VIVEKANANDA COLLEGE
THAKURPUKUR
KOLKATA-700063

NAAC ACCREDITED 'A' GRADE

Topic	: Chemotherapeutic Agents
Course Title	: Basic Microbiology and Microbial Genetics
Paper	: CC 10
Unit	: II
Semester	: 4
Name of the Teacher	: Dr. Kakali Roy
Name of the Department	: Biochemistry

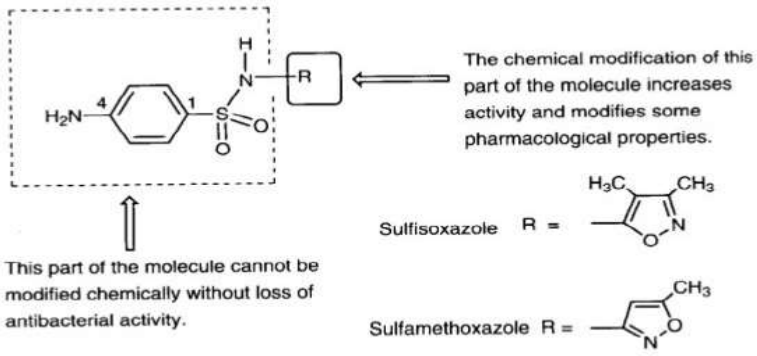
Chemotherapeutic Agents

- Chemotherapeutic Agents are the chemical substances used to directly or indirectly inhibit the proliferation of rapidly growing cells, typically in the context of malignancy.

Sulphonamides (Sulfa Drugs)

- A synthetic antimicrobial agent that kills or suppresses the growth of microorganisms but causes little or no damage to the host.

Basic Structure of sulfonamide



Sulfonamides Classes

18

- sulfonamide categorized into several types, based mainly on their indications and duration of action in the body.
- Probably the most common classification based on water solubility versus lipid solubility or duration of effect.
- In most species, sulph. administered 1–4 times/day, depending on the drug, to control systemic infections caused by susceptible bacteria.
- sulfonamide administration can be less frequent if eliminated slowly .
- **sulfathiazole, sulfamethazine (sulfadimidine), sulfamerazine, sulfadiazine, sulfapyridine, sulfabromomethazine, sulfaethoxypyridazine,**

Prof. Dr/ Nehal Afifi 4/11/2016

TABLE 45.5. Some examples of sulfonamides showing their substituents in R' position

Sulfonamides (common name)	*R' position*
Sulfanilamide	(Hydrogen)
Sulfapyridine	(Pyridine)
Sulfathiazole	(Thiazole)
Sulfadiazine	(Pyrimidine)
Sulfamerazine	(4-Methylpyrimidine)
Sulfamethazine	(4,6-Dimethylpyrimidine)
Sulfaguanidine	(Guanidyl)

SULFONAMIDES

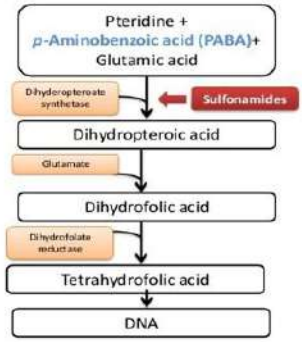
Mechanism of action:

- They are chemical analogues of p-aminobenzoic acid (PABA) → they competitively inhibit bacterial enzyme, which is responsible for the synthesis of folic acid → inhibit bacterial folic acid, which is the most important factor of microbial life.

In environments containing large amounts of PABA, such as pus or tissue breakdown products, antimicrobial action of sulfonamides is significantly weakened.

Mechanism of action

- Bacteria synthesize their own folic acid (FA) of which *p*-aminobenzoic acid (PABA) is a constituent, and is taken up from the medium.
- Sulfonamides, are structural analogues of PABA, inhibit bacterial folate synthase and formation of folate get inhibited.
- Sulfonamides competitively inhibit the PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydrofolic acid.
- Sulfonamide altered folate an which is metabolically injurious



Definition of Antibiotics

Chemical substances produced by various microorganisms that have the capacity to inhibit or destroy other microorganisms.

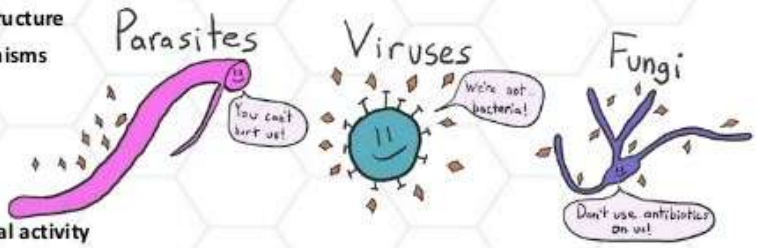
Now aday they are chemically synthesized.

They either kill bacteria(bactericidal) or keep more bacteria from growing(bacteriostatic).

Antibiotics will not cure infections caused by viruses.

Classification of Antibiotics/antimicrobials

- **Based on chemical structure**
- **Based on target organisms**
  - *Antiviral*
  - *Antibacterial*
  - *Antifungal*
  - *Antiparasitic*
- **Based on antimicrobial activity**
  - *Bactericidal*
  - *Bacteriostatic*
- **Spectrum of activity**
  - *Narrow*
  - *Broad*



Note: *Sulfonamides are both antiparasitic and antibacterial*

Based on Chemical Structure

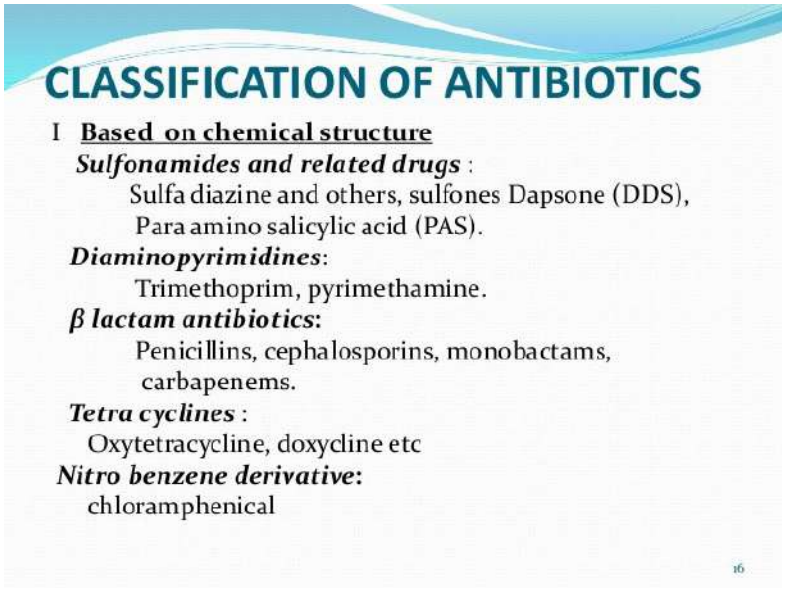
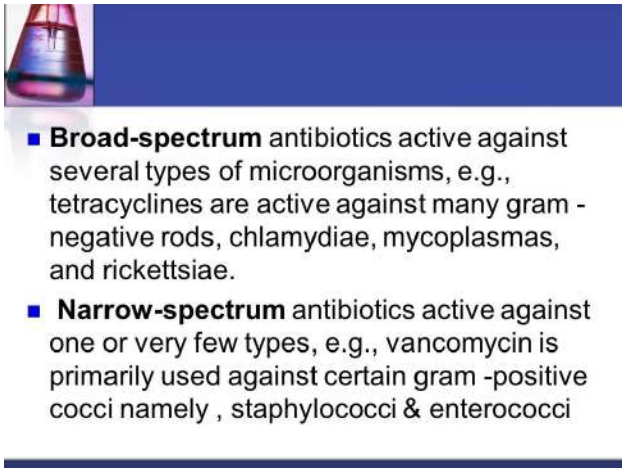


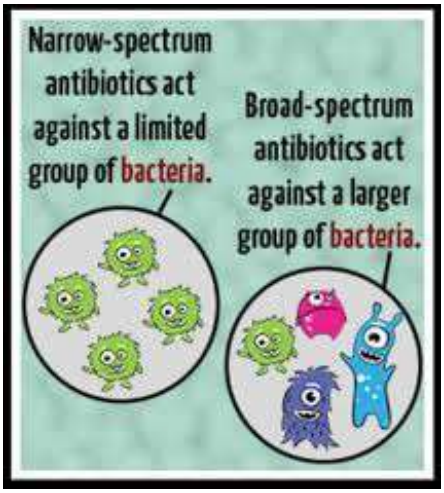
Table 25.1 Classification of Antibacterial Drugs Based on Cidal and Static Actions.

Bactericidal	Bacteriostatic
penicillins	tetracyclines
cephalosporins	chloramphenicol
aminoglycosides	macrolides
trimethoprim/sulfa combination	lincosamides
bacitracin,nitrofurans	sulfa drugs
metronidazole	trimethoprim
polymyxins	erythromycin
novobyocin	
fluoroquinolones	

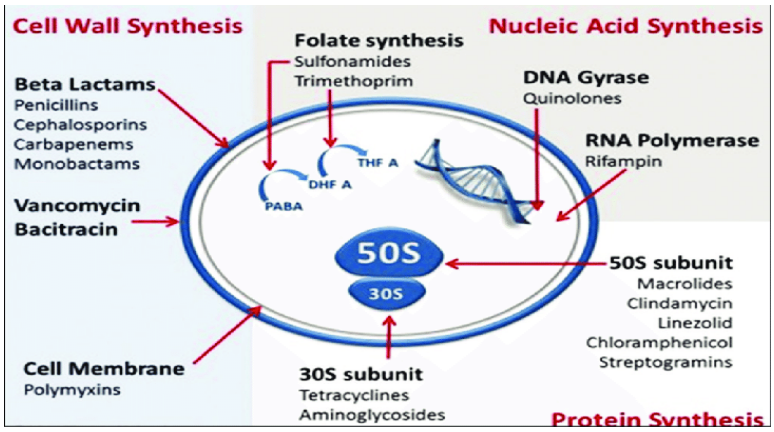
Based on Spectrum of activity

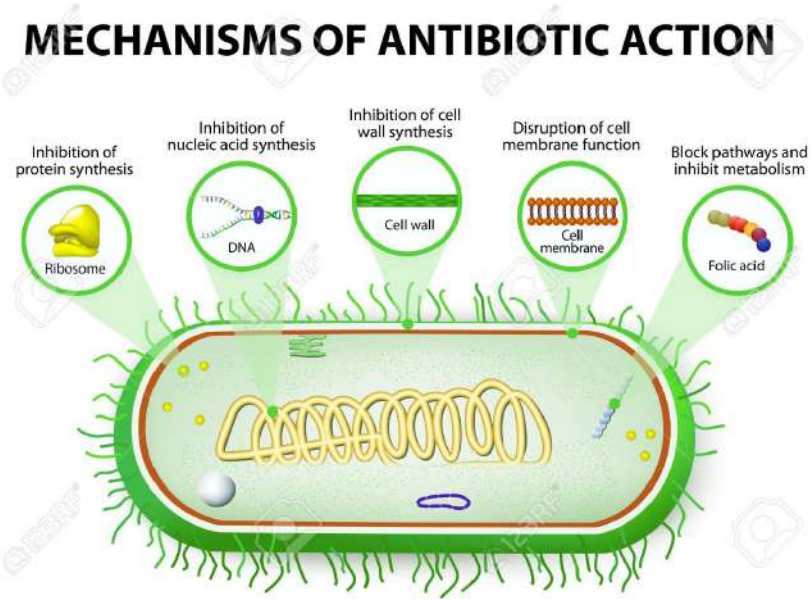


- **Broad-spectrum** antibiotics active against several types of microorganisms, e.g., tetracyclines are active against many gram - negative rods, chlamydiae, mycoplasmas, and rickettsiae.
- **Narrow-spectrum** antibiotics active against one or very few types, e.g., vancomycin is primarily used against certain gram -positive cocci namely , staphylococci & enterococci

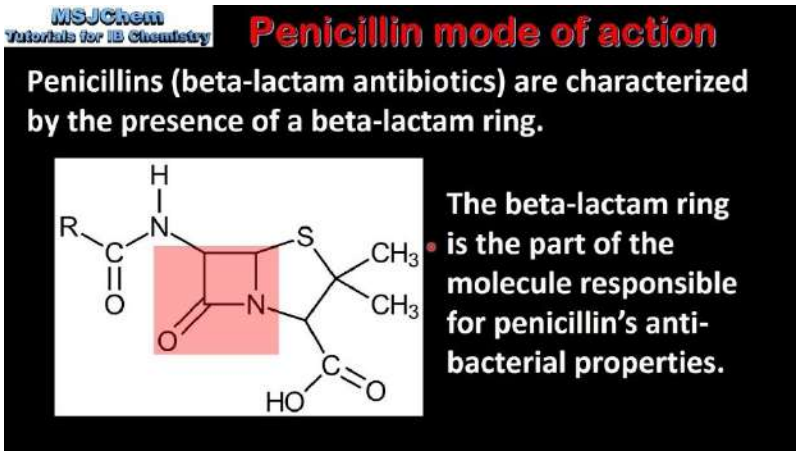


Based on the Mode of Action





Penicillin



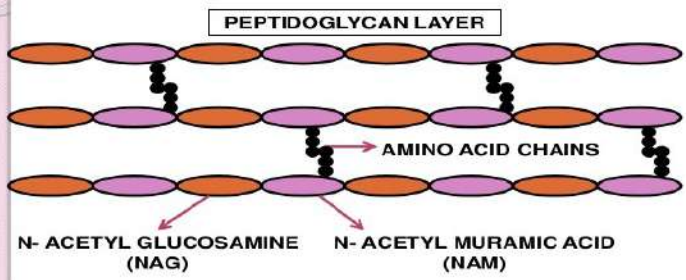
Mechanism of action

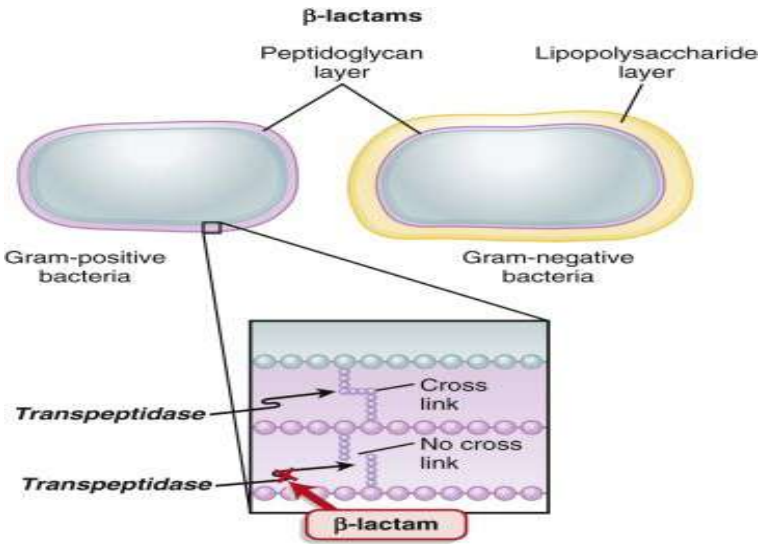
- Interfere with synthesis of bacterial cell wall.
- Cell wall composed of peptidoglycan, glycon consist of two amino sugars;
- 1)N-acetylmuramic acid (NAcM).
- 2)N-acetylglucosamine(NAcG).
- Peptidoglycan residues are linked together forming long strands &UDP is split off.
- Final step is cleavage of terminal D-alanine of the peptide by transpeptidase, process known as transpeptidation.
- This cross bridging provide neccessry strength to bacterial cell wall.
- β-lactam ABs inhibit the transpeptidase so that cross-linking does not take place.
- This will cause cell wall deficient forms of bacteria are produced

3

Mechanism of Action

- **Interferes with bacterial cell wall synthesis**





MECHANISM OF ACTION

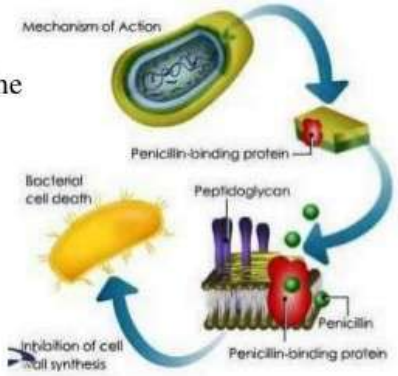
❖ Penicillins are **bactericidal** antibiotics as they kill the microorganisms when used at therapeutic dose.

❖ The synthesis of cell wall of bacteria is completely depended upon an enzyme named as **transpeptidase**.

❖Primarily, Penicillin inhibits the cell wall of bacteria by blocking transpeptidase after binding to **penicillin-binding protein (PBP)** and prevents its synthesis.

Result: bacteria cells die from cell lysis.

❖ Penicillins do not kill other cells in the body.



10. MECHANISM OF ACTION OF PENICILLINS

1.Penicillin-binding proteins:

Penicillins inactivate numerous proteins on the bacterial cell membrane. These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium.

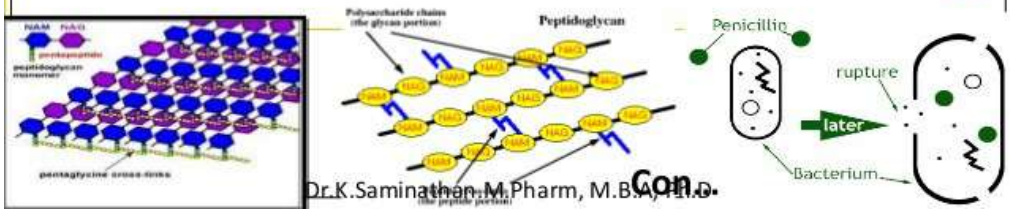
2.Inhibition of transpeptidase:

Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity. As a result of this blockade of cell wall synthesis.

3.Production of autolysins:

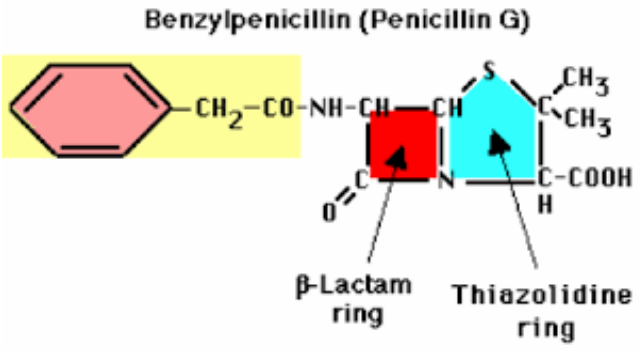
Many bacteria, particularly the gram-positive cocci, produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall.

11

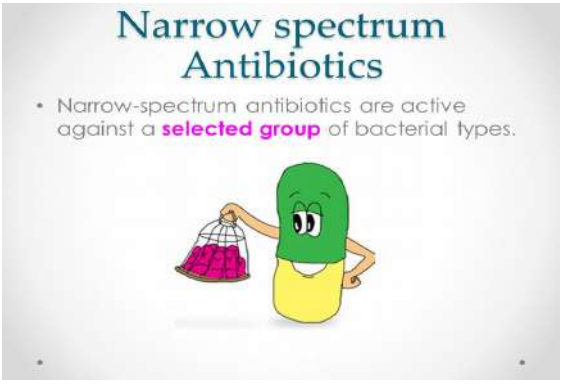


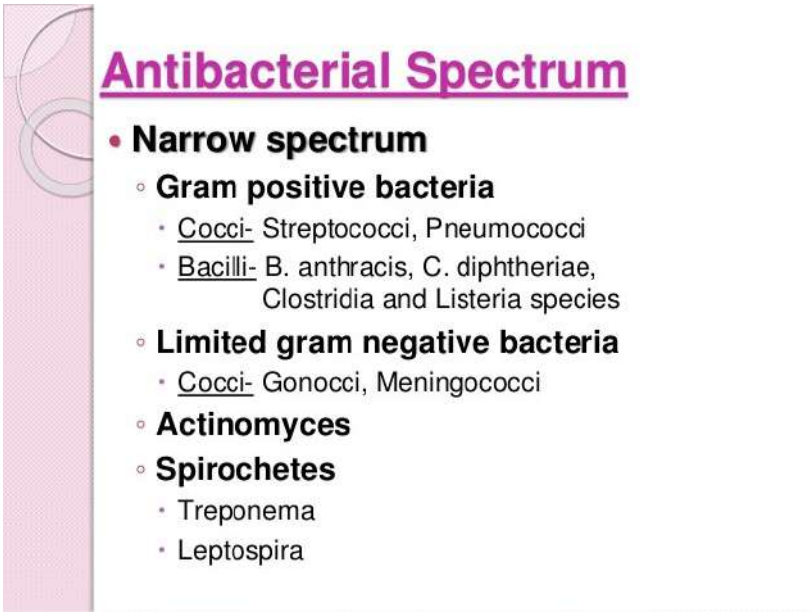
Dr.K.Saminathan, M.Pharm, M.B.A., Ph.D.

Con.



Most active





Streptomycin

- Streptomycin is characterised chemically as an aminoglycoside antibiotic.

Mechanism of Action of Streptomycin

Streptomycin is a protein synthesis inhibitor. It binds to the small 16S rRNA of the 30S subunit of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit.

- -Protein Syn . Is hampered
  - *Interferes with chain initiation
  - *Induce misreading of mRNA
  - * Incorporation of incorrect Amino Acid into peptide
  - ↓
  - Formation of Nonfunctional /toxic protein
  - *Cause break up of polysomes into monosomes
  - IRREVERSIBLE &LETHAL FOR CELL

This results in an unstable ribosomal-mRNA complex, leading to a frameshift mutation and defective protein synthesis; leading to cell death.

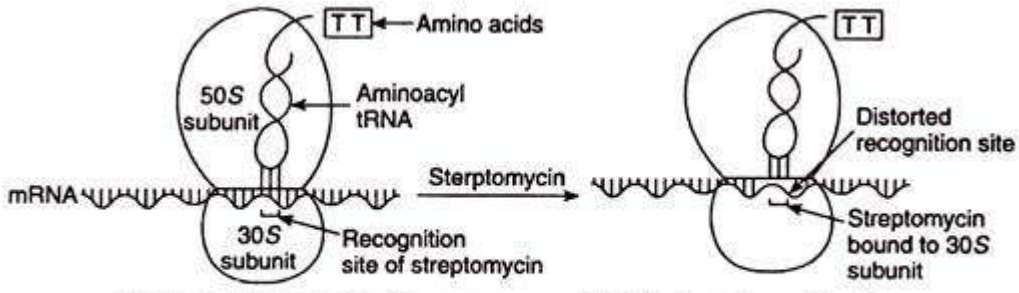
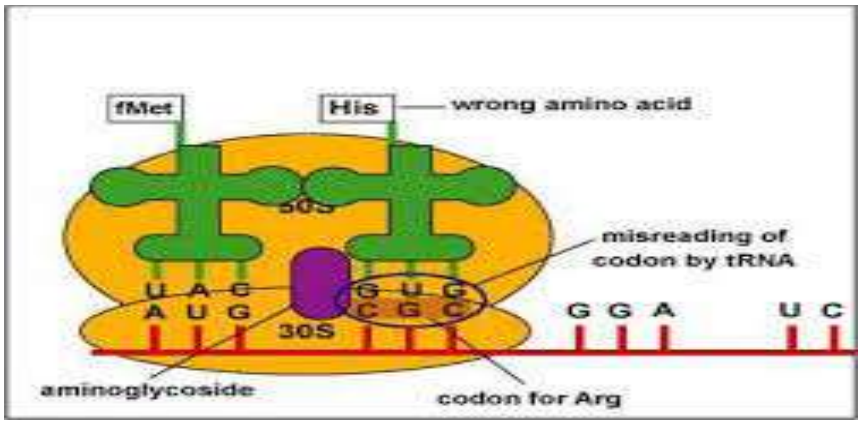
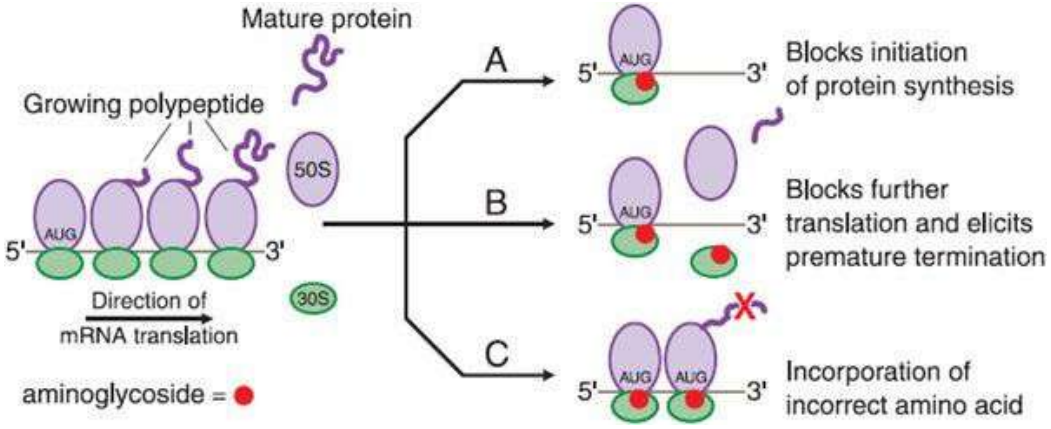


FIG. 45.10. Schematic representation of protein synthesis inhibition by streptomycin.





Effects of aminoglycosides on protein synthesis.

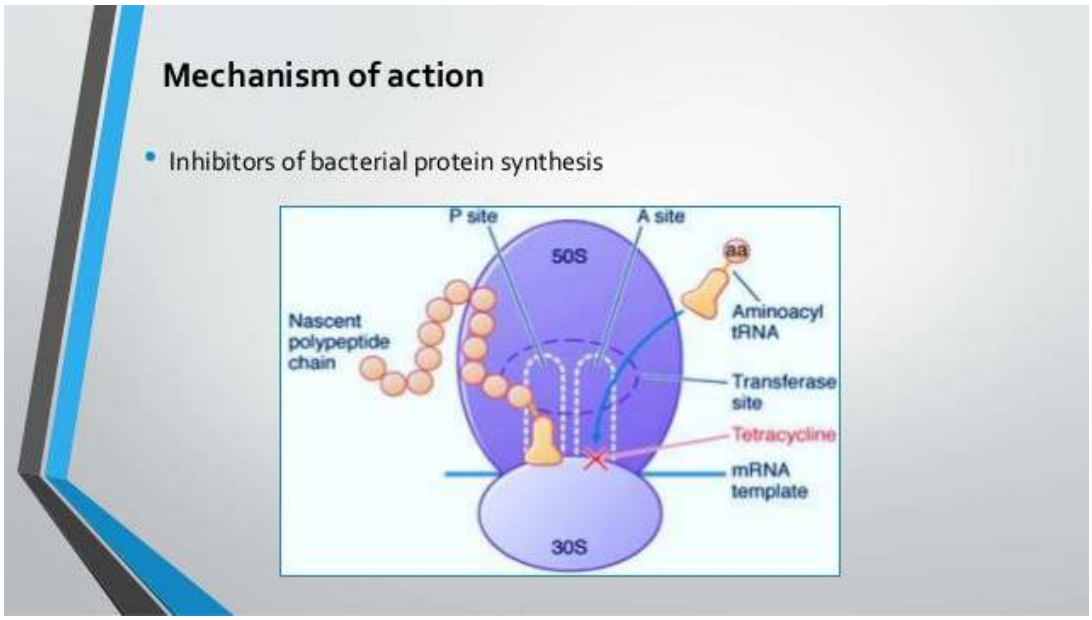
A. Aminoglycoside (represented by *red circles*) binds to the 30S ribosomal subunit and interferes with initiation of protein synthesis by fixing the 30S-50S ribosomal complex at the start codon (AUG) of mRNA. As 30S-50S complexes downstream complete translation of mRNA and detach, the abnormal initiation complexes, so-called streptomycin monosomes, accumulate, blocking further translation of the message. Aminoglycoside binding to the 30S subunit also causes misreading of mRNA, leading to **B,** premature termination of translation with detachment of the ribosomal complex and incompletely synthesized protein

C. incorporation of incorrect amino acids (indicated by the *red X*), resulting in the production of abnormal or non- functional proteins.

Antimicrobial spectrum

- Streptomycin is **bactericidal** and **broad spectrum** antibiotic.
- It is active against both gram-positive and gram-negative bacteria.
- Streptomycin is inhibitory for several species of *Mycobacterium* and is an effective antibiotic for treatment of tuberculosis caused by *M. tuberculosis*.
- Streptomycin is toxic to humans and other animals and causes side effects such as allergic responses, loss of hearing, nausea and kidney damage. Highly purified streptomycin is nontoxic when given in small doses, but it appears to have a cumulative detrimental effect on nervous system when given as a medication over long periods of time.

Tetracycline



- Messenger RNA (mRNA) attaches to the 30S subunit of bacterial ribosomal RNA.

- The P (peptidyl) site of the 50S ribosomal RNA subunit contains the nascent polypeptide chain; normally the aminoacyl t-RNA charged with the next amino acid to be added to the chain moves into the A (acceptor) site, with complementary base pairing between the anticodon sequence of t-RNA and the codon sequence of mRNA.

- Tetracycline inhibits bacterial protein synthesis (translation) by binding to the 30S subunit and blocking t-RNA binding to the A site.

- Terminates translation process

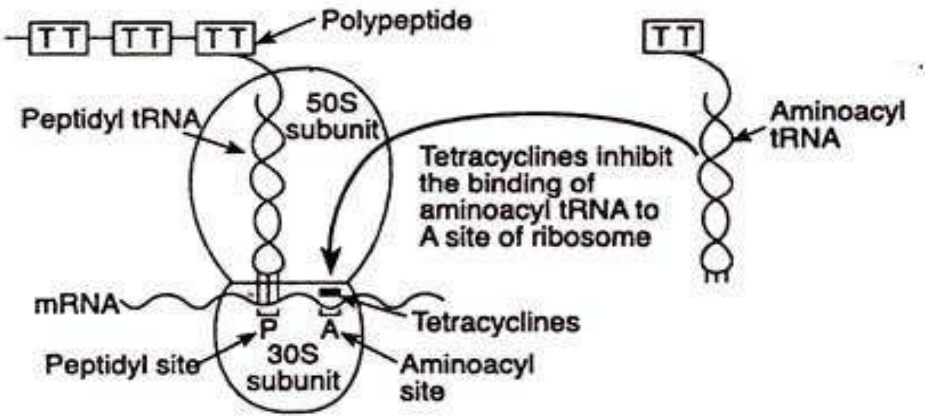


FIG. 45.15. Schematic representation of mechanism of action of tetracycline antibiotics.

Antimicrobial spectrum

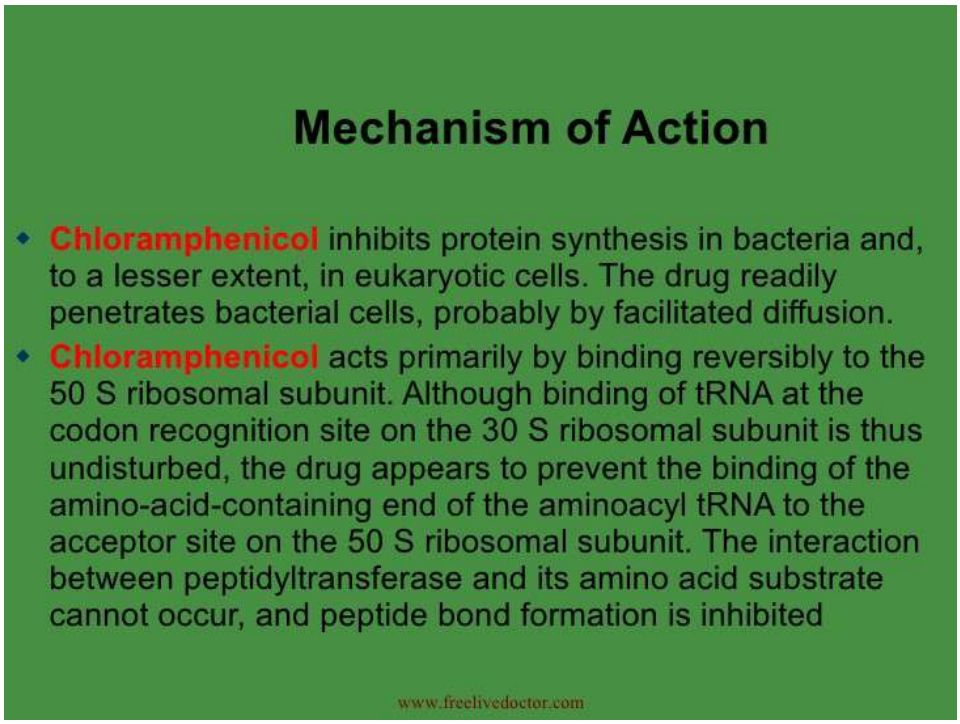
- Tetracyclines are broad-spectrum bacteriostatic antibiotics active against gram- negative and gram-positive bacteria, rickettsias, chlamydias, and mycoplasmas.

- Due to their close similarity in chemical nature, cross resistance of pathogens to them is common, i.e., a pathogen developing resistance to any one of them may show resistance to rest of them.

- Tetracycline, in general, shows low toxicity, quick absorbability, and quick excretability. Therefore these are very suitable antibiotics, but with a serious drawback which is that they destroy the natural intestinal flora and, as a result, an undesirable development of resistant staphylococci and yeasts (e.g., Candida) may gain upper-hand.

- High doses of tetracycline may cause side effects such as nausea, diarrhoea, yellowing of teeth in children, and damage to the liver and kidneys.

Chloramphenicol

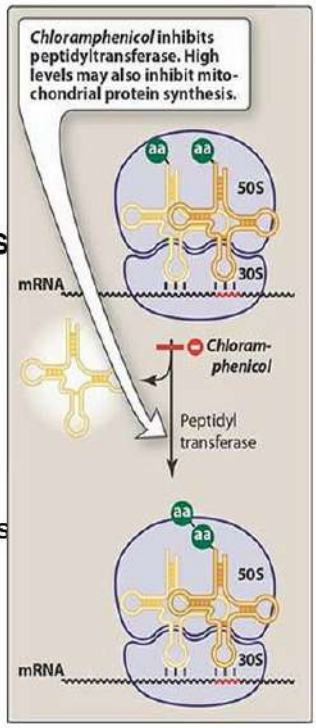


Mechanism of Action

-It readily penetrates bacterial cells, by facilitated diffusion.

-It acts primarily by binding reversibly to the 50S ribosomal subunit. The drug prevent the interaction between peptidyltransferase and its amino acid substrate, and peptide bond formation is inhibited .

Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria,protein synthesis in these organelles may be inhibited at high circulating *chloramphenicol levels, producing bone* marrow toxicity.



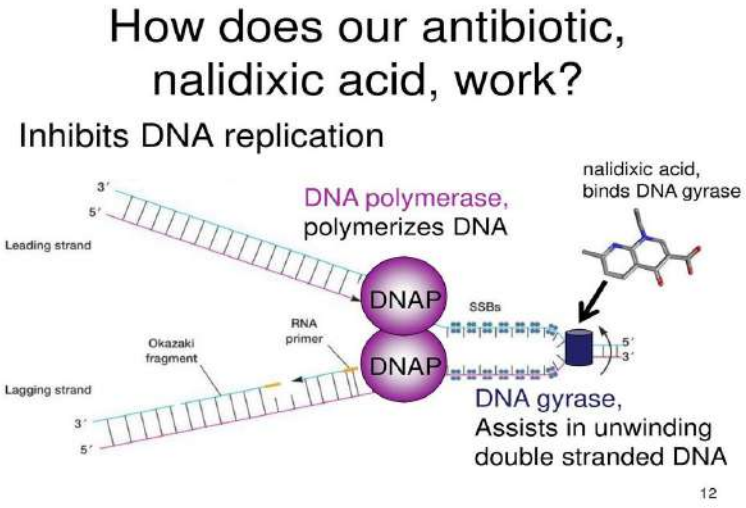
Antimicrobial spectrum

Chloramphenicol

- Bacteriostatic, broad-spectrum antibiotic.
- Active against both aerobic and anaerobic gram-positive and gram-negative organisms.
- Active also against rickettsiae.
- Haemophilus influenzae, N. meningitidis, and some strains of Bacteroides are highly susceptible, and for them chloramphenicol may be bactericidal.
- Excretion
  - changed and unchanged drug excreted by urine.
  - A small amount of active drug is excreted into bile or feces.
- Inactivated in the liver by **glucuronosyltransferase** and is rapidly excreted (80–90% of dose) in the urine.

Nalidixic Acid

- Non fluorinated quinolone



Mechanism of Action

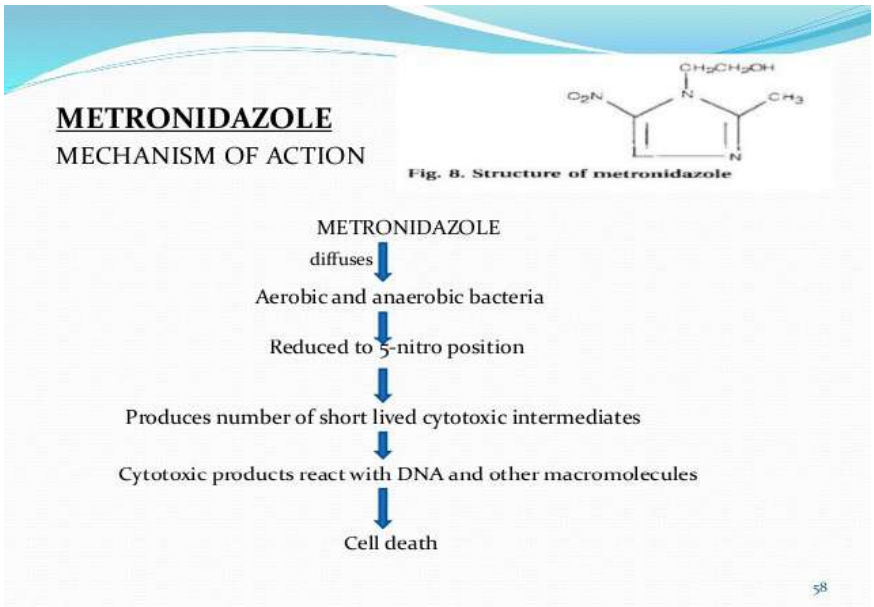
- Inhibit the replication of bacteria by interfering with the action of DNA gyrase during bacterial growth and development
- Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication.
- The gyrase is composed of two A subunits and two B subunits. The A subunits can cut one of the double strands of the DNA which is ATP dependent reaction. The energy is provided by B units.
- Nalidixic acid is an inhibitor of A subunits. Therefore the action of gyrase is inhibited and DNA replication or transcription is blocked as a result of the death of bacteria.

Antimicrobial spectrum

- Nalidixic acid is bactericidal and is effective when administered orally.
- It is a broad spectrum antibiotic and active against both Gram-negative and some Gram-positive bacteria.
- It is more active against Gram-negative species, especially coliforms---- *E.coli*, *Proteus*, *Kleibseilla*, *Enterobacter*, *Shigella*

Metronidazole

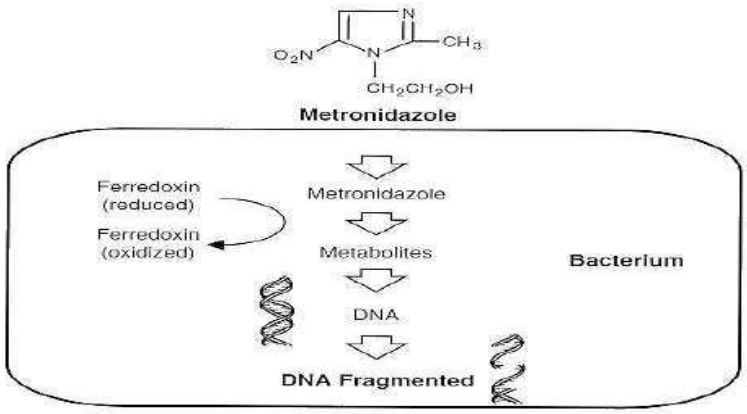
- Metronidazole is a nitro imidazole class of therapeutic drugs used mainly in the treatment of infections caused by susceptible organisms, particularly anaerobic bacteria and protozoa.



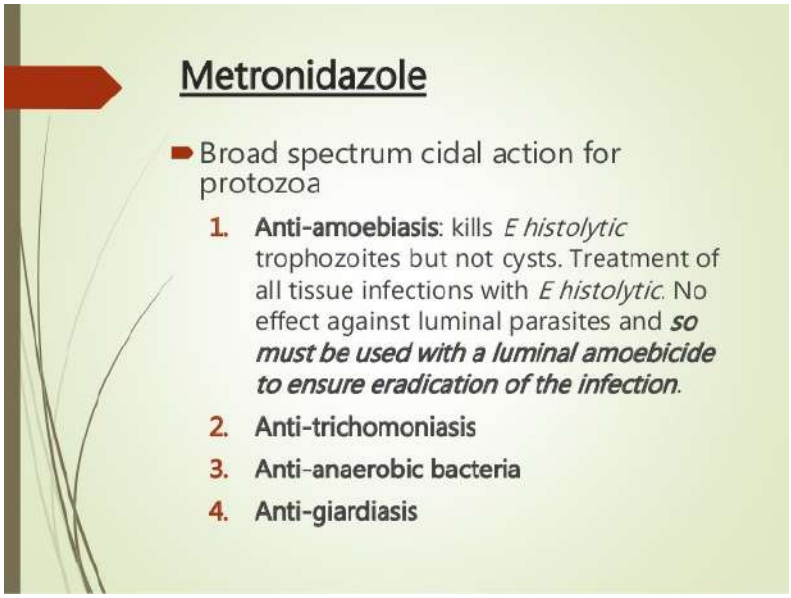
Mechanism of action of Metronidazole

- Metronidazole is a prodrug. It requires reductive activation of nitro group by susceptible organism. Its selective toxicity towards anaerobic and microaerophilic pathogens such as E. histolytica, G. lamblia, etc.
- These organisms contain electron transport components such as ferridoxin, small Fe-S proteins that have sufficiently negative redox potential to donate electrons to metronidazole.
- The single electron transfer forms a highly reactive nitro radical anion that kills susceptible organisms by radical-mediated mechanisms that target DNA, resulting in cell death.

14



Antimicrobial spectrum



Metronidazole (Flagyl®) Spectrum of Activity

- Good
  - Anaerobes: gram positive and gram negative
    - *Bacteroides, Fusobacterium, Clostridium, Prevotella*
  - Protozoa:
    - *Trichomonas, Entamoeba, Giardia*
- Moderate
  - *Helicobacter pylori*
- Poor
  - *Peptostreptococcus, Actinomyces, Propionibacterium*

Ability of these organisms to reduce metronidazole to its active form intracellularly

Reference

1. www.amboss.com
2. Biologydiscussion.com/medical-microbiology
3. Cbm.msoe.edu
4. Doctorlib.info/pharmacology/manual
5. www.google.com