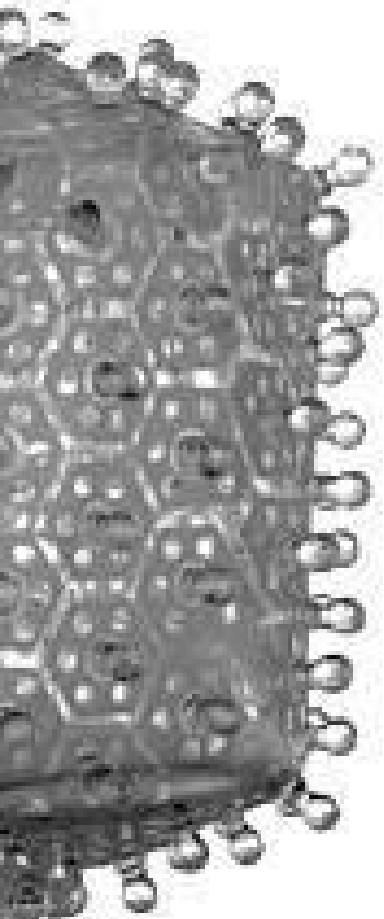


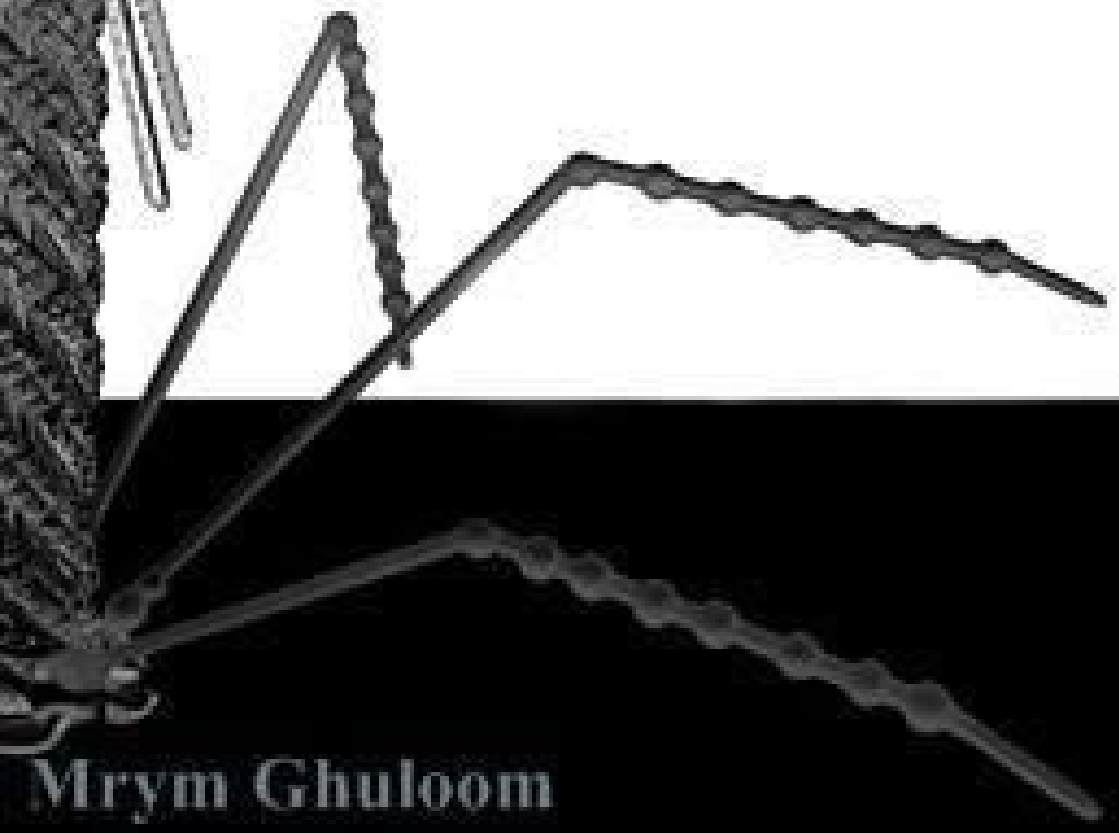
Microbiology

Lecture No: 11

Dr Name: Dr.Asem.Shehabi

Done by: Esra Odah

Sheet ■ Slide □



Mrym Ghuloom

Antimicrobial Drugs

♯ quick review of the previous lecture

As we said in last lecture we classified drugs according to:

1) the mechanism of action:

A. Bacteriostatic : Inhibition of the growth of bacterial cell.

B. Bactericidal: kill microbes.

2) the Range of activity/spectrum:

A. narrow spectrum : target only gram +ve, eg.(**Vancomycin, Penicillin**)

B. moderate spectrum : more gram +ve and gram –ve ,
eg.(**ampicillin,amoxicillin**)

C. Broad spectrum : targets large number of gram +ve and -ve , eg.
(**tetracylines**)

3) According to their cellular targets:

1-Cell wall.

2- plasma membrane.

3-nucleic acids.

4- proteins synthesis.

****

In this lecture we will discuss about the antimicrobial drugs that inhibit cell wall synthesis and cell membrane integrity.

Written by Esraa Odah

1- cell wall inhibition :

►The drugs that are responsible for inhibition of cell wall synthesis are:

β–lactam drugs (penicillin drugs)

-the mechanism of action of all penicillin drugs and its derivatives depends on their structure which is composed of **two important cycles:**

1- beta –lactam ring.

2- 5-thazolidine ring >> due to presence of sulfur

#the mechanism of action:

As we know G+Ve bacteria have multiple layers of peptidoglycans composed of (**N-acetyl glucose amine and N-acetyl muramic acid**) which connect with each other by cross linking (peptide bridges compose of penta amino acids) these bridges are important for the rigidity of the cell wall. Same thing in G-ve bacteria but the number of peptidoglycans layers is less.

Now within peptidoglycan layers we have certain specific small molecules of proteins called **PENICILLIN BINDING PROTIEN(PBP)** ►as the name indicate these proteins normally if they are exposed to beta-lactam drug "**penicillin** " it will interact and produce a complex and this complex results in inhibition of a specific enzyme called "***transpeptidase***".

► Transpeptidase from the name means transfer of amino acid in order to produce cross linking between N-acetyl glucose amine and N-acetyl muramic acid as you know already cell wall cannot be fixed (rigid) without cross linking.

So if the transpeptidase inhibited >> cross linking will not occur >> cell wall will be weak and easily damaged >>inhibition of growth of bacteria >> killing effect. **(bactericidal**)

In vitro or vivo if cell wall has been lost >> bacteria cannot be replicated

Note **low doses of penicillin lead to chronic inflammation** .HOW?!

Let's explain that …

Low doses of penicillin affect some peptidoglycan layers that's mean we still have a connection between other peptidoglycans layers that's allow to convert type of bacteria to another type ,for example : ***cocci form*** to ***L-form*** . L-form means we have cytoplasmic membrane ,some part of cell wall or without it ,which might survive for few days in infective tissue, also they lead to convert **acute infection** to **chronic infection** and might contribute in developing of **resistance against drug .** so you must care about recommendation dose and duration of treatment .

**note: penicillin drug is active during the logarithmic phase of the growth of the bacteria, not in the stationary phase.*

Now let's back again to β –lactam structure **.what's happen if we add a chemical group like: carboxylic group or ethylene group to beta-lactam ring ?** the change will happen only in **pharmacokinetic**s (distribution ,excretion …) of drugs and **spectrum of activity** against G+ve and G-ve bacteria **NOT** in **mechanism of action against cell wall** (it still inactivate formation of cell wall) ,therefore beta-lactam drugs "penicillin "divided according to its activity against G+ve , G-ve , facultative anaerobic and aerobic bacteria…

Classification of penicillin according spectrum of activity:

1-narrow spectrum penicillin :

► **Penicillin G , Penicillin V**

NOTE Penicillin G taken by injection while penicillin V taken orally .WHY?

Because, beta-lactam ring in penicillin G will be inactivated by acidic medium of stomach so it's taken by injection (intramuscular, intravenous…) . In contrast penicillin v protected against acidity of stomach so it can be given orally as tablet.

▶ Narrow spectrum means action is related to G+ve bacteria mainly (facultative anaerobes) ,example:
(streptococci, Staphylococci)

*they don't affect G-ve bacteria , but they might affect anaerobic bacteria whether cocci or bacilli (2 types)

2-moderate spectrum :

Scientists worked on changing the structures of penicillin drugs at the site of the b-lactam ring , in order to produce a drug effective against G-ve bacteria, finally producing two drugs called :

►Ampicillin, Amoxicillin.
These drugs can affect against G+ve and G-ve bacteria ,so we can use these drugs to treat any infection caused by G-ve especially for urinary tract infection which caused for example by E.coli .* E.Coli is G-ve bacteria*

Note due to the frequent contact between penicillin drug and bacteria cell, bacteria developed resistance towards it by producing an enzyme called **Penicillinase or B-lactamase .**

Beta-lactamases "Penicillinase" are enzymes produced by * some bacteria that provide resistance to β-Lactam antibiotic

▸specific **penicillin binding proteins** share in production of these enzyme " **Penicillinase**" , and these mechanism controlled by presence of specific gene on chromosome or on transferable plasmid. Therefore the chemical Pharmaceutical company they have tried to inhibit action of **Penicillinase** by producing penicillin drug specific to inhibit action of pencillinase.

3)Penicillinase –R Drugs:

(drugs that inhibit the action of penicillinase that cause resistance to the bacterial cell) *where ever you find R it stands for Resistance *

1-Oxacillin, flucloxacillin,Methicillin

Methicillin is toxic to some extent but can replaced by oxacillin, normally used to treat **staph** resistance to first generation of penicillin. Also cephalosporins drugs we will discuss about it later. So methicillin and its derivatives (**Oxacillin, flucloxacillin**) consider as pencillinase resistant drug.

NOTE first generation of penicillin are penicillin G ,V (narrow spectrum),ampicillin , amoxicillin (moderate spectrum).

Because staph is resistance to first generation drugs it also called ..MRSA>>this terms means methicillin resistance staphylococcus aureus this organism accounting approximately for 20% of all type of infection and inflammation (blood sepsis, abscesses ...etc) in the human body so you can imagine how important to have penicillin drug which can resist activity of penicillinase and cure patient
Although using resistant drugs like (oxacillin ,methicillin)that inhibit action of pencillinase , the staphylococcus or (MRSA) manage to produce another form of pencillinase which can activate against this drug by other means; not directly by producing penicillinase, but by producing some change in permeability of the cell membrane - it shuts down the pores which allow the penicillin to enter through it, thus preventing penicillin from reacting with penicillin binding proteins and producing the complex that inhibit transpeptidase that responsible of cross linking in piptidoglycans layers .

2-clavulinic acid :

It's not antimicrobial drug "it's chemical compound that attaches to ampicillin/amoxicillin structure in order to inhibit action of penicilinase so it's called "β-lactamase inhibitor"
That's mean it's related only to action of pencillinase not related to affect cell wall or affect production of polypeptide layers in the cell wall.
But again bacteria manage to escape presence of penicillinase inhibitors and develop another type of resistance .

so we use pencillin amoxicillin mehticllin Oxacillin, flucloxacillin cillin cillin cillin all of these drugs faced resistant against it O.o . WHAT IS THE SOLUTION ???????
In fact the struggle continuous between bacteria and drugs. ..والبقاء للأقوى ☺

3-Carbencillin , piperacillin :

These two drugs are modified as **carboxylpenicillin** "have carboxyl group " to be more selective in treatment of G-ve bacteria "specially against **pseudomonas** "

►**Pseudomonas**: a special group of G-ve bacteria which cannot be easily treated by antimicrobial drugs.

NOTE despite this fact, Pseudomonas mange to produce beta-lactamases against carbenicillin and piperacillin ☺ احسن يستاهل

4- Monobactam :

► As name indicate it contains only beta-lactam ring with side chain carboxyl group , amino group…etc.

►This drug have been develop to cover certain type of G-ve bacteria which is resistant to other type of penicillin like : amoxicillin and ampicillin.

►Mainly against resistant-enteric bacteria

Resistant -Enteric bacteria: that's mean rapidly growing facultative anaerobic bacteria found in intestinal tract like : E.coli..etc and these are very common causative agents of various type of infection and inflammation in our body.

►Monobactam succeeds to some extent to control certain type of resistant bacteria but again enteric bacteria manage to produce now a new type of beta-lactamases called extended spectrum b-lactamases.

*Now they cover more than 60-70 type of beta-lactamases might be produce by G+ve , G-ve .

5-carbapenem :

► Developed because resistant- Enteric bacteria produce Extended Spectrum Beta-lactamases.

►Represented by :

imipenem , meropenem.

►These two drugs are the last resort to use in treatment of Serious infection caused by G-ve enteric bacteria .

►At least 30-50% of G-ve isolated from respiratory tract or from wound infection are found to be resistant to carbapenem which is the **last available** penicillin drug to treat these infection caused by G-ve bacteria so, sometime these infection hard to be controlled .

►In clinical medicine we use two terms :

1-community acquired infection : usually the patient will develop infection in his home .

2- hospital acquired infection : patient acquired infection during presence in hospitals "nosocomial infection"

Now; if patient develop sepsis or wound infection in home and come to hospitals generally it can be easily control by using of **augmentin** "amoxicillin+clavulinic acid" Or can use **carbencillin** or **ticaricillin** (piperacillin in case of pseudomonas). **carbapenem** should use only in hospitalized patient and only in injectable form and only for serious infection caused in hospital "nosocomial infection" because these

infection usually are multi-resistance to many type of antimicrobial drug and carbapenem might cover these multi-resistance micro-organism .

Unfortunately; carbapenem become more and more useless especially in certain hospital due to the spread of multidrug resistance G-ve especially pseudomonas aurginosa and acetinobactar specious.

And so far we know many of our patient might die due to the lack of the presence of effective drugs .

4-Cephalosporins::

►similar to penicillin drug but instead of a 5-S ring structure we have a 6-S ring structure (S >> stand for sulfur)

►Also originated from living fungus like penicillin, called(cephalosporin)

►According date of discovering these drugs between (1965 to 1990) they have classified to 4 generation :

1-first generation (1960 to 1970) represented by two very common use cephalosporin drug :

►Cephalexin ,cephardin (ORALLY TAKEN)

-Have similar spectrum of activity to ampicillin ,amoxicillin

-Developed for two reason :

1-these produce less hypersensitivity to penicillin like allergic RXNs

2-they cover more G+ve ,G-ve bacteria so wider spectrum of activity .

Note : to some extent **penicillin ,ampicillin ,amoxicillin** resistant bacteria will be more susceptible to cephalosporins because it's a new drug and will take time until the bacteria manage to produce penicillin binding proteins which responsible of produce pencillinase against cephalosporin .

2- second generation : (1970-1980)

Cefoxitin ,cefuroxin (ORALLY)

-They have multiple functions :

1-they are to some extent more resistant of action of pencillinase.

2-they cover more G+ve ,G-ve (wider spectrum).

-**cefuroxin** >>used to treatment urinary tract infection due to G-ve .

-**cefoxitin** >>it's cover to some extant anaerobic bacteria because most developed types of penicillin ,ampicillin , amoxicillin ..can not cover enough anaerobic bacteria infection .

3- third generation (1980-1990)

ceftriaxone, Cefotaxime..

developed mainly to treat certain infection related to(CNS, meningitis, blood sepsis) caused by certain type of organism like : Entric G-ve bacteria and affect G+ve in particular streptococcus pneumonia (very serious pathogen) .

4- fourth generation (1990-until now)

Cefepime (injection)

Cefepime mainly against G-ve entric bacteria which produce upper and lower respiratory tract diseases, Cefepime is usually reserved to treat moderate to severe pneumonia infections caused by multiple drug-resistant microorganisms .

In some cases, all 15 types of cephalosporins may prove to be useless towards extended spectrum beta-lactamase bacteria, in which case cefepime will be used to treat the infection.

►Each drug has certain side effect for example: increase number of bacteria called g+ve "entrococcus "in intestine during treatment of Cephalosporins and these may associated

with infection. Entrococcus are naturally resistant against all types of Cephalosporins drugs so once we use Cephalosporins and if we have a few numbers of entrococcus on intestine or in any part of body you expect the entrococcus will be increased.

►In short we have penicillin drugs, Cephalosporins drugs, wide spectrum, narrow spectrum against G+ve and G-ve bacteria these bacteria Will developed resistance and producing extended spectrum of beta-lactamase by 2 factors: chromosomal and usually by presence of specific transposons which carry resistance gene against Cephalosporins and penicillin drugs, and this gene can be can be inherited or transfer from one type of bacteria to another type by conjugation, transferable plasmid.. at the end all intestinal tract will be developing resistance against drugs so it's complicated spread especially in hospitalized patients why? Because they take a lot of antibiotics so bacteria in their body always expose to these antibiotics and these contribute for selection of resistance because antibiotics susceptible type of bacteria will be killed and resistant will survive means increasing possibility to get infected by these bacteria during surgical procedures or any type of injection .

►In general all drugs have side effects different from patient to another .but at least you have to recognize penicillin drug produce allergic reaction.
Some references mentioned the Cephalosporins can be given for patients have allergic reaction of penicillin that's not true .Cephalosporins drug produce less allergic reaction than penicillin but still they associated with some allergic reaction so they have cross linking between pencillin and Cephalosporins drugs therefore to be in safe side, you should not be treat with injectable Cephalosporins if you have a history of allergic reactions to penicillin. Otherwise it might ended with "anaphylactic shock "

And we have other side effects : Sensitization, Penicillin Allergy, Fever, Serum Sickness, Nephritis, Anaphylactic Shock .

*Anaphylactic shock can develop within few hours and is a good sign of allergic rxn to antimicrobial drugs

2-inhibition of membrane integrity :

Polyene drugs

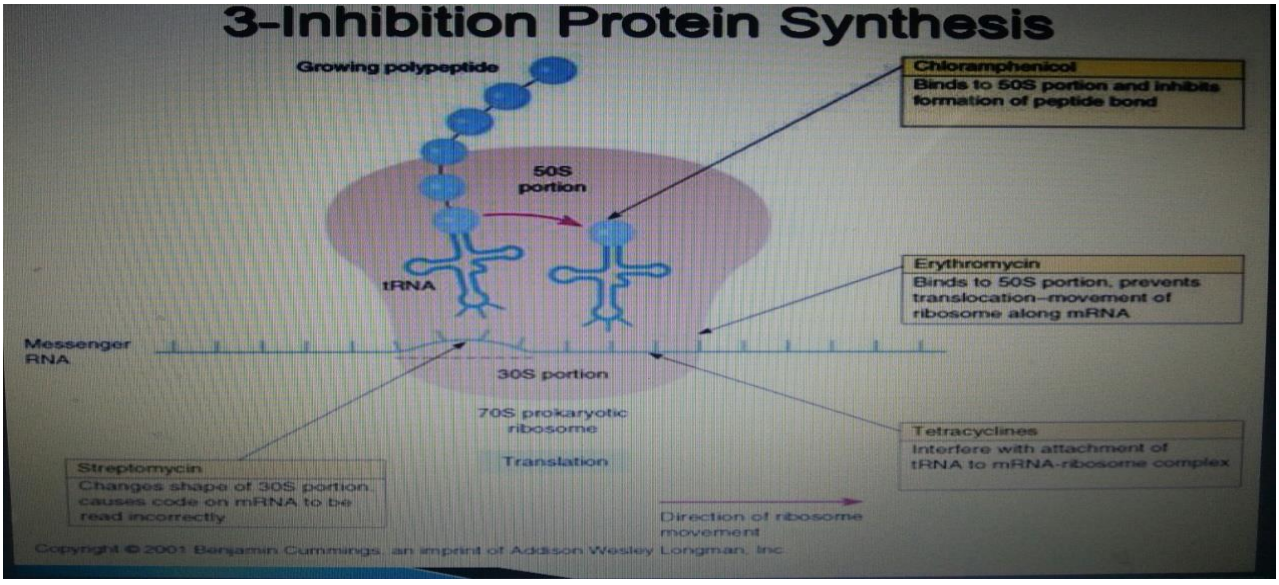
-complex structure composed of large cycle polypeptide which means it's not easily to be absorbed it might have more side effects especially in kidney, so polyene drugs represented by : colistin / polymixen E are TOXIC drugs ..developed in 1950 in order to be topical treatment not systematic but they have stop use of these drug long time until 1991 due to side effects .
They have to some extent modulated from polymixen E into colistin sulfate this new colistin sulfate less toxic, but it's very useful for using in association with presence of multi-resistant entric-bacteria especially which produce extended spectrum of β-lactamase. if the organism isolated from blood or any other part of body, multi-resistant to all cephalosporin ,penicillin any other drugs, the only choice is to use toxic drugs and you have calculate to cure patient with some side effects or leave him to die following of infection

This drug used only in certain indications mainly associated with multi-resistant drug but unfortunately the side effect especially for kidney cause renal failure and you might kill patient if use high doses for prolong time but sometimes you have no other choice of drug…

3- Inhibition protein synthesis:

Here you can see the bacterial ribosomes with the 50s ribosomal and 30s ribosomal portions, plus the chloramphenicol, erythromycin, tetracyclins and streptomycin drugs and the ways in which they can inhibit protein synthesis in the bacterial ribosomes.

Look to this picture and try to prepare some information about it before next lecture that might help you to understand what the doctor say.



#حكمة اليوم :

لم يرد لفظ السعادة في القران الكريم الا في موضع واحد "واما الذين سعدوا ففي الجنة خالدين فيها " لتعلم ان السعادة الحقيقية ليست في الدنيا بل في الجنة .

جعلني الله واياكم من اهلها .

Your colleague: Esraa Odah Al-Salamin

Sorry for any mistakes .. ☺