Antibiotics and antimicrobial chemotherapy

Antimicrobials is the treatment of infectious diseases by administration of drugs (antibiotics) which are lethal or inhibitory to the causative organisms.

Types of action of antimicrobial chemotherapeutics

From their behavior toward bacterial populations antibacterial agents are divided into two classes:

1- Bactericidal drugs: these have a rapid lethal action against the pathogenic agents e.g. penicillins, cephalosporins, and aminoglycosides.

2- Bacteriostatic drugs: these merely inhibit the division of the pathogenic agents i.e. growth of organisms e.g. sulphonamides, tetracycline and chloramphenicol.

Range of Action of Antimicrobial Chemotherapeutics:

Antibiotics fall into three main categories:

1.Active mainly against gram-positive organisms e.g. penicillin, 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, chloramphenicol, and ampicillin.

Broad Spectrum Antibiotics

Broad-spectrum antibiotics are antibiotics which are designed to work against a broad spectrum of bacteria, rather than **narrow-spectrum antibiotics**, which are only effective against a smaller range of bacteria.

Some examples of broad-spectrum antibiotics include:

penicillin, cephalosporin, tetracycline, ciprofloxacin and levofloxacin

Mechanism of Action of Antimicrobial Chemotherapeutics

Several mechanisms are known:

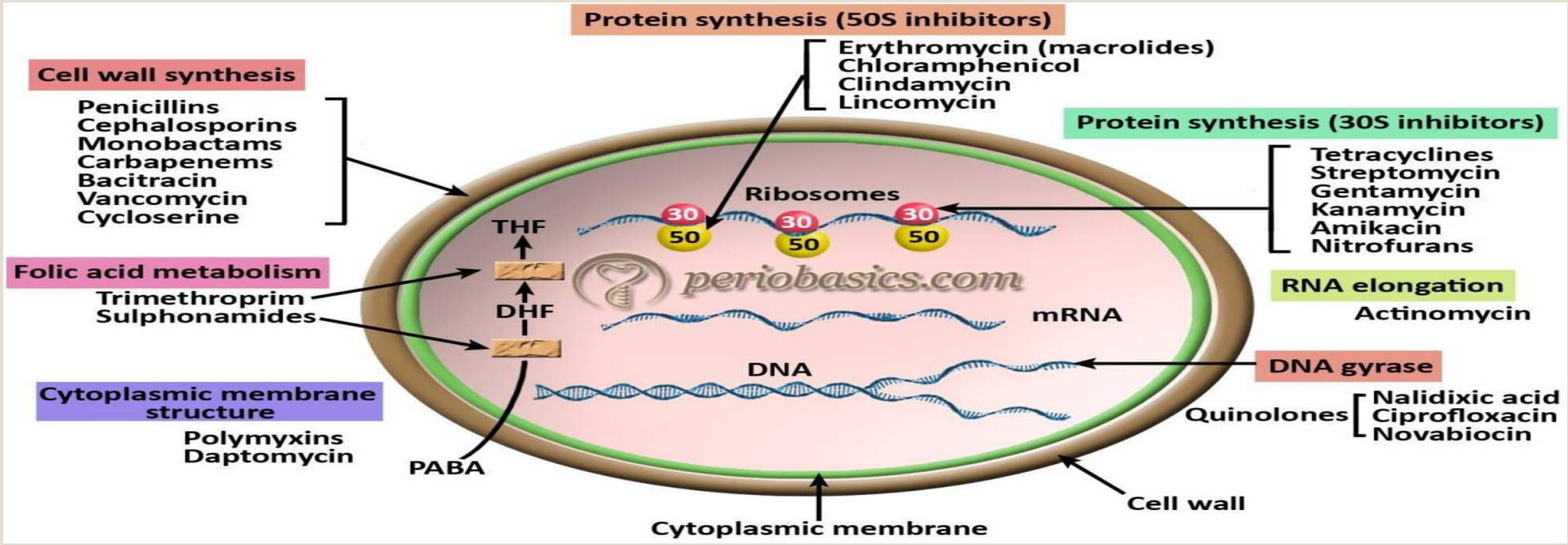
1- Inhibition of cell wall synthesis: Some antibiotics e.g. penicillin, cephalosporins and vancomycin, interfere with cell wall synthesis and cause bacteriolysis.

2- Inhibition of cytoplasmic membrane function: Some antibiotics cause disruption of the cytoplasmic membrane Polymyxins, amphotericin B, and nystatin are examples.

3- Inhibition of protein synthesis: Many antimicrobial chemotherapeutics block protein synthesis by acting on the 30s or 50s subunits of the bacterial ribosome. Examples are chloramphenicol, tetracycline, erythromycin and the aminoglycosides e.g. tobramycin, gentamycin and streptomycin.

4- Inhibition of nucleic acid synthesis: These can act on any of the steps of DNA or RNA replication e.g. quinolones, trimethoprim, rifampicin, nalidixic acid, novobiocin and metronidazole.

5- Competitive inhibition: in which the chemotherapeutic agent competes with an essential metabolite for the same enzyme e.g. p- aminobenzoic acid (PABA) is an essential metabolite for many organisms. They use it as a precursor in folic acid synthesis which is essential for nucleic acid synthesis. Sulphonamides are structural analogues to PABA so they enter into the reaction in place of PABA.



Mechanism of Action	Drugs
Inhibition of cell wall synthesis	
1. (a) Antibacterial activity inhibition of cross-linking (transpeptidation) of peptidoglycan	Penicillins, cephalosporins, imipenem, aztreonam, vancomycin
(b) Inhibition of other steps in peptidoglycan synthesis	Cycloserine, bacitracin
2. Antifungal activity inhibition of β-glucan synthesis	Caspofungin
Inhibition of protein synthesis	
Action on 50S ribosomal subunit	Chloramphenicol, erythromycin, clindamycin, linezolid
Action on 30S ribosomal subunit	Tetracyclines and aminoglycosides
Inhibition of nucleic acid synthesis	
Inhibition of nucleotide synthesis	Sulfonamides, trimethoprim
Inhibition of DNA synthesis	Quinolones (e.g., ciprofloxacin)
Inhibition of mRNA synthesis	Rifampin
Alteration of cell membrane function	
Antibacterial activity	Polymyxin, daptomycin
Antifungal activity	Amphotericin B, nystatin, terbinafine, azoles (e.g., itraconazole)
Other mechanisms of action	
1. Antibacterial activity	Isoniazid, metronidazole, ethambutol, pyrazinamide
2. Antifungal activity	Griseofulvin, pentamidine

Mechanisms of Resistance to Antimicrobial Agents

The major mechanisms that mediate bacterial resistance to drugs:

1. Certain bacteria produce enzymes that destroy the drug, ex, Beta-lactamase enzymes can inactivate penicillines and cephalosporines by cleaving the beta-lactam ring of the drug.
2. Certain bacteria synthesize modified target site of drug action.

3. Certain bacteria change their permeability to the drugs.

4. Certain bacteria increase the export of drug to the outside of the M.O

Origin of Resistance to Antimicrobial Agents

These mechanisms may be of non genetic or genetic origin:

A- Non genetic Drug Resistance:

i. Metabolic inactivity.

ii. Loss of target structure

B- Genetic Drug Resistance

i- **Plasmid mediated resistance**

Resistance (R) factors are a class of plasmids that mediate resistance to one or more antimicrobial agent. Plasmids frequently carry genes that code for the production of enzymes that inactivate or destroy antimicrobial agents e.g. β-Iactamase which destroys the p-lactam ring.

ii. **Transposon-mediated resistance**

Transposons are sequences of DNA that can move or transpose themselves to new positions within the genome of a single cell. Many transposons carry genes that code for drug resistance.

iii. Chromosomal drug resistance

This develops as a result of spontaneous mutation in a gene that controls susceptibility to an antimicrobial agent.

Chemoprophylaxis

Chemoprophylaxis is the use of antimicrobial agents to prevent rather than to treat infectious diseases. The following are principal conditions for which prophylactic antibiotics are positively indicated:

1. The use of benzathine penicillin G injections every 3-4 weeks to prevent reinfection with Strept. pyogenes in rheumatic patients.

2. A single large dose of amoxycillin given immediately prior to dental

procedures is recommended for patients with congenital or rheumatic heart disease to prevent endocarditis.

3.The oral administration of rifampicin 600 mg twice a day for 2 days to exposed persons during epidemics of meningococcal meningitis.

4 Oral administration of tetracycline to prevent cholera caused by
Vibrio cholerae.

5Chemoprophylaxis in surgery: little is known about its effectiveness. However, conditions in which

chemoprophylaxis is indicated are:

a. Large bowel surgery.
b.Major orthopedic and cardiac surgery. c- Amputation of an ischemic limb.

Notes:

A. Bacteria have the ability to develop resistance following repeated or insufficient doses, so more advanced and synthetic antibiotics are continually required to overcome them.

B. Certain bacteria are not only resistant to drug but require it for growth, called drug-dependent bacteria.

C . Most drug resistance is due to a genetic change in bacteria

(1)due to mutation in bacterial chromosome, inherited
(2) acquired resistance due to acquisition of genetic materials.

Antimicrobial susceptibility testing: An in vitro test; done to check the effectiveness of a drug against a bacterium and to select the best drug that acts against the bacterium.

Fig. 1. **Antimicrobial susceptibility test using the disc method**

This blood isolate of extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* came from a septic patient who died from the infection. There is resistance to ceftriaxone (CTX), ciprofloxacin (CIP), ticarcillin-clavulanate (TIM) and gentamicin (CN). A "keyhole" (partial zone enlargement) is present between CTX and TIM, indicating the presence of an ESBL enzyme. The size of the zone around cefepime (FEP 4th generation cephalosporin) and imipenem (a carbapenem) is sufficient to indicate susceptibility.