins and cephalosporins (including inhibitor combinations), fluroquinolones, and aminoglycosides). Extensive drug resistant (XDR) Acinetobacter spp.' shall be the Acinetobacter spp. isolate that is resistant to the three classes of antimicrobials described above (MDR) and shall also be resistant to carbapenems. Pandrug resistant or pan-resistant (PDR) Acinetobacter spp. shall be the XDR Acinetobacter spp. that is resistant to polymyxins (colistin) and tigecycline (6-8).

MECHANISMS OF RESISTANCE TO ANTIBIOTICS

a. The changes that occur in the receptor that connected to the drug and the region of the connection 'Connection of the antibiotics' target areas are different. They can be various enzymes and ribosomes. Resistance associated with alterations in the ribosomal target are the most frequently observed in macrolide antibiotics. Mutations in penicillin-binding proteins (beta-lactamase enzymes) and Staphylococcus aureus, Streptococcus pneumoniae, Neisseria meningitidis and Enterococcus faecium strains can develop resistance to penicillin . Changes in the structure of the target, beta-laktam, quinolones, glycopeptides, macrolides, tetracycline and rifampicin resistance is an important mechanism in the development (10-13).

b. Enzymatic inactivation of antibiotics: Most of Gram-positive and Gram-negative bacterias synthesize enzymes that degrade antibiotics. This enzymatic inactivation mechanism is one of the most important mechanisms of resistance. In this group, beta-lactamases, aminoglycosides, modifying enzymes (acetylase, fosforiaz adenilaz and enzymes) degrade beta-lactam antibiotics and continually increasing their number of which inactivates enzymes include chloramphenicol and erythromycin (1,5,12).

c. Reduction of the inner and outer membrane permeability: This resistance due to changes in the internal and external membrane permeability, decrease in drug

uptake into the cell or quickly ejected from the active resistance of the pump systems. As a result of a change in membrane permeability decreased porin mutations in resistant strains can occur in proteins. For example; in Pseudomonas aeruginosa strains a specific porin called OprD can cause to mutation carbapenem resistance. Reduction in permeability of the outer membrane may play an important role in resistance to quinolones and aminoglycosides (1,5,12,14).

d. Flush out of the drug (Active Pump System): Resistance developing through the active pump systems mostly common in tetracycline group of antibiotics. Tetracyclines is thrown out with energy-dependent active pumping system and can not accumulate in the cell. Such resistance is in control of the plasmid and chromosomal. Active pumping systems are effective in resisting quinolones, 14-membered macrolides, streptogramins, chloramphenicol and beta-lactams (1,5,14).

e. Using an alternative metabolic pathway: Unlike some of the changes in the target in bacteria, a new pathway for drug-susceptible eliminate the need to develop objective. In this way resistance seen among the sulfonamide and trimethoprim. Bacterias can gain property of getting ready folate from the environment instead of synthesizing folate (4,5).

MECHANISMS OF RESISTANCE BY ANTIBIOTICS GROUP

a. Resistance to Beta-lactam antibiotics: Beta-lactam antibiotics are a broad class of antibiotics, include penicillins, cephalosporins (namely, first generation, second generation, third generation, fourth generations and fifth generations), monobactams and the carbapenems.

The most common resistance mechanism is responsible for the synthesis of beta-lactamase enzymes (1,4, 5,15-17).

1. Beta-lactamases: As a result of studies molecular level 4 classes (A, B, C, D) of beta-lactamase enzymes described. A, C and D beta-lactamases which functions enzymes cool-ester mediated, B-class zinc ion in need metalloenzyme.

Class A beta-lactamases: Gram positive and Gram negative bacteria are often plasmid or transposon. Usually capable of inducible. Gram-negative bacteria TEM, SHV, ESBL (the number is 50) are included in this group. ESBL is mostly in E.coli and Klebsiella pneumoniae (1,3,5,15-17).

Class B beta-lactamases (Group 3): Stenotrophomonas maltophilia, Bacteroides fragilis, Aeromonas and Legionella detectable species, enzymes which hydrolyze carbapenems as well as penicillin and cephalosporins (3,5,17).

Class C beta-lactamases: Mainly parts cephalosporins (cephalosporins). Usually found on Gram-negative bacteria and localized to chromosome (Group I, AmpC etc.). Often the feature of inducible. Produced in high levels in the presence of a beta-lactam antibiotics and are not inhibited by clavulanic acid. They are also called Inducible beta-lactamases (IBL). They found on P.aeruginosa, Enterobacter cloacae, Citrobacter freundii, Serratia marcescens (5,17).

Class D beta-lactamases (group 2d): Oxacillin degrading enzymes (Oxacillins). Gram-positive cocci of S. aureus type that induced by beta-lactamases. Plasmids and transposons are usually movable and can be transferred by conjugation of staphylococcus species.

Enterococci also has plasmid origin beta-lactamases (18-20).

Anaerobic bacteria may also produce beta-lactamase. For example, B. fragilis can produce cephalosporinase (1,5).

2. The development of resistance in Penicillin-binding proteins (PBP) in to change: Target of beta-lactam antibiotics, peptidoglycan synthesis in the cell membrane which is responsible for penicillin-binding proteins (PBP). PBPs sarboxypeptidase and transpeptidase enzymes. PBP due to changes in resistance is the most common in gram-positive bacteria. Methicillin-resistant S. aureus (MRSA) are responsible for methicillin resistance in strains, mecA gene, this gene result in the synthesis of PBP-2a improves the resistance to beta-lactam antibiotics (1,5).

In S. pneumoniae changes in the PBP 2b is responsible for the penicillin and cephalosporin resistance (1,3,5,7,11,21).

3. Changes in membrane proteins: Porin channels' change induced by gram-negative bacteria resistance. For example, P. aeruginosa with a dedicated channel protein in OprD registration may develop resistance to carbapenems (9,17). Accumulation of the antibiotic can be prevented the in the cell of the active pump systems. As a result, the beta-lactams, tetracyclines, chloramphenicol and quinolones group may develop resistance (1,5,14).

b. Aminoglycoside group antibiotics resistance

1. Enzymes that changing the structure of aminoglycoside: In aerobic gram-negative bacteria the most important mechanism in the development of resistance to aminoglycosides is enzymatic inactivation. It plays a role in resistance to aminoglycosides modifying enzymes. These enzymes often originates from plasmid or transposon. In this group there are acetyl transferase and phosphotransferase. Modified enzymes are responsible for the high-level resistance to gentamicin in enterococci (5,22).

2. Preventing the passage of the drug to cytoplasm: Anaerobic bacteria, the main mechanism responsible for resistance to aminoglycosides.

3. Changes in the ribosomal target: Especially important to streptomycin resistance. Caused by mutations in ribosomal protein S12 30S sub-unit is not connected to the target streptomycin. This type of streptomycin resistanceis important in enterococci (1,4,5).

c. Tetracycline Resistance

1. Prevention of drug uptake into the cells and the active pump systems: Reduction in membrane permeability as result of the spontaneous chromosomal mutations in bacteria as a result of the uptake of the drug in preventing the development of resistance. Active resistance to tetracyclines may also develop in pump systems (3,4,5,23).

2. Ribosomal Protection: The second important mechanism that leads to resistance to tetracycline. With tetM, tetO, tetQ, tetS genes preventing by synthesized a cytoplasmic ribosome binding protein activity of the drug. These genes found on bacteria such as Campylobacter, Mycoplasma, Ureaplasma and Bacteroides genus. They are plasmid and chromosomal origin (1,5,14).

d. Macrolide, Lincosamide, Streptogramin (MLS) groups antibiotics resistance

Because Gram - negative bacteria is impermeable to these antibiotics which have hydrophobic outer membranes, Gram-negative bacteria are naturally resistant to MLS group antibiotics.

1. Modification of the Ribosomal Target: The most common resistance mechanism in Gram-positive bacteria. This is connected to the drug in the 50S ribosomal subunit with the 23S ribosome in rRNA specific methylation of an adenine molecule has a structural change and binding of the drug to ribosomal RNA is reduced. The enzymes responsible for methylation genes encoded in erm (erythromycin ribosome methylation) gene region. This resistance is in the nature which structural or inducible (1,3-5).

2. Enzymatic inactivation: Erythromycin and other macrolides by inactivating the enzymes which play a role in resistance plays a role in resistance (4,5).

e. Chloramphenicol resistance

The main mechanism of chloramphenicol acetyl transferase, an enzyme synthesized by the control plasmid enzyme activity. Gram-positive and gram-negative widely available enzyme plasmid can be transferred with transposons (4,5).

f. The resistance to fluoroquinolones

They are in origin of chromosomes and mechanism of DNA gyrase (topoisomerase II) enzyme mutations (gyrA, gyrB). The enzyme of DNA gyrase consists of four subunits, A sub-unit is the main target of quinolone group antibiotics. This subunit encoding gyr; A gene-resistance mutations in bacteria responsible for the development of all quinolones. gyrB gene mutations, especially P. aeruginosa and E. coli quinolone shown resistance (5,24).

g. Rifampicin Resistance

Rifampicin is a drug that affects binding to the subunit of RNA polymerase enzyme dependent upon the DNA in Gram-positive bacteria and mycobacterias. The chromosal mutations that emerge in rpo B gene certificate encoding the RNA polymerase enzyme cause rifampicin resistance (4,5).

h. Sulfonamide and trimethoprim resistance

Sulphonamides are paraaminobenzoic acids analogues(PABA) and the metabolic pathways of synthesis of dihydropteroate (DHPS) enzyme and trimethoprim the dihydrofolate reductase (DHFR) in bacteria by inhibiting the synthesis of tetrahydrofolic acid prevents. Sulfonamides and trimethoprim resistance encoded by chromosome and plasmids. The most frequently observed sulfonamide resistance, bacterial expression of DHPS sulfonamides low affinity plasmid containing this event (3-5).

I. Glycopeptide antibiotic resistance

This group of antibiotics (vancomycin, teicoplanin, ristocetin, avoparisin) bind to D-alanine-D-alanine in peptidoglycan and inhibite a late stage in bacterial cell wall peptidoglycan synthesis.

Glycopeptide antibiotics can not pass the outer membrane of Gram-negative bacterias are naturally resistant to these antibiotics.

In gram-positive bacterias enterococci glycopeptide antibiotic resistance is a major problem. Vancomycin resistance in enterococci identified three phenotypes; VanA, VanB, VanC. VanA-type resistance plasmid origin, and easily transferred to other bacteria, bacteriais resistant both vancomycin and teicoplanin.

VanB-type resistance is inducable, but it is a resistance that chromosomally encoded. While low-level resistance to vancomycin-resistant bacteria susceptible to teicoplanin. VanA and VanB-type resistance have been reported in E. faecium and Enterococcus faecalis. Vancetype resistance in Enterococcus gallinarum is a specific structural and can not be transferred or induced (3,5,20).

Control and Prevention of resistance to antibiotics

Both inappropriate and indiscriminate use of antibiotics may cause in community-acquired and nosocomial infections developing resistance with microorganisms. Antibiotic resistance of microorganisms can spread in different ways.

The introduction of new antibiotics against resistant microorganisms as well as the high costs and requires that takes a long time. Therefore, rather than the discovery of new antibiotics, the rational use of antibiotics (the appropriate indications, the appropriate dosage, proper way and proper time), strict implementation of infection control measures in hospitals, community as intelligent use of antibiotics in the control, antibiotic resistance training are the most basic measures.

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