Antimicrobial chemotherapy

Drugs have been used for the treatment of infectious diseases since the 17th century (e.g. emetine for amebiasis); however, chemotherapy as a science began in the first decade of the 20th century with understanding of the principles of selective toxicity, the specific chemical relationships between microbial pathogens and drugs, the development of drug resistance, and the role of combined therapy.

The development of antimicrobial chemotherapy began in 1935 with the discovery of the sulfonamide. In 1940, it was demonstrated that penicillin, discovered in 1929, could be an effective therapeutic substance. During the next 25 years, research on chemotherapeutic agents centered largely around substances of microbial origin called antibiotics. The isolation, concentration, purification, and mass production of penicillin were followed by the development of streptomycin , tetracyclines and many other agents.

1- **Bacteriocidal drugs** :- these have a rapid lethal action e.g. pencillins , cephalosporins & aminoglycosides .
2- **Bacteriostatic drugs** :- these are inhibit the division i.e. growth of organism e.g. sulfonamides , tetracyclines & chloramphenicol .

Range of action of antibiotics

Antibiotics fall into 3 main categories :-
a – a ctive mainly against G^{+ve} organisms like : penicillin , erythromycin & lincomycin .
b – active mainly against G^{-ve} organisms like : polymyxin & nalidixic acid .
c – active against both G^{+ve} & G^{-ve} organisms (broad spectrum activity) like : ampicillin & ciprofloxacin .

Mechanisms of action of chemotherapeutic agents

An ideal antimicrobial agent should have selective toxicity i.e. it can kill or inhibit the growth of a microorganism in concentration that are not harmful to the cells of the host . Disinfectants e.g. phenol and antiseptics e.g. alcohol & iodine , destroy bacteria but they are highly toxic to tissue cells & are unsuitable for use as chemotherapeutic agents .

Thus , the mechanisms of action of a chemotherapeutics must depend on the inhibition of a metabolic channel or a structure present in the microbe but not in the host cells . several mechanisms are known :-

1 – Inhibition of cell wall synthesis :-

Due to its unique structure & function , the bacterial cell wall is an ideal point of attack by selective toxic agents , such as ß-lactams that include penicillins & cephalosporins interfere with cell wall synthesis and cause bacteriolysis .

2 – Inhibition of cytoplasmic membrane function :-

Some antibiotics cause disruption of the cytoplasmic membrane and leakage of cellular proteins & nucleotides leading to cell death , for example polymyxins.

3 – Inhibition of protein synthesis :-

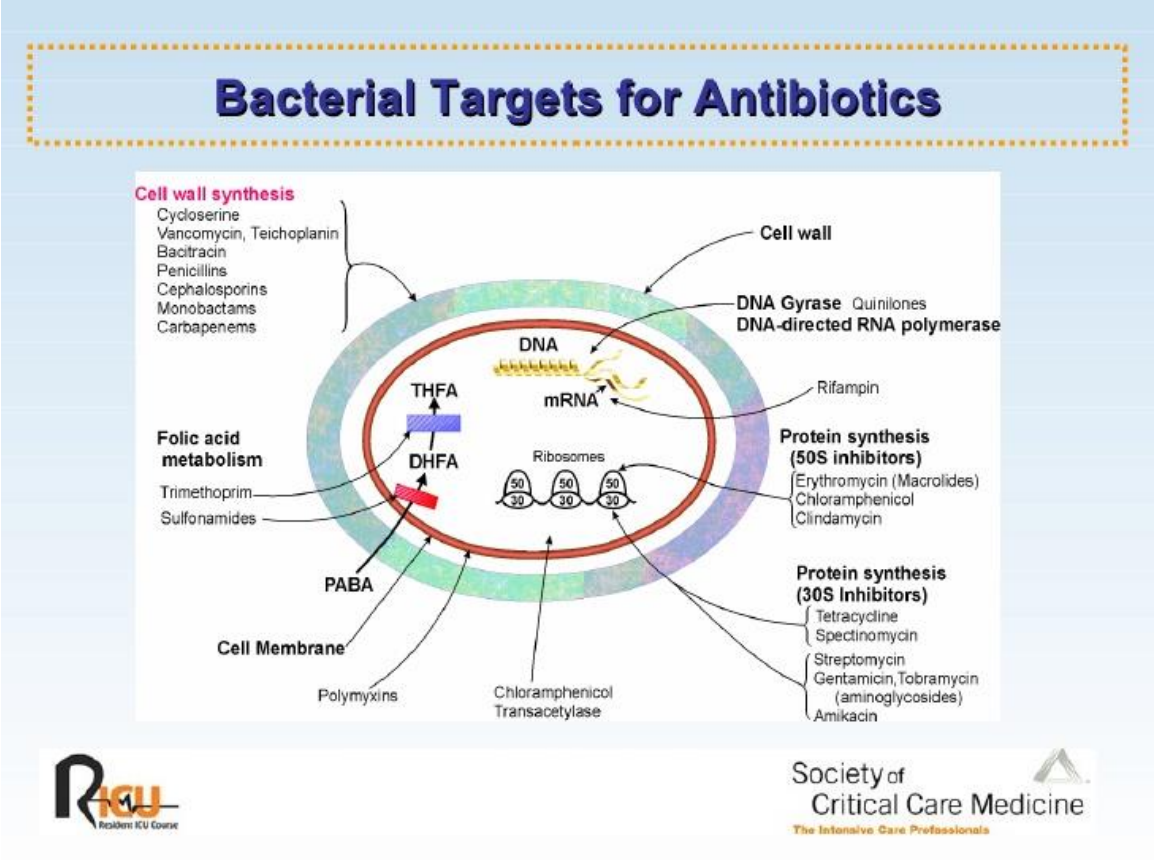
Many chemotherapeutic block protein synthesis by acting on the 30_s or 50_s subunit of bacterial ribosomes such as : tetracyclines , erythromycin and aminoglycosides e.g. tobramycin & gentamycin . Bacteria have 70_s ribosome while mammalian cells have 80_s ribosome the composition of each type ,their subunit and function explain why drugs can inhibit protein synthesis in bacteria but not in mammal .

4 – Inhibition of nucleic acid synthesis :-

These can act on any steps of the DNA replication or RNA synthesis e.g. quinolone , refampicin , novobiocin & sulfonamide . rifampen inhibit bacterial growth by binding to DNA-dependent RNA polymerase of bacteria , thus it inhibit RNA synthesis . While quinolones inhibit DNA synthesis by blocking of DNA gyrase.

5 – Competitive inhibition :-

In which the drugs compete with an essential metabolite for the same enzyme e.g. p – aminobenzoic acid (PABA) is an essential metabolite for many organisms because its precursor in folic acid synthesis which is used in nucleic acid synthesis , sulfonamide are structural analogues to PABA so its enter in the reaction in place of PABA & compete for the active center of the enzyme thus inhibiting folic acid synthesis .



Mechanisms of resistance to antimicrobial agents

In the treatment of infectious diseases , one of the serious problem is the development of bacterial resistance to the antibiotic used . The mechanisms by which the organism develop resistance may be one of the following :-

1 – The organism produced enzymes that destroy the drug e.g. production of ß–lactamases that destroy penicillin by penicillin resistant staphylococci & acetyltransferase which produced by gram negative bacilli to destroy chloramphenicol.

2 – The organism change its permeability to the drug by modification of protein in the outer cell membranes , thus impairing its active transport into the cell e.g. resistance to polymyxins .

3 – The organism develop an altered receptor site for the drug e.g. resistance to aminoglycosides is associated with alteration of a specific protein in the 30_s subunit of the bacterial ribosome that serve as a binding site in susceptible organisms .

4 – The organism develop an altered metabolic pathway that by passes the reaction inhibited by the drug e.g. sulfonamide-resistant bacteria acquire the ability to use performed folic acid with no need for extracellular PABA .

Origin of resistance to antimicrobial agents

These mechanisms may be of non genetic or genetic origins:

A – **Non genetic drug resistance** :- this include
1 – **Metabolic inactivity** :- Most antimicrobial agents act effectively only on replicating cells , non multiplying organisms are phenotypically resistant to drugs such as *M. tuberculosis* which survive for years in the tissues & their resistance is due to metabolic inactivity but if they start multiply after suppression of cellular immunity of the patient , they become susceptible to the drugs .
2 – **Loss of target structure** :- Protoplast or L-forms of bacteria are penicillin resistant because they lost their cell wall which is a structural target site of the drug .
3 – **Bacteria may infect the host in** the sites where antimicrobial are exclude or not active.

B – **Genetic drug resistance** :- this include
1 – **Plasmid mediated resistance** :- Plasmid is an extra-chromosomal genetic elements associated with bacterial resistance to antibiotics , plasmids frequently carry many genes that code for the production of enzymes that inactivate or destroy the antibiotics e.g. ß- lactamases which destroys the ß- lactam ring in penicillin & cephalosporin , plasmids may result in epidemic resistance among bacteria by moving from one to the other by conjugation , transduction or transformation .
2 - **Transposon-mediated resistance** :- Many transposons carry genes that code for drug resistance , as they move between plasmids & chromosomes they can transfer this property to bacteria . the process called transposition .
3 – **Chromosomal drug resistance** :- This develop as a result of spontaneous mutation in a genes that controls susceptibility to an antimicrobial agents , the most common result of chromosomal mutation is alteration of the receptors for a drug . For example : streptomycin resistance can result from a mutation in the chromosomal gene that controls the receptor for streptomycin located in the 30s bacterial ribosome .

Complications of antibacterial chemotherapy

1 – Development of drug resistance :-
This is one of the most serious complications of chemotherapy , the emergence of resistant mutants is encouraged by inadequate dosage , prolonged treatment , the presence of closed focus of infection and the

abuse of antibiotics without in vitro susceptibility testing . The problem is more serious when resistant strain develop in the community e.g. in hospitals its common to find that about 90 % of *Staphylococcus aureus* strains are resistant to penicillin .

2 – Drug toxicity :-

Many of antibacterial drugs have toxic side effects , this can be due to the over dosage , prolonged use or narrow margin of selective toxicity e.g. streptomycin affect on the 8^{th} cranial nerve leading to deafness , aminoglycosides are nephrotoxic , tetracyclines inhibit growth & development of the bones and teeth in the developing infants & children .

3 – Super infection :-

a – this may occur by pre-existing resistance strains present in the environment e.g. penicillin resistance *Staph. aureus* in hospital infection .

b – Another type of super infection is due to suppression of normal flora by the antibiotic used and their replacement with drug resistant organisms which cause disease like : *Candida* in the mouth causing oral thrush .

4 – Hypersensitivity :-

The drug may act as hapten , binds to tissue proteins and stimulates an immune response leading to tissue damage i.e hypersensitivity .

Any type of hypersensitivity reaction can occur with the several antibiotics . the more serious is anaphylactic shock which may occur with penicillin & cephalosporins . Mild manifestations are urticaria , skin rash , diarrhea , vomiting and jaundice .

Chemoprophylaxis

Is the use of antimicrobial agents to prevent rather than to treat infectious diseases . The following are principal conditions for which prophylactic antibiotics are positively indicated :-

1 – The use of benzathine penicillin G injections every 3-4 weeks to prevent reinfection with *Streptococcus pyogenes* in rheumatic patients

2 – A single large dose of amoxicillin given immediately prior to dental procedures is recommend for patients with congenital or rheumatic heart disease to prevent endocarditis .

3 – Rifampicin 600 mg twice a day for 2 days give to the exposed patients during epidemics of meningitis .

4 – Oral administration of tetracycline to prevent cholera .

5 – The use of ampicillin to prevent neonatal sepsis & meningitis in children born to mothers carrying group B streptococci in the vagina .

6 – Ceftriaxone to prevent gonorrhea .

7 – Chemoprophylaxis in surgery .

Clinical use of antibiotics

The following principles should be observed :-

1 – Antibiotics should not be given for trivial infections .

2 – They used for prophylaxis in special conditions .

3 – Treatment should be based on a clear clinical and bacteriological diagnosis .

4 – Antibiotics for systemic treatment must be given in a full therapeutic doses for adequate period .

5 – Combined therapy with two or more antibiotics is required for some conditions : -

a – serious resistant infections such as meningitis .

b – Severe mixed infections e.g. peritonitis following perforation of the colon.