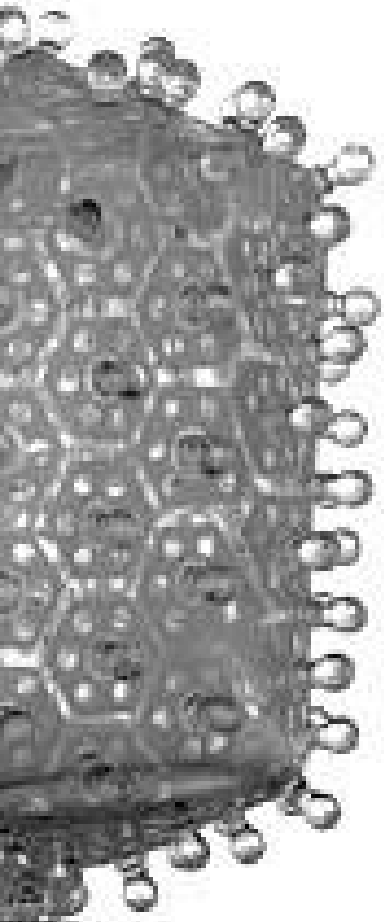


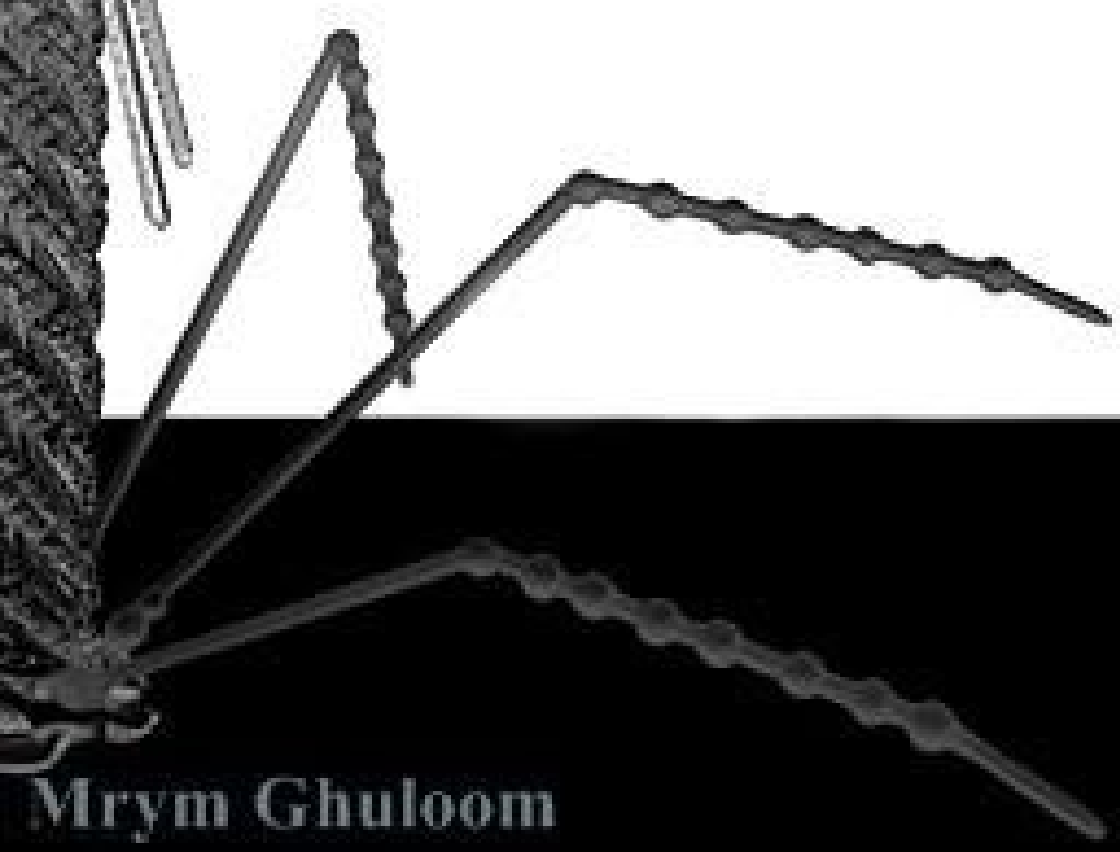
Microbiology

Lecture No: 13

Dr Name: Asem.Shehabi

Done by: Leen..Younis....

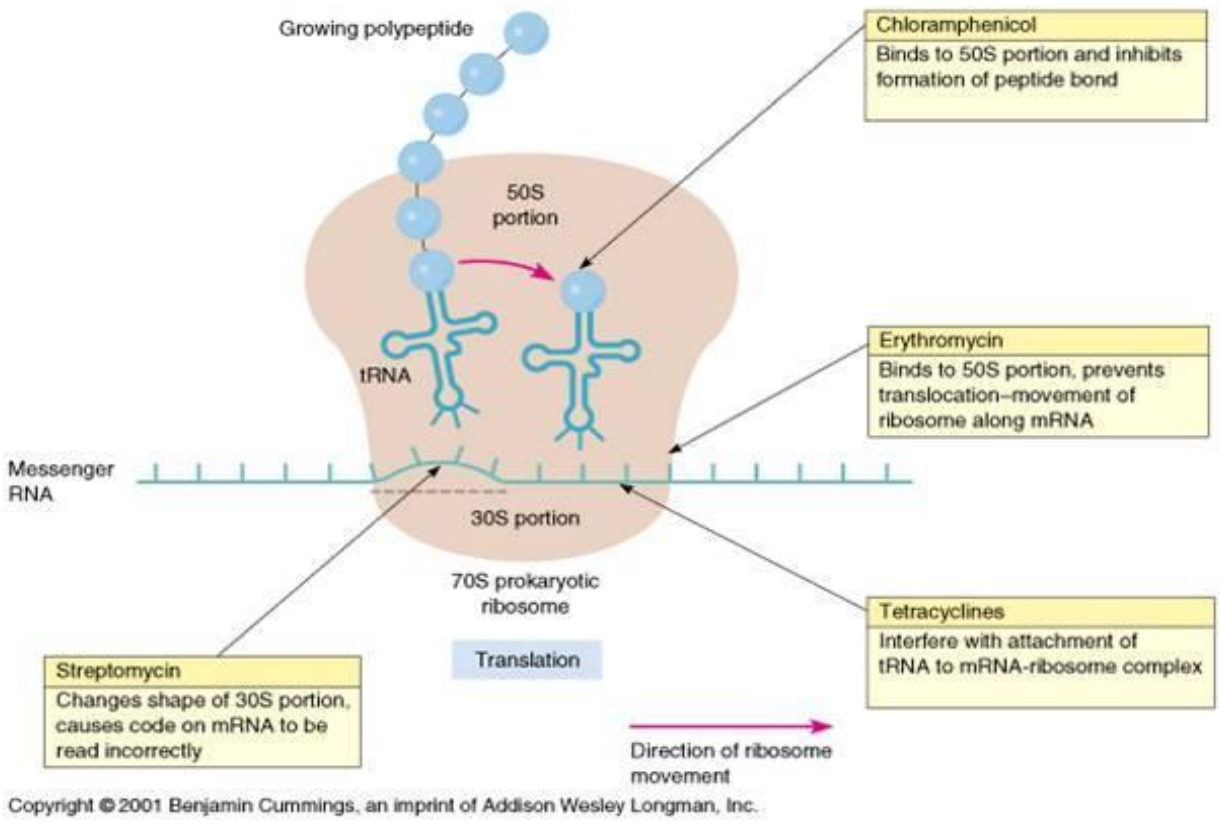
Sheet ■ Slide □



Mrym Ghuloom

Inhibiting Protein Synthesis

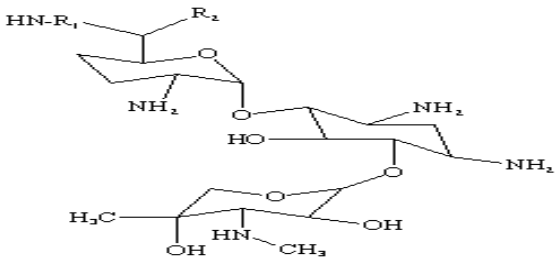
Continuing with our topic which is the antimicrobial drugs, and to understand the mechanism of action of some types of these drugs which are widely used in treatment of infection, this picture summarizes the general concept.



These types of antimicrobial drugs are related to inhibiting protein synthesis. That means that they interfere with ribosomes subunits (either the 30s or 50s) of the 70s bacterial ribosome. In other words, any interference with tRNA or the transfer of one amino acid in a subunit 50 or 30 or the inhibition of any enzyme that's responsible of translocation of small amino acids in order to produce the polypeptide necessary for the production of a specific protein for the growth of a bacterial cell. That might result in bactericidal effect.

According to that, we have 4 classes:

1. **<u>Aminoglycosides.</u>**



- A complex structure composed of 3 molecules of amino cyclic compound.
- Side chains can be acetyl, amino, hydroxyl, etc..
- Structure is represented by more than 6 important clinical drugs.
- Wide spectrum activity, their effect is mostly against G –ve and affects G+ve but to a lesser extent. **Except anaerobes,** they can't be used to treat anaerobic bacteria.
- Bactericidal effect.
- <u>Inhibition mechanism:</u> it inhibits the complex between tRNA and mRNA which inhibits the formation of the polypeptide chain that's important in protein synthesis.
- Used in hospitalized patients. They aren't given orally, only injected, done in the hospital or the health center through IM, IV.. to control the administration of the drug and the <u>side effects</u>.
- In some of these drugs, If the dose exceeds the recommended concentration, it can seriously affects the cranial nerve system causing deafness, damage in the kidney so the concentration should be controlled.

As we mentioned, there are 6 important types of aminoglycosides which are used;

Streptomycin and neomycin, introduced in the mid 1950's, they're rarely used due to their side effects.

Amikacin and Gentamicin are widely used to treat serious and hospitalized infections caused by G-ve bacteria. The use of these drugs might result in developing resistance against them, specifically their side chains (hydroxyl,

amino and acytel..) by producing adenylate ,phoshphorylate and acytelate enzymes. These enzymes are important for the effectiveness of the drug. It will be produced by the bacteria in relation to the chromosome, if there's a change in the sequence of the chromosomes due to the presence of the drug so it develops these enzymes or it might be associated with the plasmid.

2. **Tetracyclines**:

- Are not bactericidal, they're bacteriostatic; inhibition of this drug is limited according to the concentration. If there's no immune response by the patient, it'll result in regrowth of the bacteria and infection might persist. (The presence of tetracyclines may not be enough to kill the bacteria).
- Wide spectrum activity, considered one of the most effective drug against a wide range of G-ve and G+ve.
- It has been used successfully since the mid 1950's till now to treat infections despite that its misuse leads to some side effects.
- Inhibition mechanism: It inhibits tRNA resulting in inhibition in the production of the polypeptide in relation to the 30s subunit of the bacterial ribosome.

Tetracycline should be mainly given to adults, not to children below the age of 8 years because it might stain and interfere with the growth of teeth, it also shouldn't be given to pregnant women as it might cause side affects on the fetus.

The old and classical forms of tetracycline (chlortetracycline, fluortetracycline) were related to so many side effects. The modified forms of it, which were done by changing the structure and reducing the side chains especially the hydroxyl one like (**Doxcycline and Minocyclline**) are now the used forms, they're used in *less amounts* therefore reducing the side effects and used for treatment of cholera in the respiratory tract, mycoplasma, chlamydia and other infections.

Bacteria can develop resistance to tetracycline. However, it is slowly developed being similar to aminoglycosides in that, and both developing slower resistance than penicillin or cephalosporin.

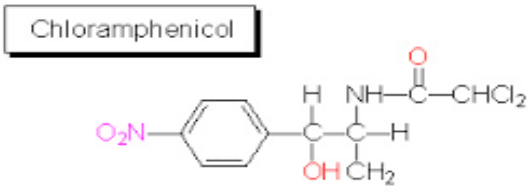
If any change in the cell membrane permeability occurs, tetracycline will be kept outside the membrane and it won't reach the cytoplasm and interfere with the protein synthesis.

Also, the change in the membrane will inhibit the pumps (not allowing tetracycline to cross the membrane), and instead of pumping it to the inside, it'll be towards the outside.

So resistance is done by **reduced active transport** and **pumping efflux.**

They have developed a new type of tetracycline called Tigecycline, it's a complex tetracycline which doesn't have a wide spectrum like doxcycline and minocycline, works against G-ve to treat serious infections. This drug is very expensive and it has been produced only two years ago. It is considered as a second treatment not first, or it might be used for cases of serious infection that can't be treated by other antimicrobial drug.

3. Chloramphenicol



- Has a small structure.
- Can be easily distributed in the blood stream, distributed everywhere in the body including the spinal fluids in cases of meningitis (the presence of bacteria in the spinal fluid) following infection of blood or respiratory tract reaching the internal parts of the body.
- One of the best drugs that cover the intracellular organisms as it goes inside macrophages and monocytes, for example.
- Used to treat meningitis
- Very cheap and available on the market.

- Wide spectrum of activity, used against infections especially if we don't know the causative agent, in relation to septicemia and meningitis.
- It is bacteriostatic. But it can go bactericidal as we increase the concentration.

*Notice that the border line between a drug being bactericidal and bacteriostatic depends on the amount of drug. But increasing the concentration of the drug in the blood stream or the abdominal tissue might cause side effects.

Which is why chloramphenicol shouldn't be used by increasing the dose, it should be given in a low dose for fewer side effects. It is often used when treating cases of severe infections of meningitis, septicemia or typhoid fever.

In rare conditions, less than 0.5% (1 in 1,000 of the cases), chloramphenicol might cause a toxic effect on bone marrow and plastic anemia.

4. Macrolides

- Have a complex structure (composed of 14- 16 rings).
- Have different types of side chains, 10-14 types (hydroxyl,carboxyl, amine)
- In comparison to aminoglycosides, tetracyclines and chloramphenicol, it is considered as a safe drug.
- Have a bacteriostatic effect.
- Inhibition mechanism: Affect the 30s ribosomal subunit by inhibiting the translocation and formation of the polypeptide.
- Widely used in clinical medicine.
- Excellent for treatment of respiratory tract infections caused by a variety of microorganisms.
- Narrow spectrum. Used mostly against G+ve associated in respiratory infections.

First classical form of macrolides is represented by erythromycin (taken orally) is given 2-4 grams, 4 times per day. Then, they developed long active macrolides (Clarithromycin, Azithromycin) given two times a day. And there is a tablet that

works for 24 hours, it's easier for the patient and produces the same effect but it's expensive.

There are two drugs, in relation to macrolides which are harmful to some extent. They are related in structure and mechanism of action against the 30s bacterial ribosome subunit. In addition, these drugs have a narrow spectrum affecting G+ve (staphylococcus and streptococcus) as well as anaerobic bacteria. **The first drug that affects anaerobes**

KEEP IN MIND! Aminoglycosides, chloramphenicol, tetracycline and macrolides (erythromycin) → **can't cover anaerobic bacteria.**

- **Lincosamides: lincomycin & clindamycin**

- Lincomycin is more used.
- Commonly used by dentists since the oral cavity is composed of facultative anaerobic and anaerobic bacteria, and the anaerobic bacteria is more common so it can cover any abscess or any form of infection.
- It is also used in treatment of bone infection which is not covered by other drugs.
- Used for anaerobes

The majority of intestinal bacteria, about 95% of the it, is anaerobic bacteria, so lincomycin might change the *biological equilibrium* of the intestinal flora, by affecting a large number of anaerobic bacteria.

Lincomycin affects G+ve and G-ve bacteria except **clostridium difficile** which is an anaerobic spore forming bacteria found in few numbers in the intestine of humans, consists of 20-30% of the normal bacteria found in a colon of a healthy person.

Under certain conditions, especially when using this lincomycin drug -in addition to any other drug- that affects the anaerobic bacteria, an increase in the number of clostridium difficile is observed.

This increase of Clostridium Difficile in the intestinal canal produces toxins (enterotoxins) that causes bloody diarrhea, irritation in the mucosa of the large intestines, necrosis in large intestine and causes **Pseudomembranous colitis** which is a serious disease that might lead to death. In such a case, lincomycin should be stopped and replaced with another drug, to decrease the effect of the clostridium difficile.

- **Fusidic acid**

- Has a complex structure
- bactericidal
- Affects G+ve, cocci (staph aureus)
- Used to treat infections in the skin due to staph (staphylococcus aureus or staphylococcus coagulase-negative "epidermidis").
- Often associated with majority of wounds and superficial skin infection.
- Inhibition mechanism: it inhibits protein synthesis in a similar way to macrolides and lincomycin.

* Inhibition of nucleic acid synthesis

This group consists of several subgroups; we'll simplify it and mention the mechanism of action with little details.

1. **Nalidixic acid.**

- A complex structure (Quinolone structure)
- Inhibit *DNA Gyrase* which is responsible for developing the double helix, affecting the DNA.
- Bactericidal
- Works mainly against **G-ve bacilli** **this is not mentioned in the slides!**

Knowing the type of organisms the drug affects is important in understanding the pharmacokinetics of the drug.

Nalidix acid is an oral antimicrobial drug, produces action in the stomach or the intestine. Works great for 95% of bacteria in urinary bladder which means

that this drug is only effective in the urinary tract infections. It is considered as an anti uropathogenic drug. Exactly like Nitrofurantoin.

2. Nitrofurantoin

- Has a complex structure, by the presence of a nitrogen atom.
- It's not a quinolone
- Considered as an anti uropathogenic drug, used for treatment of urinary tract infections especially caused by E.coli.
- Bactericidal.

This is also related to pharmacokinetics, in order to control urinary tract infections, you need to give nitrofurantoin at least for two weeks to eradicate the presence of microorganisms in the urinary bladder or from other parts of the urinary tract. While in nalidixic acid, one week may be enough to cure the patient.

[Introducing of a (F) atom to the quinolone structure of nalidixic acid gives Floroquinolones].

3. Floroquinolones

- Widely used in treatment of different infections in the respiratory tract and gastrointestinal tract.
- Bactericidal effect.
- Wide spectrum activity G-ve and G+ve.
- Replaces penicillin, cephalosporins, aminoglycosides and other drugs.
- Mechanism: inhibits *DNA Gyrase* and Interferes with transcription of tRNA.
- Antimicrobial resistance against it (especially against the inhibition of DNA Gyrase) develops slowly. Unlike other drugs that can be recognized during treatment and develop resistance during the treatment.
- Many types of floroquinolones, most used is ciprofloxacin in respiratory tract, gastrointestinal and urinary tract infections, levoflocaxin mainly in repiratory tract infection, there's also ofloxacin and norfloxacin etc..

  *It's enough to keep in mind at least 3 of these drugs.

4. Rifamycin/Rifampin

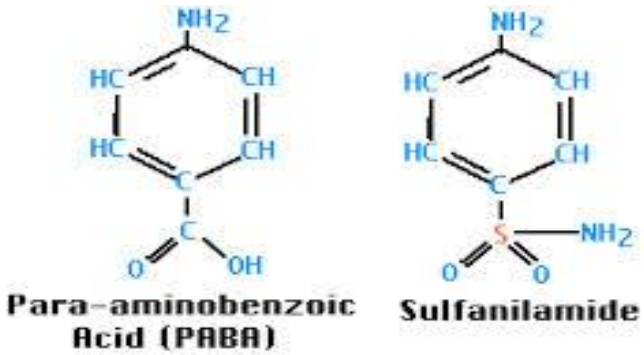
- Related to the inhibition of nucleic acid, mainly the RNA polymerase. Leading to inhibition of the growth of bacteria.
- Bactericidal effect
- Shouldn't be used for treatment of all types infections despite the fact that it might work for many infections but according to the WHO it recommends its use for certain infections that include TB, Malta fever.
- Should be kept as a last resort for treatment of certain infections.
- Affects intracellular organisms, being similar to chlorophenicol and doxacycline or minocycline in combination with rifampicin. For example the microorganism that causes the malta fever, the brucellosis, usually resides in the macrophages and monocytes.
- Should NOT be used in treatment as a single drug, especially in cases of TB.

Inhibition Synthesis of Essential Metabolites

Humans need folic acid from nutrients (food) for protein synthesis. Whereas bacteria can produce their own folic acid, in order to do that, they must have a chemical structure called (para aminobenzoic acid - PABA) which is the first subunit that must be available in the medium so that they can later produce – via chemical reactions- tetrahydrofolic acid which is then turned to folic acid.

PABA, para aminobenzoic acid, is an essential metabolite.

Sulfonmide drug, which was developed in the 1934, has a similar structure to para aminobenzoic acid. The sulfonamide drug might compete with PABA for the enzyme that's used to turn dihydrofolic acid to tetrahydrofolic acid.



Sulfonamides are **bacteriostatic,** with inhibition action related to the amount of the drug, competes with para aminobenzoic acid. Normally, in order to use it for treatment of infections, the patient should be given (4-8) grams which is a huge amount of a chemical substance. It has been replaced by a modified form of sulfonamides also in combination with other chemical structures, that resulted in Cotrimoxazole.

Contrimoxazole is a combination of two drugs; sulfamethoxazole and trimethoprim (first available in the market in 1960's)

- Wide spectrum, used against G-ve and G+ve.
- Used for upper respiratory tract and urinary tract infections. Pediatricians use it for treatment respiratory tract infections caused by streptococci and other agents.
- Bacteria can develop resistance.

Antituberculosis drugs

- Used in treatment of tuberculosis, pulmonary tuberculosis and other types of it.
- They all have one function which is the inhibition of Mycolic acid which is an essential part of the cell wall of mycobacteria, bacilli and not found in other types of bacteria, whether G-ve or G+ve.
- Uses a complex structure that causes damage to the cell wall.

Mycobacteria is a difficult organism, not easily treated with any drug, the treatment duration is from 3 months to a year or 2. All cases of TB should be treated with combinations of 2 or 3 drugs according to response of the patient and development of resistance.

For example, the use of antiTB drugs like Isoniazid (INH) with rifampin or with ethambutol or cycloserine, and so on..

AND FINALLY**..**

Metronidazol

The only available drug that's used for treatment of **2 classes** of microorganisms; anaerobic bacteria and protozoa (Ameoba, garnia) .

It's a complex structure and It might cause side effects especially if used for a long time.

GOOD LUCK! :)
LEEN YOUNIS