Antimicrobial Chemotherapy

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Introduction

- Drugs have been used for the treatment of infectious diseases since the 17th century (eg, quinine for malaria, 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. Experiments led to the arsphenamines for syphilis, the first planned chemotherapeutic regimen.
- Chemotherapy means treating a disease with a specific chemical that's designed to target the exact cause of that disease.
- Antimicrobial chemotherapy is the clinical application of antimicrobial agents to treat infectious diseases.

Type of Antimicrobial Chemotherapeutic Agents drugs

- 1-Synthetic drugs (agents):- They synthesized chemically. For example (sulfonamides, Imidasoles, Metronidazoles, flucytion, ethambutol, Isoniazid, Nalidixic acid, Nitrofurantion).
- 2-Natural products (antibiotics):- These substance of microbial origin, i.e., synthesized by the microbe; and have antimicrobial action, So these antibiotic produced by fungi or bacteria or even plants animals such as algae.
- Examples of antibiotic from fungi are Penicillin's and cephalosparins.
- Examples of antibiotic from bacteria are Bacitracin and Polymyxins.-Examples of antibiotic from streptomyces species are Tetracyclin, Choloramphenicol, erythromycin, Streptomycin, Vancomycin, Kanamycin, lincomycin, Cycloserine and Polyenes….etc.

Classification of antimicrobial drugs according to their mode of action "site of action"

- The treatment of bacterial infections is increasingly complicated by the ability of bacteria to develop resistance to antimicrobial agents.
- Antimicrobial agents used for the treatment of bacterial infections are often categorized according to their principal mechanism of action.
- There are six major modes of action:
- (1) interference with cell wall synthesis,
- (2) inhibition of protein synthesis,
- (3) interference with nucleic acid synthesis,
- (4) inhibition of a metabolic pathway,
- (5) inhibition of membrane function,
- (6) inhibition of ATP Synthase.
- Therefore, according to its mechanism of action, the targets of antibacterial drugs include cell membrane, cell wall, protein synthesis, nucleic acid synthesis, and biological metabolic compound synthesis.

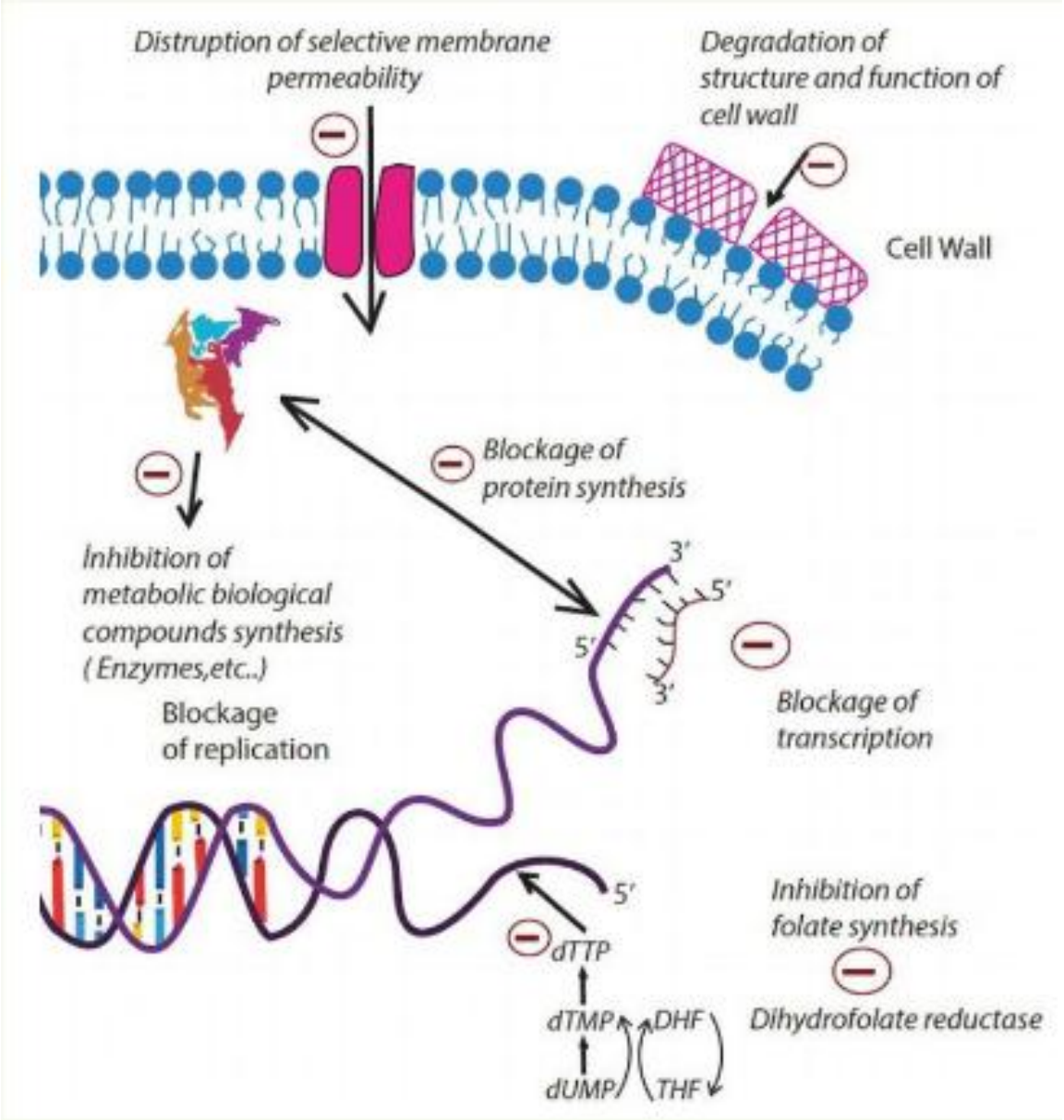

Fig.1 Targets of antimicrobials. (Kırmusaoğlu, 2019)

Antibiotics targeting cell wall

- Bacterial cells are surrounded by a cell wall made of peptidoglycan, which consists of long sugar polymers.
- The peptidoglycan undergoes cross-linking of the glycan strands by the action of transglycosidases, and the peptide chains extend from the sugars in the polymers and form cross links, one peptide to another.
- The D-alanyl-alanine portion of peptide chain is cross linked by glycine residues in the presence of penicillin binding proteins (PBPs).
- This cross-linking strengthens the cell wall.
- β-lactams and the glycopeptides inhibit cell wall synthesis.
- Cephalosporins follow same mechanism of action as beta-lactam antibiotics (such as penicillins)

Beta-lactam antibiotics

- The primary targets of the β-lactam agents are the PBPs. It has been hypothesized that the β-lactam ring mimics the D-alanyl D-alanine portion of peptide chain that is normally bound by PBP. The PBP interacts with β-lactam ring and are not available for the synthesis of new peptidoglycan. The disruption of peptidoglycan layer leads to the lysis of bacterium.

Glycopeptides

- The glycopeptides binds to D-alanyl D-alanine portion of peptide side chain of the precursor peptidoglycan subunit. The large drug molecule vancomycin prevents binding of this D-alanyl subunit with the PBP, and hence inhibits cell wall synthesis.

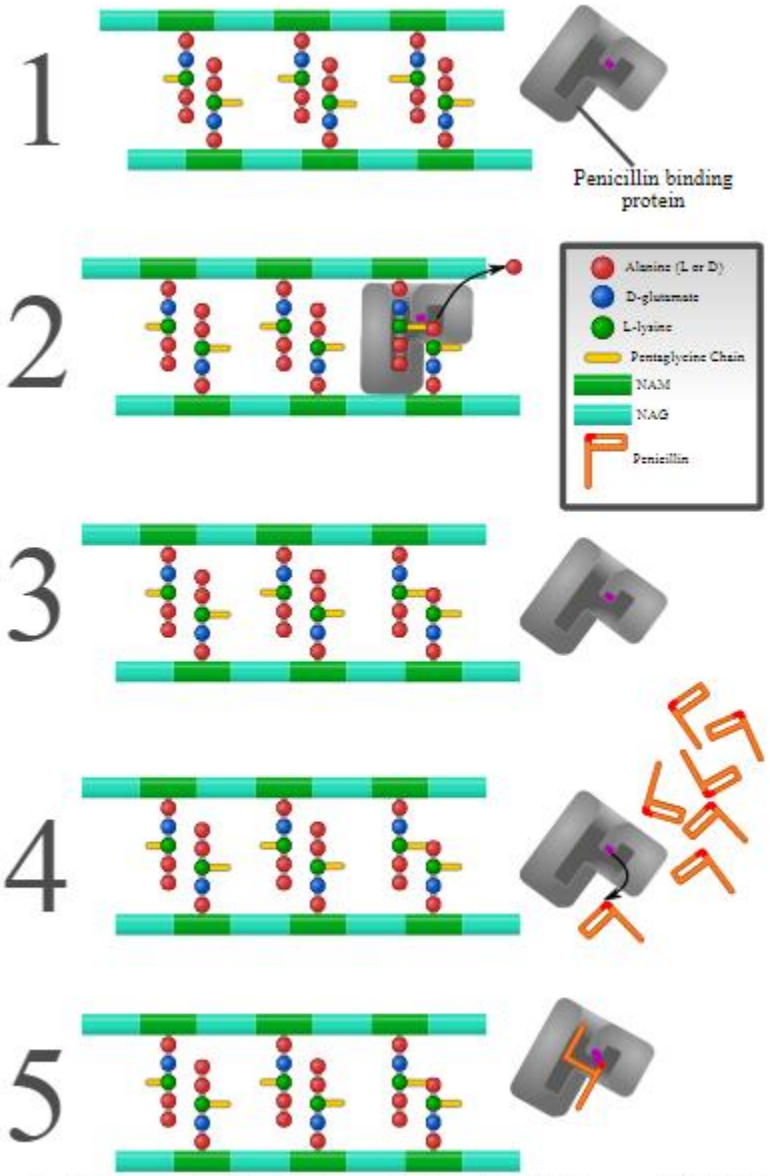

Figure: **Mechanism of penicillin inhibition:** Penicillin and most other β-lactam antibiotics act by inhibiting penicillin-binding proteins, which normally catalyze cross-linking of bacterial cell walls.

Inhibitors of protein biosynthesis

- The bacterial 70S ribosome is composed of two ribonucleoprotein subunits, the 30S and 50S subunits.
- Antimicrobials inhibit protein biosynthesis by targeting the 30S or 50S subunit of the bacterial ribosome.
- **Aminoglycosides:** The aminoglycosides (AG's) are positively-charged molecules which attach to the OM which is negatively charged leading to formation of large pores, and thus allow antibiotic penetration inside the bacterium. The main target of action is bacterial ribosome.
- AG's interact with the 16S r-RNA of the 30S subunit near the A site through hydrogen bonds. They cause misreading and premature termination of translation of mRNA. Eg. Gentamicin, amikacin, tobramycin, neomycin, streptomycin.
- **Tetracyclines:** act upon the conserved sequences of the 16S r-RNA of the 30S ribosomal subunit to prevent binding of t-RNA to the A site.
- Chloramphenicol: It interacts with the conserved sequences of the peptidyl transferase cavity of the 23S r-RNA of the 50S subunit. Hence, it inhibits the protein synthesis by preventing binding of t-RNA to the A site of the ribosome.

Inhibitors of DNA replication

- **Quinilones :** The fluoroquinolones (FQ) inhibit the enzyme bacterial DNA gyrase, which nicks the double-stranded DNA, introduces negative supercoils and then reseals the nicked ends.
- This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription.

Folic acid metabolism inhibitors

- Sulfonamides and trimethoprim
- Each of these drugs inhibits distinct steps in folic acid metabolism.

Inhibition of membrane function

- Polymyxins antibiotics which have a general structure consisting of a cyclic peptide with a long hydrophobic tail.
- They disrupt the structure of the bacterial cell membrane by interacting with its phospholipids.

Inhibitors of ATP synthase

- The importance of ATP synthase as a promising target for drug development is evident from the fact that many antibiotics such as efrapeptins, aurovertins, and oligomycins inhibit its function.
- Antibiotics efrapeptins and aurovertins inhibit both synthesis and hydrolysis of ATP by ATP synthase.