Microbiology
Lecture 4

Antibiotic 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
- 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

antibacterial according to behavior toward bacterial populations :

- Bactericidal : kill bacteria e.g .penicillins, cephalosporins, and aminoglycosides .
- Bacteriostatic : these can inhibit the growth and multiplication of pathogens e.g .sulphonamides, tetracyclines and chloramphenicol .

Principles of antimicrobial therapy

Antimicrobial agents should be prescribed for patients in one or more of the following:

- Fever & acute infections
- Spreading infections
- Chronic infections
- Infections in immunocompromised patients
- Cases of osteomyelitis, bacterial sialadenitis and some periodontal diseases; as ulcerative gingivitis and localized aggressive periodontitis .

Mode of Action of Antimicrobials

Antimicrobial agents work by different mechanisms. And thus can be classified based on :

A. target site
B. their sources
C. Spectrum of activity of Antimicrobial agents

A- Classification based on target site:

1. cell wall; interfere with its synthesis
2. cytoplasmic membrane; disrupting the function
3. Ribosome; prevent protein synthesis
4. nucleic acid ; replication sites & synthesis

B- Classification of Antibiotics Based on their sources

- Antibiotics from microbes(natural products)
- Antibiotics from algae
- Antibiotics from higher plants
- Antibiotics from animals

Antibiotic from microbes(natural products)

a. **Antibiotics from fungi (Penicillin from P. notatum),(Cephalothin from Cephalosporium ssp.)**
b. **Antibiotics from bacteria (Polymyxin from Bacillus polymyxa) , (Bacitracin from Bacillus subtilis)**
c. **Actinomycetes (Streptomycin from Streptomyces griseus) , (Nystatin from Streptomyces noursei) , (Gentamyicin from Micromonospora purpurea)**

****Selective toxicity** : It is the ability of drug to kill or inhibit the growth of microorganisms without harming the host cells ** **which is an essential requirement for any successful antibiotic**

C. Classification Based on Spectrum of activity of Antimicrobial agents

Antibiotics fall into three main categories :

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

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

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

Broad Spectrum Antibiotics

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

- Penicillin+ B lactamase inhibitor,
- Cephalosporin ,
- Tetracycline ,
- Ciprofloxacin ,
- Levofloxacin.
- Metronidazole

Broad Spectrum Antibiotics

**These drugs work on both gram-negative and gram-positive organisms .When a patient appears to have a mixed bacterial infection, a broadspectrum 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

A- Classification based on target site:

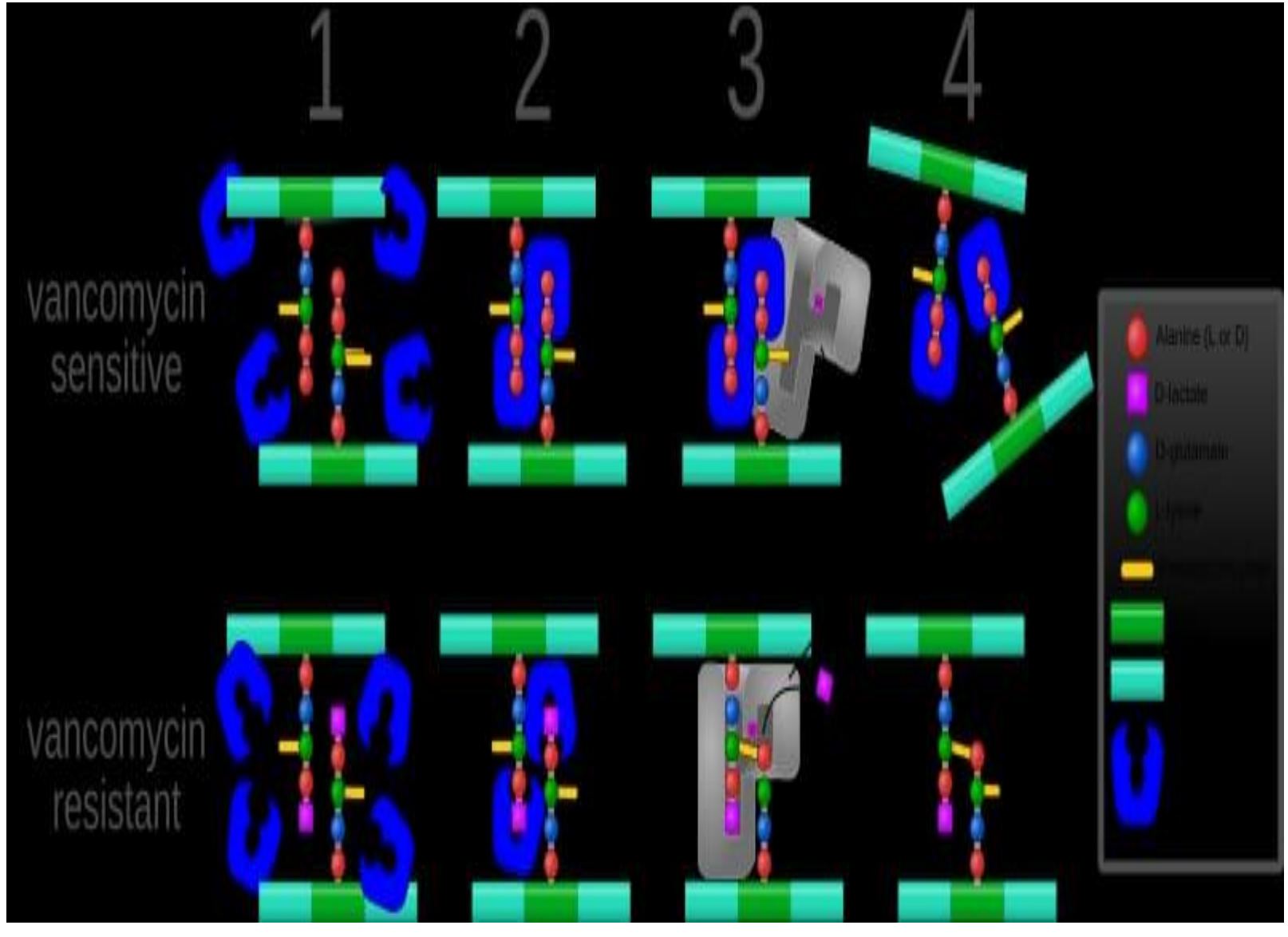
1) Inhibition of cell wall synthesis(bactericidal effect)

penicillins vancomycin, bacitracin, cephalosporin

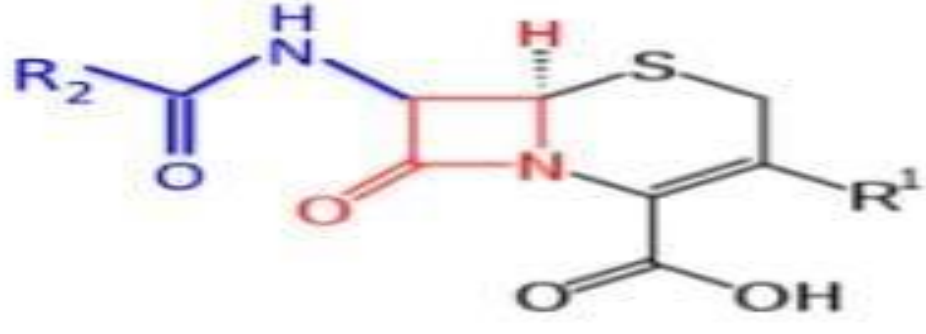
Penicillins and cephalosporins are β-lactam drugs and are selective inhibitors of the peptidoglycan layer synthesis of the bacterial cell walls specially for gram positive bacteria as Staphylococci and Streptococci.

***In dentistry, penicillins are widely used because they are non toxic 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 anintact β-lactam ring.


1
2
3
4
vancomycin sensitive
vancomycin resistant
Alanine (L or D)
D-lactate
D-glutamate

penicillins



cephalosporins

Resistance TO PENICILLIN is due to one of the followings:

- Bacteria produce β-lactamase enzyme
- The abscence of some penicillin receptors due to chromosomal mutation.
- Failure of the β-lactam drug to activate the autolytic enzymes in the bacterial cell wall.

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 polymyxin B mixed with \ 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 infection including endocarditis, septicemia specially in patients having penicillin allergy, it has limited clinical use due to its toxic side effect on kidneys

2) Disruption of cell membrane function

- ✓ Antibacterial Polymyxins (B,E),Amphotericin B and Colistins
- ✓ Antifungal: Polyenes, Nystatin .

Polymyxins: active againt many G-ve organisms , Due to their toxicity they are usually used topically

❖ Antifungal cell membrane inhibitors

- Polyenes:

  - Nystatin:- Used topically for Candida infections
  - Amphotericin :It is the drug of choice for treating systemic candidiasis

- Azoles:

  - Miconazole •It is fungicidal and bacteriostatic for Staphylococci.
  - Fluconazole: used to prevent candida infection in HIV infected individuals

3) Inhibition of protein synthesis:

i. Aminoglycosides (amikacin) : bactericidal most commonly used for serious infection caused by aerobic Gr – rods

ii. Tetracyclines: broad- spectrum , useful for oral pathogens, however, they cause discoloration (staining) to human teeth, the FDA issued a warning regarding its administration by pregnant women and young children ,

iii. Chloramphenicol:is used for treating Salmonella, meningococci and Haemophilus influenzae infections

iv. Macrolides & Azides (Erythromycins, Clarithromycin & Azithromycin) Bacteriostatic and useful for the treatment of patients allergic to penicillin. Typically used to treat infections caused by beta- hemolytic Streptococci, pneumococci, staphylococci and enterococci

v. Lincomycin &Clindamycin : Active against anaerobic bacteria causing dental, respiratory tract, soft tissue & skin infections and peritonitis. These drugs can induce sever ulcerative colitis.

4) Inhibition of nucleic acid synthesis

- Sulfonamides :Bacteriostatic for some G+ve & G-ve bacteria, Chlamydia and Protozoa
  Mechanism of action: through its 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 .

5) Inhibition of DNA replication:

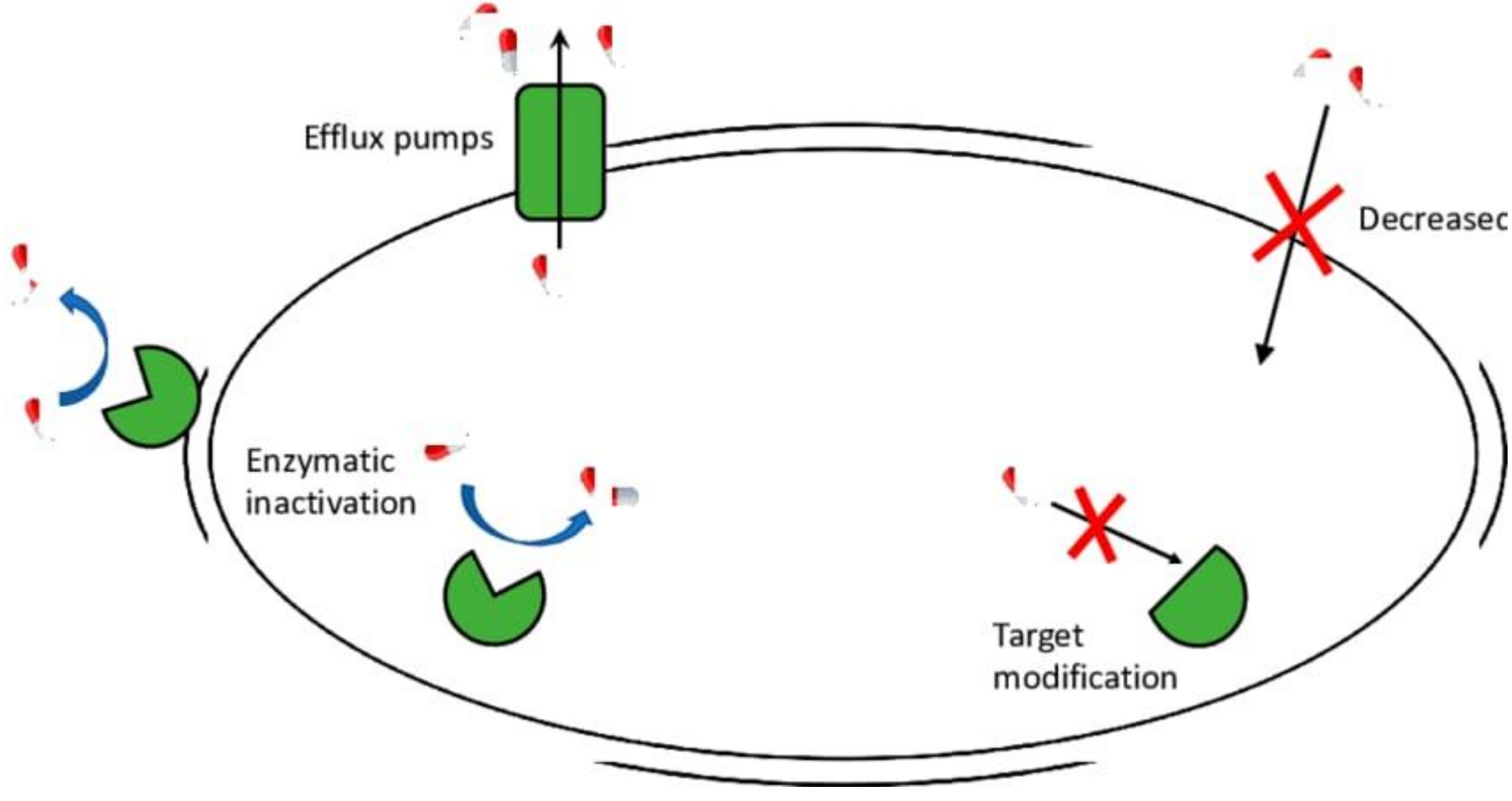
- Quinolones and Nalidixic acid : useful as urinary antiseptics, not taken orally.
- Ciprofloxacin, levofluxacin :active against Enterobacteriaceae and bacteria resistent to the 3rd generation cephalosporines as Neisseria and Haemophilus
- Metronidazole :Broad spectrum ,bactericidal(bacterial vaginosis) and is an anti protozoal drug. Effective against oral anaerobic bacterial infections caused by Bacteroides, Prevotella, Fusobacterium and Peptostreptococci spp. Even against isolates from infected necrotic pulps
- Isoniazid (Anti- tuberculosis)

WHY WE USE Antimicrobial Combination Therapy ?

1. For the initial therapy of severely infected patient
2. Polymicrobial 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
6. 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 antibiotic resistance

1. Production of enzymes destroying and modifying AB ß-lactamases
2. Decrease of cell membrane permeability
3. Active efflux of AB from cell
4. Modification of AB target Site



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.

- 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 receptor for streptomycin located in the gene

Other Typical Antimicrobial Agents having been developed to target oral bacteria that cause oral diseases

1.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.

2.Chlorhexidine Is one of the first antiseptic agents proposed for dental caries and has proved to be the most effective and the “gold standard” of antiplaque agents. Chlorhexidine is active against gram-positive and gram-negative bacteria ,facultative anaerobes, aerobes, and yeasts

- ✓ by damaging the inner cytoplasmic membrane, it block the acidic groups of glycoproteins present in saliva
- ✓ reduce plaque adhesion
- ✓ can reduce the binding of bacteria to tooth surfaces

.However, chlorhexidine causes genotoxicity by inducing DNA damage in leukocytes, kidney cells and oral mucosal cells, and it can also induce cellular apoptosis.

3.Quaternary Ammonium Salts Are widely used as antimicrobial agents, and were first incorporated into mouth rinses to inhibit oral plaque, used as additives in dental materials to give them antimicrobial abilities , they promote the bacterial lysis by binding to bacterial membranes. Their side effects include gastrointestinal symptoms, coma, convulsions ,hypotension, and death

4.Antimicrobial Peptides (AMPs) Are host-defense molecules that exert potent antimicrobial activities against a broad spectrum of microorganisms. In the oral cavity, there are many natural AMP molecules , such as (human β-defensin-1,2,3), LL-37 (a cathelicidin) , nisin and histatins, which possess antimicrobial activities against oral

pathogenic bacteria and biofilms .Their antimicrobial mechanism is cell permeabilization followed by membrane disruption

5.Remineralizing Agents Many of these agents are used clinically to treat dental caries.In addition to fluorides, calcium phosphate materials , nanoparticles, polydopamine, oligopeptides and many others are used for remineralization and teeth repair and to restore the presence of minerals to the hydroxyapatite (HAP) crystal lattice in ionic forms.