Antibiotics and antimicrobial chemotherapy

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Terminology in Chemotherapy

- **Chemotherapeutic drug**: are chemical agents used for the treatment, relief or prophylaxis of a disease
- **Prophylaxis**: use of drug to prevent infections which are about to happen for a person at risk
- **Antimicrobial compounds**: include antibacterial , antiviral, antifungal and antiprotozoal agents, all of these except the last group are prescribed in dentistry.
- **Antibiotics**: substances produced by the natural processes of some microorganisms that kills or inhibits the growth of other microorganisms
- **Semi synthetic drugs**: drugs which are chemically modified in the lab after being isolated from natural sources
- **Synthetic drugs**: the use of chemical reactions to synthesize antimicrobial agents
- In 1928 **Alexander Fleming** a professor in bacteriology discover Penicillin . In 1940 **Howard Florey and Ernst chain** performed the first clinical trails of penicillin. In 1943 Penicillin was on market

Types of antimicrobial drugs:

- From their behavior toward bacterial populations antibacterial agents are **divided into two groups**:

- **Bactericidal agents:** these have a rapid **lethal** action against the pathogenic microbes, kill bacteria; e.g. penicillins, cephalosporins, and aminoglycosides.

- **Bacteriostatic agents:** these can inhibit the growth and multiplication of pathogens without killing them; . e.g. sulphonamides, tetracyclines and chloramphenicol.

Mode of Action of Antimicrobials

Antimicrobial agents inhibit the growth of or kill microorganisms by different mechanisms. However, one or more of the following target sites are involved:

1.cell wall; interfere with its synthesis

2.cytoplasmic membrane; disrupting the function

3.Ribosome; prevent protein synthesis

4.nucleic acid ; replication sites & synthesis

Classification of Antibiotics Based on their sources

a. Antibiotic from microbes(natural products)

1.Antibiotics from fungi Penicillin from ***P. notatum, Cephalothinfrom Cephalosporium ssp.***

2.Antibiotics from bacteria

- Polymyxin from ***Bacillus polymyxa***
- ***Bacitracin from Bacillus subtilis***

3. Actinomycetes

- Streptomycin from ***Streptomyces griseus***
- Nystatin from ***Streptomyces noursei***
- Gentamyicin from ***Micromonospora purpurea***

b **. Antibiotics from algae**

c. Antibiotics from higher plants

d. Antibiotics from animals

Spectrum of activity of Antimicrobial agents

- **Antibiotics fall into three main categories:**

1.Active mainly against gram-positive organismse.g. penicillins, flucloxacillin, cephalosporins, erythromycin and lincomysin.

2.Active mainly against gram-negative organisms e.g. polymyxin and nalidixic acid.

3.Active against both gram-positive and gram-negative organisms(**broad-spectrum activity**) e.g. tetracyclines, metronidazole,chloramphenicol

Antibiotics according to their mechanism of action:

A. Inhibition of cell wall synthesis (bactericidal effect) penicillins, vancomycin, bacitracin, cephalosporin, Penicillins and cephalosporins.

areβ-lactam drugs and are selective inhibitors of the peptidoglycan layer synthesis of the bacterial cell walls specially for Gram-positive bacteria as Staphylococci and Streptococci.

•In dentistry, penicillins are widely used because they are nontoxic and effective, but all share the problem of allergy, however, about 10% of patients sensitive to penicillins show cross reactivity to cephalosporins

Mode of action : the first step is binding the drug to the cell receptor (Penicillin Binding Protein receptor (PBPs) They inhibit the bacterial cell wall synthesis by combining with the transpeptidase responsible for cross linking the peptidoglycan, **its activity depends on an intact β-lactam ring.**

Cephalosporins :

Initially isolated form the mould *Cephalosporium.*

They are more resistant to ß-lactamase hydrolysis than penicillins and have wider antibacterial spectrum.

Other cell wall peptidoglycan inhibitors (Non-β-lactam drugs) as:

1-Bacitracin: (polypeptide AB)

•It is only used topically(on skin) for wounds or mucous membranes and mixed bacterial surface lesions specially when mixed with polymyxin B or neomycin.
•Is bactricidal for G+ves and Neisseria but not for other G-ves

2-Vancomycin:

Inhibit the cell wall synthesis

•Used systemically for Staphylococcal and Streptococcal infections including endocarditis, septicemia specially in patients having penicillin allergy,
•And orally in case of Antibiotic Associated Pseudomembranous Entero-colitis and periodontitis, however, it has limited clinical use due to its toxic side effect on kidneys

B. Disruption of cell membrane function :

- **Antibacterial: Polymyxins (B,E) ,Amphotericin B and Colistins**
- **Antifungal:Polyenes, Nystatin**
- **Polymyxins**: active againt many G-ve organisms as **Pseudomonas** , **Brucella (Malta fever)**, **Klebsiella(Pneumoniae)** and **Bordetella pertusis.**

- Due to their toxicity they are **usually used topically**

C. Inhibition of protein synthesis:

Aminoglycoside :

•Inhibit protein synthesis of Gram-negative bacteria as *Pseudomonas* and *Enterobacter*.

•They include
•Streptomycin used against tuberculosis.
•streptomycin and amikacin has been eclipsed (because of their toxicity ,they are only used for multiple-drug-resistant strains and some anaerobic bacilli
•In the past, the aminoglycosides have been used with beta-lactam antibiotics in **Streptococcal infections** for their synergistic effects, in particular in **endocarditis.**

D-Inhibition of nucleic acid synthesis:

1-Antimetabolites(sulfonamides, trimethoprim)

•Sulfonamides:

•Bacteriostatic for some G+ve& G-ve bacteria, Chlamydia and Protozoa.

•**Mechanism of action**: through its a competitive inhibition of Para amino benzoic acid(PABA) utilization.

•Trimethoprim:

•Effective for the treatment of urinary tract infection(UTI), also act synergistically with sulfonamides and is effective against Salmonella infection and chronic bronchitis

E-Inhibition of DNA replication:

- **Quinolones and Nalidixic acid :**

useful as urinary antiseptics**, not taken orally .**

- **Ciprofloxacin, levofluxacin**:

- active against enterobacteriaceae and bacteria resistent to the 3rdgeneration cephalosporines as Neisseria and Haemophilus

- **Metronidazole:**

- Broad spectrum ,bactericidal(bacterial vaginosis) and is an anti-protozoal drug .

- Effective against oral anaerobic bacterial infections cased by Bacteroides, Prevotella, Fusobacterium and Peptostreptococci spp. Even against isolates from infected necrotic pulps.

- **Isoniazid (Anti-tuberculosis)**

Other antimicrobial agents having been developed to target oral bacteria that cause oral diseases, such as fluoride, chlorhexidine, quaternary ammonium salts, and antimicrobial peptides (AMPs).

•**Fluoride:**is a successful cavity prevention agents and dental caries, incorporated in mouthwashes, toothpastes, and oral supplements in small quantities.

•Its mechanism is that fluoride ions contact the mineral of the tooth surface and increase remineralization to prevent the acid-induced demineralization caused by cariogenic bacteria as mutans streptococci and Lactobacillus acidophilus .It inhibits the bacterial growth and reduced acid production of *S. mutans*.

•However, the development of fluoride-resistant oral bacteria, has led to a reconsideration of the administration of fluoride.

Broad Spectrum Antibiotics:

•Broad-spectrum antibiotics are those designed to work against a wide range of bacteria .

•Penicillin(2nd generation when combined with B lactamase inhibitor, 4thgeneration anti-Pseudomonal PCNs, Penicillin V active against gram positive aerobes as Pneumococci and anaerobic streptococci ,and against gram negative anaerobes as Bacteroides, Fusobacteria .

•Cephalosporin,
•Tetracycline,
•Ciprofloxacin,
•Levofloxacin.
•Metronidazole

These drugs work on both gram-negative and gram-positive organisms. When a patient appears to have a mixed bacterial infection, a broad-spectrum antibiotic is the most likely to provide an effective treatment.

•**One problem with broad-spectrum antibiotics** which began to grow in the late 20th century was the **emergence of antibiotic resistance in bacteria.**

•Almost as soon as humans started developing antibiotics, bacteria started swapping genes which they could use to survive antibiotic therapy

Antimicrobial Combination Therapy

Few reasons justify the use of antimicrobial combinations:

(1)For the initial therapy of severely infected patients .
(2)Poly microbial infections .
(3)To prevent selection of resistant microorganisms when a high mutation rate of the causal organism exists to the antibiotic indicated;
(4)Reduction of dose-related toxicity ; related to the use of sulfonamides
(5)Antimicrobial synergistic activity. It is likable to use combinations and treat two types of infections—infections resulting from resistant or relatively resistant organisms and infections requiring a bacterial eradication (high bactericidal effect), considering the site of infection and the host defenses

Mechanisms of Resistance to Antimicrobial Agents:

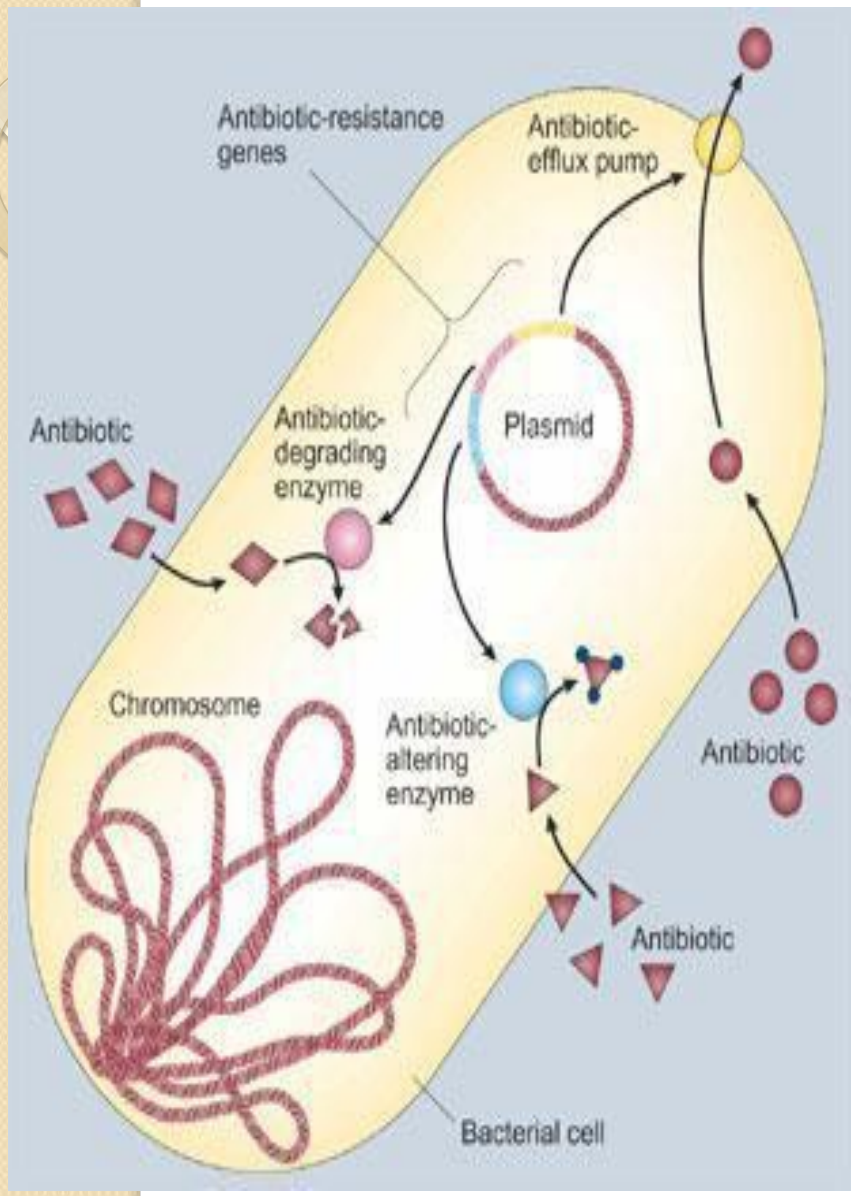
•**1-The organism produces enzymes that destroy the drug** e.g. production of:

•**β-lactamase enzyme** –produced by penicillin -resistant Staphylococci that destroy the beta lactam ring of **penicillins**
•**Acetyltransferase** produced by gram negative bacilli destroys **chloramphenicol**.

•**2-The organism changes the drug permeability , by modification of protein in their outer cell membranes**, thus impairing its active transport into the cell e.g. resistance to **polymyxins**.

•**3-The organism develops an altered receptor site for the drug** e.g. resistance to **aminoglycosides** is associated with alteration of a specific protein in the 30s subunit of the bacterial ribosome.

•**4-The organism develops an altered metabolic pathway that by passes the reaction inhibited by the drug** e.g. **sulphonamide-resistant** bacteria acquire the ability to use preformed folic acid with no need for extracellular PABA.



1. Production of enzymes destroying and modifying AB ß-lactamasesAG modifying enzymes.

2. Decrease of cell membrane permeability.

3. Active efflux of AB from cell.

4. Modification of AB target sites.

Origin of Resistance to Antimicrobial Agents :

A-Non genetic Drug Resistance:

•**Metabolic inactivity:**
Most antimicrobial agents act effectively only on replicating cells. Non multiplying organisms are more resistant to drugs. Tubercle bacilli survive for several years in tissues and their resistance to drugs is due ,in part, to their metabolic inactivity (dormancy).

•**Loss of target structure:** L-forms are penicillin resistant bacteria , have lost their cell wall, which is the target site of the drug.

B-Genetic Drug Resistance :

•**Plasmid mediated resistance :**

Resistance(R) factors are a class of plasmids frequently carry genes that code for the production of enzymes that inactivate or destroy antimicrobial agents e.g. –**beta lactamase which destroys the beta-lactam ring in penicillin and cephalosporins**.

•Transposon-mediated resistance .

Many transposons **(jumping genes)** carry genes that code for drug resistance. As they move between plasmids and chromosomes they can transfer this property to bacteria. The process is called transposition.

•Chromosomal drug resistance

This develops as a result of spontaneous mutation in a gene that controls susceptibility to an antimicrobial agent e.g. **streptomycin resistance** can result from a mutation in the **gene that controls the receptor for streptomycin located in the 30s bacterial ribosome**