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Antibiotics

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Antibiotics

Mode of Action

Antibiotics: Substances that inhibit or destroy selective pathogens, generally at low concentrations .

Antimicrobial agent: is a chemical substance derived from a biological source or produced by chemical synthesis that kills or inhibits the growth of microorganisms .

Selective toxicity: It is the ability of drug to kill or inhibit the growth of

microorganisms without harming the host cells

Broad-spectrum antibiotics: They are active against several types of microorganisms (Gram-positive and Gram-negative bacteria), such as tetracycline .

Narrow-spectrum antibiotics: Are active against one or very few types, like vancomycin, which is used against Gram-positive cocci, namely staphylococci and streptococci.

-The effect of antimicrobial activity on microorganism :

Bactericidal drugs: Drugs kill bacteria e.g .penicillins, cephalosporins, and aminoglycosides .

Bacteriostatic drugs: Drugs inhibit the growth of bacteria but do not kill them.



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e.g sulphonamides, tetracyclines and chloramphenicol

Mechanisms of action:

There are four mechanisms :

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 .

- ✚ 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 .

Resistance TO PENICILLIN is due to one of the followings :

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



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Cephalosporins were initially isolated from the mould *Cephalosporium*. They are more resistant to β -lactamase hydrolysis than penicillins and have a wider antibacterial spectrum.

Cycloserine and bacitracin (bactericidal) for fungi.

2. Alteration of cell membrane function :

Polymyxin E (colistin) disrupts the phospholipids of the cell membrane of bacteria.

Amphotericin B effects on bacteria. Azoles and nystatin on fungi.

Metronidazole (Flagyl) affects Protozoa, and it is also used against anaerobic bacteria.

3. Inhibition of protein synthesis :

a. Drugs act on the 30S subunit :

- Aminoglycosides (amikacin) : bactericidal most commonly used for serious infection caused by aerobic Gr – rods
- Tetracyclines: broad- spectrum , useful for oral pathogens; however, they cause discoloration (staining) to human teeth, the FDA issued a warning regarding their administration by pregnant women and young children ,



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b. Drugs act on the 50S subunit :

- Chloramphenicol: is used for treating Salmonella, meningococci and Haemophilus influenzae infections
- 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
- Lincomycin & Clindamycin: Active against anaerobic bacteria causing dental ,respiratory tract, soft tissue & skin infections and peritonitis. These drugs can induce severe ulcerative colitis .

4 -Inhibitors of Nucleic Acid Synthesis and Function

The selectivity of these agents is a result of differences in prokaryotic and eukaryotic enzymes affected by the antimicrobial agent .

1. Inhibitors Of RNA Synthesis and Function

Rifampin, rifamycin, rifampicin (bactericidal)

- Mode of action: These antimicrobials bind to DNA-dependent RNA polymerase And inhibit the initiation of RNA synthesis.



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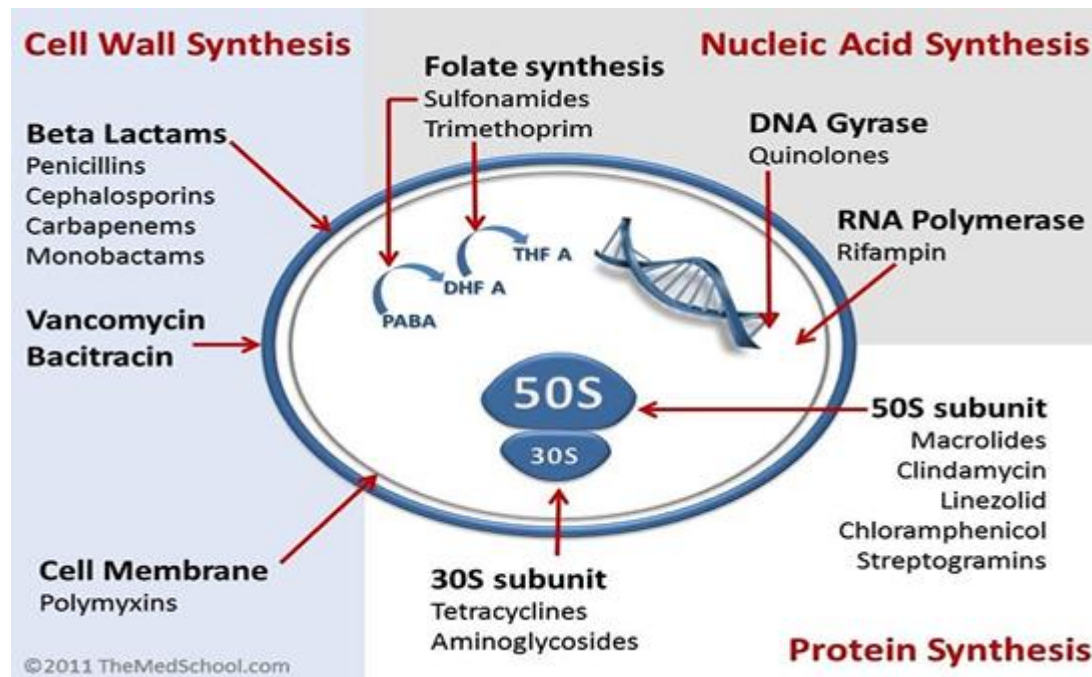


- Spectrum of activity: They are a wide spectrum of antibiotics but are used most commonly in the treatment of tuberculosis

2. Inhibitors Of DNA Synthesis and Function

Quinolones - nalidixic acid, ciprofloxacin, oxolinic acid
(bactericidal)

- Mode of action: These antimicrobials bind to the A subunit of DNA gyrase (topoisomerase) and prevent supercoiling of DNA, thereby inhibiting DNA synthesis .
- Spectrum of activity: These antibiotics are active against Gram-positive cocci and are used in urinary tract infections.





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There are many factors that affect the activity of antibiotics *in vitro* and *in vivo*.

Factors affecting antimicrobial activity *in vitro* :

1. PH of environment: some drugs are active at acidic pH; others, at alkaline pH.
2. Components of medium.
3. Stability of drug: Some drugs are unstable at incubator temperature.
4. Size of inoculum: The large bacterial inoculum affects the susceptibility of the organism.
5. Length of incubation: The long incubation may give the chance for the resistant mutants to multiply.

Factors affecting antimicrobial activity *in vivo* :

1. Environmental factors (distribution of the drug, location of organisms ,Concentration and interfering substances .
2. Alteration of host response: Some therapies suppress the immune response ,and this enhances the infection .
3. Alteration of microbial flora: It occurs in patients who receive antimicrobials for a long time, which leads to suppression of the normal microbial flora .

Antibiotic Resistance

Antibiotic resistance occurs when bacteria develop the ability to defeat the drug which is produced to kill them. In some cases,



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bacteria developed resistance to more than one type of antibiotic, so in this case, the bacteria are called **Multiple-Drug-Resistant (MDR) bacteria**

According to the World Health Organization (WHO), antibiotic resistance leads to many problems .

- Antibiotic resistance is one of the biggest threats to global health, food security, and development today .
- Antibiotic resistance occurs naturally, but misuse of antibiotics in humans and animals is accelerating the process .
- A growing number of infections – such as pneumonia, tuberculosis ,gonorrhoea, and salmonellosis – are becoming harder to treat as the antibiotics used to treat them become less effective .
- Antibiotic resistance leads to longer hospital stays, higher medical costs ,and increased mortality .

Four major mechanisms mediate bacterial resistance to drugs :

1. Bacteria produce enzymes that inactivate the drugs; ex. β -lactamase can inactivate penicillins and cephalosporins by cleaving the β -lactam ring of the drug .



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2. Bacteria synthesize modified targets against which the drug has no effect; ex mutant protein in the 30S ribosomal subunit can result in resistance to streptomycin .
3. Bacteria decrease their permeability such that an effective intracellular concentration of the drug is not achieved; exchange in porins can reduce the amount of penicillin entering the bacterium .
4. Bacteria actively export drugs using a multidrug resistance pump (MDR pump) .

The basis of resistance :

1. Genetic basis of resistance:

This is due to a mutation in the gene that codes for either the target of the drug or the transport system in the membrane that controls the uptake of the drugs.

- Chromosome -mediated resistance:
- Plasmid –mediated resistance (R factor).
- Transposon-mediated resistance

2. Non –genetic basis of resistance; this may be due to :

- 1) Bacteria can be walled off within an abscess cavity that the drug fails to penetrate effectively .
- 2) Bacteria can be resting (not growing); they are therefore insensitive to cell wall inhibitors such as penicillins and cephalosporins .



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- 3) Under certain conditions, bacteria survive as protoplasts and are insensitive to cell wall antibiotics .
- 4) Antibiotic resistance may be due to the administration of the wrong drug or the wrong dose .

Resistant bacteria may be developed by overuse and misuse of antibiotics, because some physicians and patients use multiple antibiotics in self-limited infections like viral infections. Also, in many countries, antibiotics are sold over the counter to the general public .

Chemoprophylaxis: It is the process in which antibiotics are used to prevent diseases from occurring. This process is used in three circumstances :

- 1) Before surgery .
- 2) .In immunocompromised patients .
- 3) In people with normal immunity who have been exposed to certain pathogens .

Adverse effects of antimicrobial drugs :

Some antibiotics have side effects on some patients :

Penicillins: Allergic reactions. Metronidazole: Headache and dry mouth .

Refampicin: Liver damage .



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Tetracycline: Staining and deformity of teeth in children up to 8 years.

Trimethoprim :Rash and nausea.

Use of antibiotic combinations: There are several instances in which two or more drugs are commonly given :

1. To achieve a synergistic inhibitory effect against certain organisms .
2. To prevent the emergence of resistant organisms (If bacteria become resistant to one drug, the second drug will kill them, thereby preventing the emergence of resistant strains)
3. For the treatment of mixed infections .

Synergistic: In which the effect of the two drugs together is significantly greater than the effects of the two drugs acting separately (Penicillin+Gentamycin) .

Antagonistic: In which the result is significantly lower activity than the sum of the activities of the two drugs alone (Chloramphenicol +Penicillin) .

Minimal inhibitory concentration (MIC): It is defined as the lowest concentration of a drug that inhibits the growth of the organism .



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Minimal bactericidal concentration (MBC): The concentration of the drug that actually kills the organism rather than the concentration that inhibits growth .

Measurement of antimicrobial activity :

Dilution method: A graded amount of antimicrobial substances is incorporated into liquid or solid bacteriologic media .

Diffusion method: (Kirby-Bauer test)The most widely used method is the "Disk diffusion". A filter paper disc containing a measured quantity of a drug is placed on the surface of a solid medium that has been inoculated on the surface with the test organism. After incubation, the diameter of the clear zone of inhibition surrounding the disk is taken as a measure of the inhibitory power of the drug against the test organism .

VITEK test: The VITEK device is an automated photometric system used for identification and antimicrobial susceptibility testing of both gram-negative and gram -positive bacteria.