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**MATRIC NO: I8/MHS07/045**

**Biochemical mechanism**

Antimicrobial resistance can develop at any one or more of steps in the process

* Reduced entry of antibiotic into pathogen
* Enhanced export of antibiotic by efflux pumps
* Release of microbial enzyes that destroy the antibiotic
* Alteration of microbial protein that transforms pro-drugs to the effective moieties
* Alteration of target protein
* Development of alternative pathways to those inhibited by the antibiotic

**Reduced Entry of Drug into Pathogen :**

• Small polar molecules & antibiotics, enter the cell through protein

channels called Porins.

• Absence of, mutation in, or loss of a favored porin channel can slow the rate of drug entry into a cell or prevent entry altogether reducing drug concentration at the target site.

• If target is intracellular mutation or phenotypic change that slows or abolishes this transport mechanism resistance.

Examples :

• The penicillin-resistant gonococci are less permeable to penicillin G.

• Chloroquine-resistant P. Falciparum accumulates less chloroquine.

**Resistance Due to Drug Efflux :**

• Microorganisms can overexpress efflux pumps and then expel antibiotics to which their susceptible.

 Five major systems of efflux pumps ;

- The multidrug and toxic compound extruder (MATE)

 - The major facilitator superfamily (MFS) transporters

 - The small multidrug resistance (SMR) system

 - The resistance nodulation division (RND) exporters

 - ATP binding cassette (ABC) transporters

 **Hetero-resistance and Viral Quasi Species :**

• It is said to be present when only a subset of the total microbial population is resistant.

• Increased therapeutic failures and mortality is seen.

• Viral evolution due to drug and immune pressure of Quasi species.

• Quasi species are resistant to antiretroviral agents , failure of antiretroviral therapy.

**MUTATION MECHNISM**

• Mutation and antibiotic selection of the resistant mutant are the molecular basis for development of resistance in many bacteria, viruses, and fungi.

• Mutations are not caused by drug exposure. They occur as a survival advantage, when drug is present.

• Mutations may occur in the gene encoding

(1) The target protein, altering its structure so that it no longer bindsthe drug

(2) A protein involved in drug transport

(3) A protein important for drug activation or inactivation

(4) In a regulatory gene or promoter gene affecting expression of the target, a transport protein, or an inactivating enzyme

• Suboptimal dosing strategies, selective kill of the more susceptible population, which leaves the resistant isolates to flourish.

• A single-step mutation ;high degree of resistance.

• The Multi-step mutation ;clinically significant resistance.

• E.g : Combination of pyrimethamine and sulfadoxine inhibits Plasmodium falciparum’s folate biosynthetic pathway via inhibition of dihydrofolate reductase (DHFR) by pyrimethamine and dihydropteroate synthetase (DHPS) by sulfadoxine.

**GENE TRANSFER MECHANISM:**

• Drug resistance may be acquired by passage of the trait vertically to daughter cells, but more commonly it is acquired by horizontal transfer of resistance by,

- Transduction

- Transformation

- Conjugation

• Horizontal transfer of resistance genes is greatly facilitated by Mobile genetic elements which are Plasmids, Transducing ,Transposable, Integrons Gene phages elements cassettesm ,Insertion sequences ,Transposons ,Transposable phages.

* **Transduction** - Is acquisition of bacterial DNA from a phage that has incorporated DNA from a previous resistant host bacterium.e.g. strains of S. aureus.
* **Transformation** - Is the uptake and incorporation into the host genome by free DNA released into the environment by other bacterial cells. E.g. Penicillin resistance in Pneumococci and Neisseria.
* **Conjugation** - Is gene transfer by direct cell-to-cell contact through a

sex pilus or bridge. Multiple resistance genes can be transferred in a single event.Genetic transfer by conjugation is common among gram-negative bacilli, and Enterococci.

**CROSS RESISTANCE MECHANISM**:

• Acquisition of resistance to one AMA conferring resistance to another AMA to which the organism has not been exposed e.g. - resistance to one sulfonamide means resistance to all others,

-resistance to one tetracycline means insensitivity to all others

• Partial cross resistance is sometimes seen in unrelated drugs e.g. - between tetracycline’s and chloramphenicol

- Between erythromycin and lincomycin.

• Cross resistance may be;

 Two-way, e.g. between erythromycin and clindamycin and vice versa

One-way, e.g. development of neomycin resistance by

enterobacteriaceae makes them insensitive to streptomycin but many

streptomycin-resistant organisms remain susceptible to neomycin.