FACULTY OF ENGINEERING &TECHNOLOGY
DEPARTMENT OF BIOTECHNOLOGY

Antibiotic resistance

Antimicrobials are one of the most successful forms of therapy in medicine; however the efficiency of antimicrobials is compromised by a growing number of antibiotic resistant pathogens. This situation arises due to overuse of antibiotics. In fact, the World Health Organization has named antibiotic resistance as one of the three most important public health threats of the 21st century.

Now question arises what is antibiotic resistance?
Two types of antibiotic resistance can be identified:

- Antibiotic resistance I (Epidemological breakpoint) and
- Antibiotic resistance II (Clinical breakpoint).

Antibiotic resistance I: The ability of a microorganism to survive at a given concentration of an antimicrobial agent at which the normal population of the microorganism would be killed. This is called “epidemiological breakpoint”.

Antibiotic resistance II: The ability of a microorganism to survive treatment with a clinical concentration of an antimicrobial agent in the body. This is called the “Clinical breakpoint”

Mechanism of antibiotic resistance

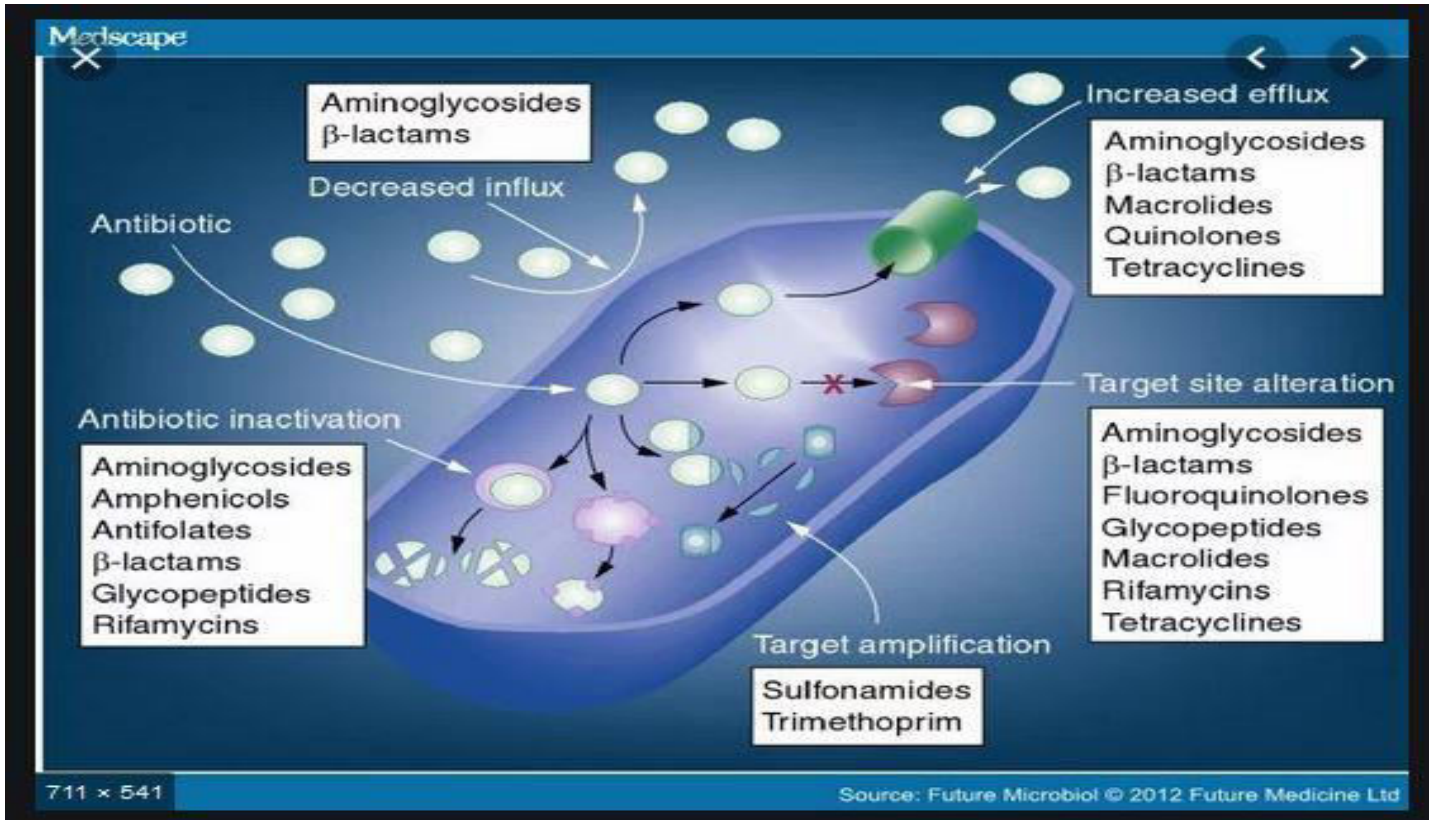

Figure: Various mechanism of antibiotic resistance along with example of antibiotic against which these various mechanism acts for antibiotic resistance

Antibiotic resistance can be described in following three ways:

A). **Intrinsic resistance** whereby microorganisms naturally do not posses target sites for the antimicrobials and the antimicrobial does not affect them.

B). **Acquired resistance** whereby a naturally susceptible microorganism acquires mechanism not to be affected by the antimicrobial. Mechanisms of acquired resistance include:

The inactivation or modification of the antibiotic;

An alteration in the target site of the antibiotic that reduces its binding capacity;
The modification of metabolic pathways to circumvent the antibiotic effect;

The reduced intracellular antibiotic accumulation by decreasing permeability and/or increasing active efflux of the antibiotic.
post- transcriptional or post-translation modification of the antimicrobial target

C) **Genetic mechanism**

The inactivation or modification of the antibiotic;
One of the most successful bacterial strategies to cope with the presence of antibiotics is to produce enzymes that inactivate the drug by adding specific chemical moieties to the compound or that destroy the molecule itself, rendering the antibiotic unable to interact with its target.

Chemical alterations of the antibiotic—The production of enzymes capable of introducing chemical changes to the antimicrobial molecule is a well-known mechanism of acquired antibiotic resistance in both gram-negative and gram-positive bacteria. Interestingly, most of the antibiotics affected by these enzymatic modifications exert their mechanism of action by inhibiting protein synthesis at the ribosome level. Many types of modifying enzymes have been described, and the most frequent biochemical reactions they catalyze include ***i)*** acetylation (aminoglycosides, chloramphenicol, streptogramins), ***ii)*** phosphorylation (aminoglycosides, chloramphenicol), and ***iii)*** adenylation (aminoglycosides, lincosamides). Regardless of the biochemical reaction, the resulting effect is often related to steric hindrance that decreases the avidity of the drug for its target, which, in turn, is reflected in higher bacterial MICs. For e.g. One of the best examples of resistance via modification of the drug is the presence of aminoglycoside modifying enzymes (AMEs) that covalently modify the hydroxyl or amino groups of the aminoglycoside molecule thereby rendering the drug ineffective against the bacterial population.

Destruction of the antibiotic molecules:

The main mechanism of β-lactam resistance relies on the destruction of these compounds by the action of β- lactamases. These enzymes destroy the amide bond of the β-lactam ring, rendering the antimicrobial ineffective.

The predominant mechanism of resistance to β-lactams in gram-negative bacteria is the production of β-lactamases, whereas resistance to these compounds in gram-positive organisms is mostly achieved by modifications of their target site, the penicillin-binding proteins (PBPs).

It has been argued that this phenomenon is likely due to major differences in the cell envelope between gram-negatives and gram-positives.
In the former, the presence of an outer membrane permits to “control” the entry of molecules to the periplasmic space. Indeed, most β-lactams require specific porins to reach the PBPs, which are located in the inner membrane.

Therefore, the bacterial cell controls the access of these molecules to the periplasmic space allowing the production of β-lactamases in sufficient concentrations to tip the kinetics in favor of the destruction of the antibiotic molecule. Conversely, this “compartmentalization” advantage is absent in gram-positive organisms, although production of β-lactamases also seems to be successful in certain scenarios (e.g., staphylococcal penicillinase).

The reduced intracellular antibiotic accumulation by decreasing permeability and/or increasing active efflux of the antibiotic

Decreased permeability:

Many of the antibiotics used in clinical practice have intracellular bacterial targets or, in case of gram-negative bacteria, located in the cytoplasmic membrane (the inner membrane). Therefore, the compound must penetrate the outer and/or cytoplasmic membrane in order to exert its antimicrobial effect. Bacteria have developed mechanisms to prevent the antibiotic from reaching its intracellular or periplasmic target by decreasing the uptake of the antimicrobial molecule. This mechanism is particularly important in gram-negative bacteria (for the reason specified above), limiting the influx of substances from the external milieu. In fact, the outer membrane acts as the first-line of defense against the penetration of multiple toxic compounds, including several antimicrobial agents.

Efflux Pumps—

The production of complex bacterial machineries capable to extrude a toxic compound out of the cell can also result in antimicrobial resistance. Many classes of efflux pumps have been characterized in both gram-negative and gram-positive pathogens. These systems may be substrate-specific (for a particular antibiotic such as tet determinants for tetracycline and mef genes for macrolides in *pneumococci*) or with broad substrate specificity, which are usually found in MDR bacteria. This mechanism of resistance affects a wide range of antimicrobial classes including protein synthesis inhibitors, fluoroquinolones, β-lactams, carbapenems and polymyxins. The genes encoding efflux pumps can be located in MGEs (as initially described for the tet gene) or in the chromosome. Importantly, chromosomally encoded pumps can explain the inherent resistance of some bacterial species to a particular antibiotic (e.g. *E. faecalis* intrinsic resistance to streptogramin A