Antimicrobial Chemotherapy

Antimicrobial agents commonly used in the treatment of patients with bacterial infections by eradicating the infecting pathogens using substances that actively inhibit or kill it. Some of these substances are obtained and **purified from other microbial organisms** and are known as **antibiotics**, others are **chemically synthesized**. Collectively, these natural and synthesized substances are referred to as **antimicrobial agents**.

Unfortunately, with widespread antibiotics use we have a problem of the emergence of (**1**) multidrug resistant pathogens (**2**) reduced efficacy of many of most powerful antimicrobials (**3**) recognized many adverse effects of antimicrobials (**4**) the cost of medical care is increased due to overuse of antibiotics and treating infections caused by resistant organisms.

Principle of antimicrobial therapy

Selective toxicity

An ideal antimicrobial agent exhibits **selective toxicity**, which means that the drug is harmful to a pathogen without being harmful to the host cells. Selective toxicity may be a function of **(1):** a specific receptor required for drug attachment, or it may depend on **(2):** the inhibition of biochemical events essential to the pathogen but not to the host.

Mechanisms of action of antimicrobial drugs

There are four major sites in the bacterial cell that are different from the human cells that they serve as the basis for the action of clinically effective drugs: **cell wall**, **cell membrane**, **ribosomes**, and **nucleic acids**. So, the antimicrobial drugs act by:

1.Inhibition of cell wall synthesis

All β-lactam drugs (penicillins and cephalosporins) are selective inhibitors of bacterial cell wall synthesis and therefore active against growing bacteria. The initial step in drug action consists of binding of the drug to cell receptors **(penicillin-binding proteins PBPs)**, attachment of penicillin to one PBPs may result in abnormal elongation of the bacterial cell, or lead to a defect in the periphery of the cell wall, leading to cell lysis.

2.Inhibition\ alteration of cell membrane function

The cytoplasm of all living cells are bounded by the cytoplasmic membrane, which serves as a selective permeability barrier and carries out active transport functions and thus controls the internal composition of the cell. If the functional integrity of the cytoplasmic membrane is disrupted, macromolecules and ions escape from the cell, and cell damaged. **Polymyxins** (polymyxin B and colistin) are older agents that disrupt bacterial cell membranes. This disruption results in leakage of macromolecules and ions essential for cell survival.

3.Inhibition of protein synthesis (ribosomes synthesis)

Several drugs inhibit protein synthesis in bacteria without interfering with protein synthesis in human cells. This selectivity is due to the differences between bacterial and human ribosomal proteins. Bacteria have 70S ribosomes with 50S and 30S subunits, whereas human cells have 80S ribosomes with 60S and 40S subunits. Macrolides, lincosamides, tetracyclines, aminoglycosides, and chloramphenicol can inhibit protein synthesis in bacteria.

4.Inhibition of nucleic acid synthesis

Fluoroquinolones (ciprofloxacin and ofloxacin), these agents bind to and interfere with DNA gyrase enzymes involved in the regulation of bacterial DNA supercoiling, a process that is essential for DNA replication and transcription.

Broad-spectrum antibiotics: are active against wide range of bacteria, both Gram positive and Gram negative (e.g., tetracyclines and chloramphenicol).

Narrow-spectrum antibiotics: are effective against specific type of bacteria, either Gram positive or Gram negative (e.g., penicillin G, erythromycin, streptomycin).

Bactericidal antibiotics: antimicrobials that kills bacteria.

Bacteriostatic antibiotics: antimicrobials inhibits growth of bacteria, but not kill them.

Resistance to antimicrobial drugs

There are **four** major mechanisms that mediate bacterial resistance to drugs:

(1) Bacteria **produce enzymes** that inactivate the drug (e.g., β-lactamases can inactivate penicillins and cephalosporins by cleaving the β-lactam ring of the drug).

(2) Bacteria synthesize **modified antibiotic target site** result in decreasing the affinity for the drug, then drug has a reduced effect (e.g., a mutant protein in the 30S ribosomal subunit can result in resistance to streptomycin).

(3) Bacteria **reduce permeability** to the drug, such that an effective intracellular concentration of the drug is not achieved (e.g., changes in porins* can reduce the amount of penicillin entering the bacterium).

[*Porins: are proteins that cross a cellular membrane and act as a pore, through which molecules can diffuse. They act as channels that are specific to different types of molecules. They are present in the outer membrane of Gram-negative bacteria. Specific antibiotics have been designed to travel through porins in order to inhibit cellular processes, due to selective pressure, bacteria can develop resistance through mutations, resulting in the antibiotics having a lower permeability or being completely excluded from transport].

(4) Bacteria actively export drugs, using a **multidrug-resistance pump or efflux pump** which mean pumping the drug out the bacterial cell. Efflux pumps are transport proteins involved in the extrusion of toxic substrates (including all classes of antibiotics) from within cells into the external environment.

Controlling of antimicrobials resistance

The basic principles of controlling resistance to antimicrobials are: (**1**) reduce inappropriate use of antibiotics (**2**) encourage targeted treatment with narrow spectrum drugs (**3**) limit adverse effects.

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