General Characteristics & types of Antibiotics

Microbiology III

Introduction

- Microbial pathogens grown on and within the body of living organisms and cause disease, disability & death.
- Thus the control & destruction of microbial pathogens within humans and other animals and to prevent the disease is very important.
- The treatment of a disease with a chemical substance is called chemotherapy.
- The chemical substance used for this purpose is known as **chemotherapeutic drug/agent**.

Antibiotics

- Greek: *anti* – against, *bios* – life
- Antibiotics are the major part of chemotherapeutic agents of modern times that are used for treatment of diseases.
- They were defined by S.A. Waksman in 1945 as:
- Chemical substances produced by microorganisms which can kill or inhibit growth of other microorganisms at very low concentration.
- This definition has be changed, as antibiotics have been chemically modified in laboratory.
- **ANTIBIOTICS**: naturally produced microbial products or their derivatives that can kill or inhibit growth of other microorganisms at very low concentration.

General Characteristics

- Selective toxicity & therapeutic index
- Side effects
- Range of effectiveness
- Natural or synthetic
- Microbicidal or microbistatic
- Determination of effectiveness

Selective toxicity and therapeutic index

- Selective toxicity: it must kill or inhibit the microbial pathogen without damaging the host
- Therapeutic index: is the ratio of the toxic dose the therapeutic dose.
- Toxic dose: refers to the drug level at which the agent becomes too toxic for the host.
- Therapeutic dose: represents the drug level required for clinical treatment for a particular infection.
- Ex. Penicillin inhibits the cell wall synthesis in bacteria.

- **Side effects :**
- The undesirable effects on the host which can affect the same process or damage the host cell.
- Ex. Penicillin – allergic responses (nausea, anemia)
- Chloramphenicol – depressed bone marrow function, allergic reactions.

Antibiotics and their side affects:

Therapeutic Drug	Side Effects
Ampicillin	Allergic responses (diarrhea, anemia)
Bacitracin	Kidney injury if injected
Chloramphenicol	Allergic responses, kidney injury
Penicillin	Allergic responses (kidney, toxicity, anemia)
Streptomycin	Allergic responses , nausea, kidney damage
Tetracyclines	Allergic responses (kidney & hepatic injury, anemia

- **Range of effectiveness:**
- Narrow spectrum – effective only against a limited pathogens
- Broad spectrum – attack many different kinds of pathogens
- Based on microbial group – antibacterial, antifungal, antiprotozoan and antiviral.

Narrow & broad spectrum Antibiotics

Spectrum	Antibiotics
Narrow range	Penicillin (gram positive)
	Bacitracin (gram positive)
	Vancomycin (gram positive)
	Gentamycin (gram negative)
Broad range	Streptomycin (gram +ve, gram –ve, Mycobacteria)
	Chloramphenicol (gram +ve, rickettsia, chlamydia)
	Ampicillin (gram +ve, some gram –ve)
	Ciprofloxacin (gram +ve, gram –ve)

- **Natural or synthetic:**
- It can be synthesized by microorganisms or manufactured by chemical procedures independent of microbial activity.
- **Natural antibiotics:** synthesized by certain bacteria or fungi.
- Ex. **Bacitracin, Penicillin and Streptomycin**,
- **Synthetic antibiotics:** chemically synthesized.
- Ex. **Chloramphenicol, Isoniazid.**
- Many antiviral & antiprotozoan drugs.

- **Semisynthetic antibiotics:** are natural antibiotics that have been chemically modified by the addition of extra chemical groups to make them less susceptible to inactivation by pathogens.
- Ex. **Ampicillin, Methicillin**.

Natural & synthetic antibiotics

Source	Microorganism	Therapeutic drug
Natural	Bacteria:	
	Bacillus spp.	Bacitracin, Polymixins
	Streptomyces spp.	Streptomycin, Nystatin, Tetracycline
	Fungi:	
	Penicillium spp.	Penicillin, Griseofulvin
Synthetic		Chloramphenicol, isoniazid, Ciprofloxacin
Semi synthetic		Ampicillin, Methicillin

- Microbicidal or Microbistatic:
- **Microbicidal** – the agent kills the target pathogen.
- Its activity depends on concentration.
- At low concentration it may be microbistatic.
- The effect varies with the target species.
- An agent may be microbicidal for one species and microbistatic for another.

- **Microbistatic –** agents reversibly inhibits growth of the pathogen.
- If the agent is removed the microorganism will recover and grow again.
- They do not directly destroy the pathogen
- Elimination of the infection depends on the host's own resistance ability.

Microbicidal & Microbistatic Antibiotics

Mode of action	Antibiotics
Microbicidal	Penicillin, Streptomycin, Ampicillin, Bacitracin, Methicillin
Microbistatic	Chloramphenicol, Rifampin, Tetracyclin

- Determination of effectiveness:
- Minimal inhibitory concentration (MIC) – the lowest concentration of a drug that prevents growth of a particular pathogen.
- Minimal lethal concentration (MLC) – is the lowest drug concentration that kills the pathogen.
- A microbicidal drug kills pathogens at levels only two to four times the MIC
- A microbistatic drug kills at much higher concentration.

Types of Antibiotics

- The different types of antibiotics are classified based on:

➢ Target groups of microorganisms

➢ Structure

➢ Antimicrobial spectrum

➢ Mode of action

Based on target group of Microorganisms

1. Antibacterial 2. Antifungal and 3. Antiviral

Antibiotic category	Target group	Antibiotics examples
Antibacterial	Bacteria	Penicillins, Streptomycin, Chloramphenicol, Tetracyclins, Vancomycin, Rifamycin, Gentamycin
Antifungal	Fungi	Griseofulvin, Nystatin, Amphoptericin B
Antiviral	Viruses	Acyclovir, Azidothimidine (AZT), Amantadine

Based on structure

Chemical classes	Sub classes	Antibiotics
Alicyclic derivatives	Cycloalkane derivatives Steroids	Chlorohexamide Fusidic acid
Aliphatic compounds	Phosphorous containing compound	Fosomycin
Amino acid & peptides	**β-lactam antibiotics**	**Penicillins**
Aromatic compounds	**Benzene derivatives**	**Chloramphenicol**
Carbohydrate containing compounds	**Aminogyclosides**	**Streptomycin**
Heterocyclic with nitrogen	Nucleosides	Polyoxins
Heterocyclic with oxygen	Polyethers	Monensin
Macrocyclic lactones	Ansamycins	Rifamycin
Oxazolidone	Cyclic lactone	2-Oxazolidinone
Quinolone	4-Quinolone	Nalidixic acid
Quniones & related compounds	Teracyclines	Tetracycline

Based on Antimicrobial Spectrum

- It refers to the range of effectiveness of antibiotics on different kind of microorganisms.
- Mode of action – inhibition, killing or lysis
- Susceptibility of microorganisms to antibiotics varies
- Classified into 2 groups:

➢ Broad spectrum

➢ Narrow spectrum

Broad spectrum Antibiotics

- They attack many different kinds of microbial pathogens.
- Have wider medical use
- Bacterial pathogens: gram positive and gram negative, Mycobacteria, Rickettsia & Chlamydia.

Broad spectrum Antibiotics

Category	Antibiotics	Microbial groups attacked
Antibacterial	Ampicillin	Gram +ve, some Gram –ve
	Chloramphenicol	Gram +ve, Gram –ve , rickettsia & chlamydia
	Tetracyclines	Gram +ve, Gram –ve , rickettsia & chlamydia
	Rifamycin	Gram +ve, mycobacteria
	Streptomycin	Gram +ve, Gram –ve , mycobacteria
Antifungal	Ketoconazole	Fungal Dermatophytes and Candida
Antiviral	Cidofovir	Adenoviruses, papovaviruses

Narrow spectrum Antibiotics

- They are effective only against a limited variety of microbial pathogens.
- They are valuable for the control of microbial pathogens that fail to respond to other antibiotics.
- Ex. Vancomycin for Gram positive penicillin-resistant bacterial pathogens – *Staphylococcus*, *Bacillus*, and *Clostridium*.

Narrow spectrum Antibiotics

Category	Antibiotic	Microbial group attacked
Antibacterial	Penicillin	Gram positive
	Bacitracin	Gram positive
	Clindamycin	Gram positive, anaerobes
	Polymixin B	Gram negative
Antifungal	Nystatin	Yeasts (Candida), molds - Aspergillus

Based on mode of action

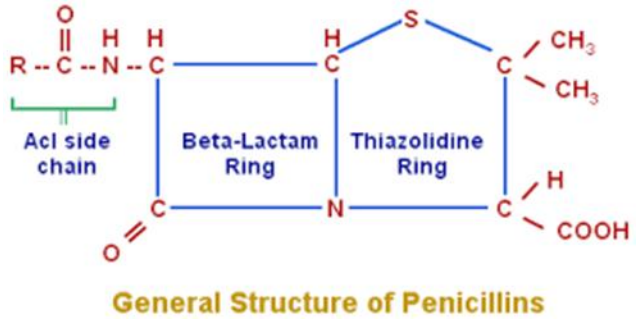
Mode of action	Antibacterial	Antifungal
Cell wall synthesis inhibitors	Penicillin, Vancomycin, Bacitracin	Polyoxins
Cell membrane inhibitors	Polymixin B	Nystatin
Protein synthesis inhibitors	Streptomycin, Chloramphenicol, Tetracyclines	-
Nucleic acid synthesis inhibitors	Rifamycin	5-Fluorocytosine
Microtubule formation inhibitors	-	Griseofulvin

Mode of action of Antibiotics

- **Penicillin**
- **Streptomycin**
- **Chloramphenicol**

Penicillins

- It was 1st discovered by Alexander Fleming in 1929
- Penicillin G is produced by the fungus *Penicillium notatum*
- Penicillins are a group of β-lactam antibiotics
- Penicillin types consisits of:
- Natural
- Semisynthetic



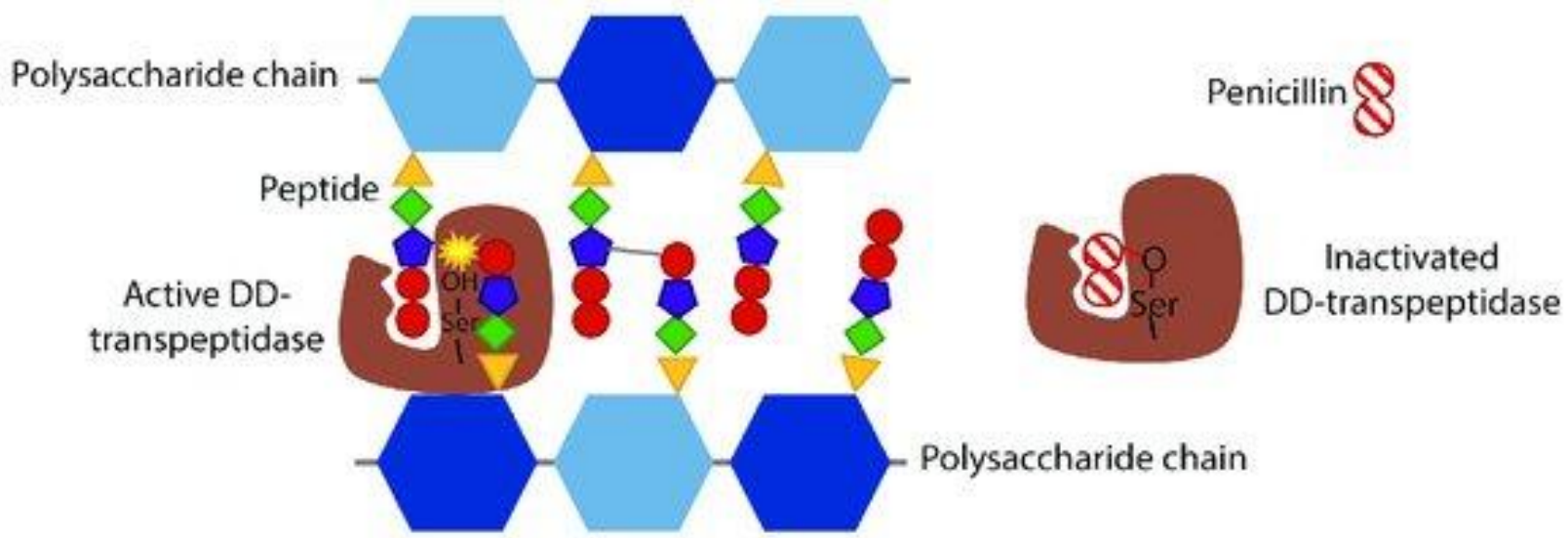
General Structure of Penicillins

- Penicillin G: is a narrow spectrum antibiotic
- Active against gram positive bacteria. Ex. Gram positive cocci & some spirochaetes.
- It is not active against gram negative bacteria as they are impermeable to these bacteria.

Mode of action

- **Penicillin interferes with the cell wall synthesis of bacteria.**
- Its activity is due to the β-lactam ring structure.
- **Inhibition of transpeptidase:**
- Penicillin inhibits the enzyme transpeptidase catalyzing the transpeptidation reaction because of their structural similarity.
- Transpeptidase is involved in the crosslinking of the polysaccharide chains of peptidoglycan in bacterial cell wall.
- Peptidoglycan is the main constituent in Gram positive bacterial cell wall.

Penicillin mode of action:



- **Penicillin Binding proteins:**
- Transpeptidase enzymes can bind to penicillin or other β-lactam antibiotics.
- They are also known as penicillin binding proteins (PBPs)
- The PBPs bind penicillin forming penicillin-PBP- complex
- they fail to catalyze the transpeptidation reaction but the cell wall continues to be formed.

- **Osmotic lysis of cell wall:**
- The newly synthesized wall is not cross-linked.
- Hence the synthesis of complete, fully cross-linked peptidoglycan is blocked.
- The newly synthesized cell wall is defective, and can not maintain strength.
- It fails to protect bacterial cells against osmotic shocks.
- This results in osmotic lysis – bursting of the plasma membrane and results in cell death.
- **Production of autolysins:**
- Also the penicillin-PBP-complex stimulates the release of autolytic enzymes.
- Cause autolysis – digest the existing cell wall.

Streptomycin

- Streptomycin was discovered by Selman Waksman, Schatz & Bugie in 1944.
- It was isolated from the *Streptomyces griseus*, a soil inhabiting actinomycete.
- Streptomycin is chemically a **aminoglycoside** antibiotic.
- It is bactericidal & broad-spectrum antibiotic.
- It is active against both gram-positive & gram-negative bacteria and *Mycobacterium*.

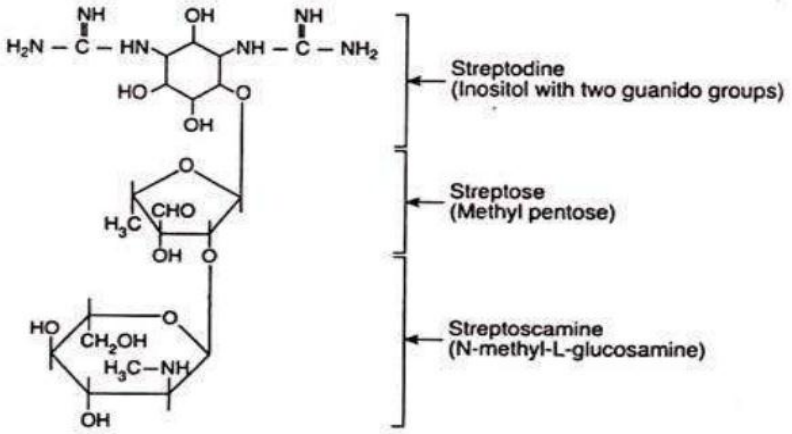


FIG. 45.9. Chemical structure of streptomycin.

Mode of action

- Streptomycin inhibits protein synthesis in bacterial cells by binding to the 30S subunit of the ribosomes.
- It causes a structural change which interferes with the recognition site of codon-anticodon interaction
- This results in misreading of the genetic message carried by mRNA.
- This causes defective protein synthesis, leading to cell death.

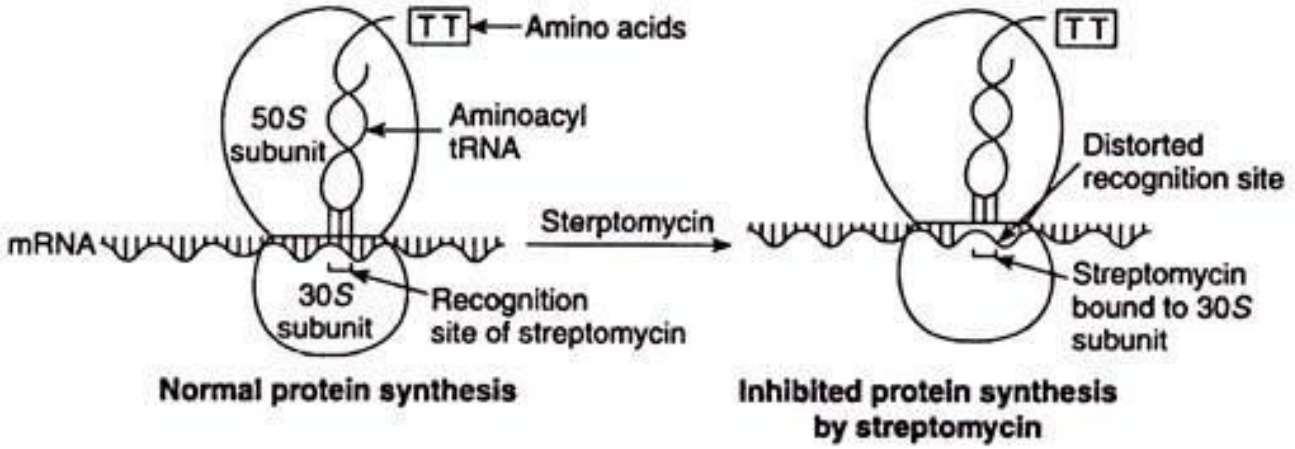
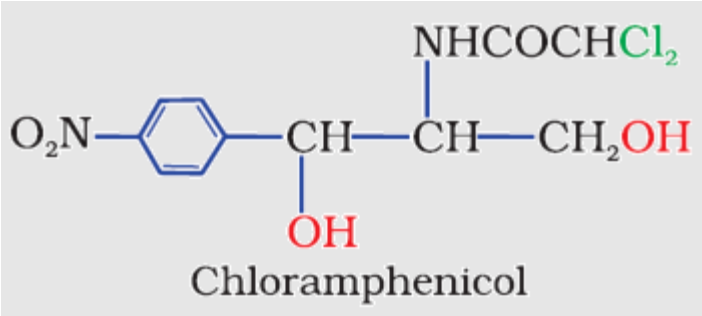


FIG. 45.10. Schematic representation of protein synthesis inhibition by streptomycin.

Chloramphenicol

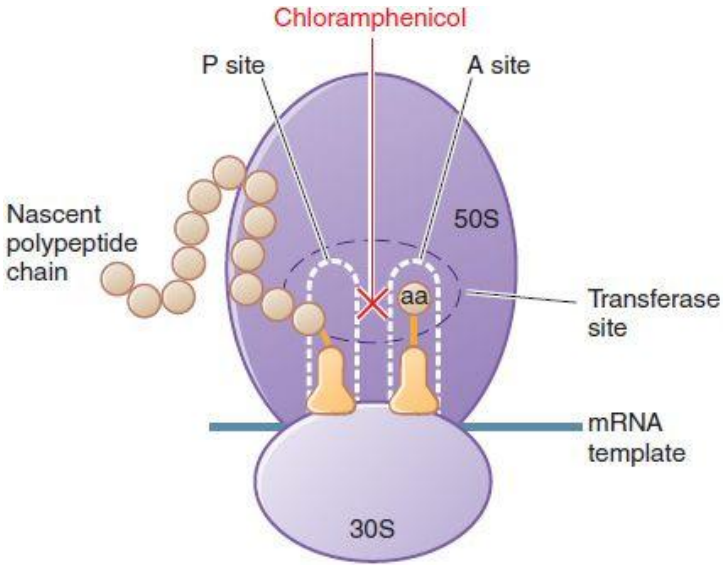
- It was isolated from *Streptomyces venezuelae* in 1947
- Its chemical structure is made of nitrobenzene ring with non ioinic chlorine.
- It is bacteriostatic & broad spectrum antibiotic.
- Active against gram positive & gram negative bacteria, Rickettsia & Chlamydia.



Chloramphenicol

Mode of action

- Chloramphenicol is a protein synthesis inhibitor in bacteria.
- It inhibits protein synthesis by binding irreversibly to the **50S ribosome subunit** of bacteria.
- It hinder the access of **aminoacyl-tRNA** to the acceptor site for incorporating amino acid
- It prevents formation of peptide bonds.
- Thus inhibits protein synthesis at peptidyl transferase reaction.



Multi Drug Resistance

- Drug resistance refers to the acquired ability of a microbial pathogen to **resist the effects of a antimicrobial drug** to which it is normally susceptible.
- To survive, the microbial pathogens have developed resistance mechanisms to neutralize or destroy their own antibiotics.
- **Horizontal Gene transfer:** Most antimicrobial drug resistance involves the **resistance genes** which get transferred among microorganisms by genetic exchange.

Drug resistance and disease treatment

- The drug resistance in microbial pathogens has become a serious threat to the successful treatment of microbial disease.

- Example of drug resistant microbes and their disease:
- ***Niesseria gonorrhoea:*** the causative agent of gonorrhoea.
- Gonorrhoea was 1st successfully treated with sulfonamides (1936), most strains became resistant and were treated with penicillin.
- After 16 years, penicillin-resistant strains emerged.

- ***Staphylococcus:***
- Most of the strains are resistant to penicillin G.
- Some are also resistant to methicillin or gentamicin, and can be treated with vancomycin.
- MRSA – Methicillin resistant *S. aureus*.

- ***Shigella:***
- Caused an epidemic of dysentry in 1968 in Guatemala causing 12,500 deaths
- Carried an R plasmid that gave resistance to chloramphenicol, tetracycline, streptomycin.
- A same type multipe-drug resistance resulted in typhoid epidemic caused by *Salmonella typhi* (In 1972, Mexico).

- ***Haemophilus influenzae:***
- *H. influenzae* type B causes childhood pneumonia, middle ear infections, respiratory infections and meningitis.
- It is resistant to tetracyclines, ampicillin and chloramphenicol.

Origin of Drug Resistance

- Drug resistance can be genetically encoded by microbial pathogen.
- These genes are present on both the chromosome and plasmids.
- Drug resistance by 2 means:
- Chromosome mediated: spontaneous mutations, transposons
- Plasmid mediated: R plasmids (resistance plasmids)

Drug resistance Mechanisms:

Bacteria become drug resistant using several different mechanisms:

1. Reduced permeability to antibiotic
2. Efflux/ pumping antibiotic out of the cell
3. Drug inactivation through chemical modification
4. Target modification
5. Development of resistant biochemical pathway

1. Reduced permeability to antibiotics:

- Bacteria prevent the entry of the drug.
- Many Gram-negative bacteria are unaffected by penicillin G
- As the drug fails to penetrate the envelope's outer membrane
- Decrease in permeabitilty also occurs as a result of loss of porin proteins. Ex. *E. col*i.

2. Efflux/ pumping antibiotic out of the cell:

- Microbial pathogens pump the drug out of the cell after it has entered.
- Some pathogens have plasma membrane translocases called **efflux pumps,** that expel drugs.
- These are non specific and can pump many different drugs.
- These proteins are often called multidrug-resistance pumps.
- Ex. *E. coli*, *Staphylococus aureus*

3. Drug inactivation through chemical modification:

- Many bacterial pathogens show resistance to drug by inactivating drugs through chemical modification.
- Ex. hydrolysis of the β-lactam ring of penicillins by the enzyme penicillinase.
- Drugs are also inactivated by the addition of groups.
- Ex. Acetylation of hydroxl groups in Chloramphenicol.

4. Target modification:

- Since the antibiotics acts on a specific target, resistance arises when the target enzyme or organelle is modified so that it no longer susceptible to the drugs.
- Ex. Affinity of ribosomes to chloramphenicol & erythromycin can be decreased by a change in 23S rRNA to which they bind.

5. Development of a resistant biochemical pathway:

- Resistant bacteria may either use an alternate pathway to bypass the sequence inhibited by the agent
- Or increase the production of the target metabolites.
- Ex. Bacteria resistant to sulfonamides use preformed folic acid from their surrounding rather than synthesizing it.

Transmission of drug resistance:

- Factors responsible for development & spread of drug resistance:

1. Drug misuse (wrong prescription to infections)
2. Extensive drug treatment (destroys normal microflora, leads to superinfection by drug resistant pathogens)
3. Movement of resistance genes (transposons)
4. Use of drugs in animal feeds
5. Use of triclosan (antibacterial substance in soaps)