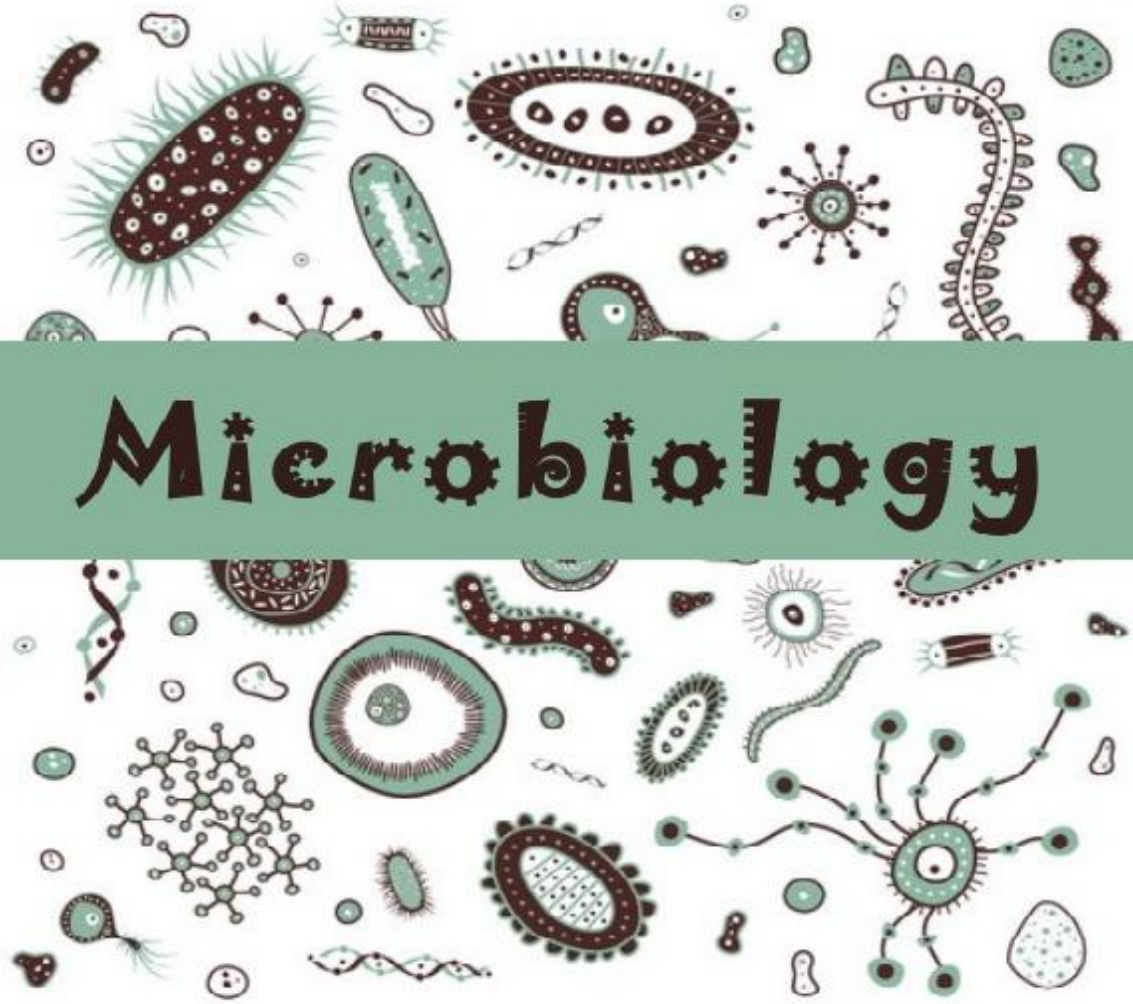

Microbiology

◉ Sheet ○ Slides

Number : 7

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Subject: Anti-Microbial Drugs

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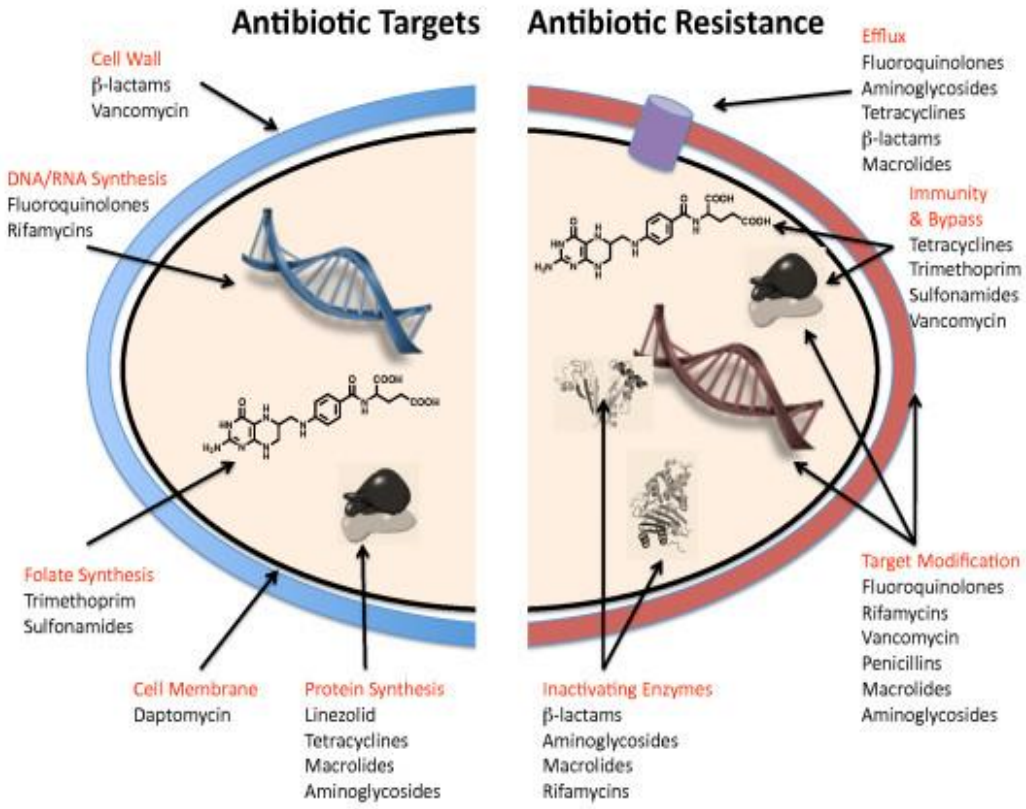
Anti-Microbial Drugs:

The following slide shows the main groups of anti-microbial drugs in relation to specific targets of microbial cells, also it shows how these microbes resist the drugs by different ways.

- Ex: β-lactamase (an enzyme) that resists the antibiotic drug "Penicillin", it expels the drug and prevent it from reaching the cell membrane this action is called **Efflux** resist mechanism.



- Each group of antimicrobial drugs affects one target in the microbial cells, and might affects more than one target.

General Classification of antimicrobial drugs according to their spectrum of activity (action):

1-**Narrow spectrum**: affects against few (1-3) groups of microbial (bacterial) cells in relation to the target of that drug (cell wall, cell membrane, etc).

Ex: Vancomycin a drug used to treat infections caused by gram-positive bacteria.

2-**Moderate spectrum**: affects gram +ve and gram –ve at the same time (more advanced).

Ex: modified types of ampicillin drugs.

3-**Broad spectrum**: affects large numbers of gram +ve and gram –ve bacteria.

Ex: Tetracycline and chloramphenicol.

There are some drugs that don't follow that classification such as:

- **Anti-mycobacterial drugs**: is used to treat infections caused by mycobacteria (ex: Tuberculosis), although it may be effective against other types of bacteria we don't use it, because it may develop a resistance in the bacterial cells or it may cause many side effects.
- There are drugs that only affect obligate anaerobic bacteria, so when we suspect an infection caused by anaerobic bacteria we use this type of drug before any other type.
- Drugs that treat urinary tract infections, those drugs excreted in high amounts in the urine (Ex: 90% of the drugs are excreted by the kidney (not absorbed)).

1-Drugs that target the cell wall:

The cell wall is very important for the bacterial cell so any damage or interaction that prevent the formation of the cell wall will stop the bacterial growth and activate cell autolysins.

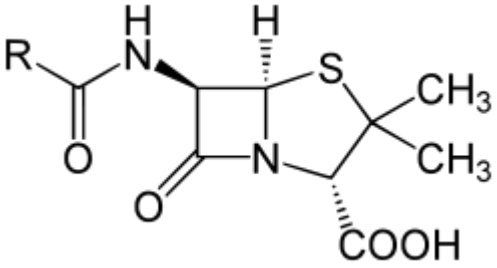
Autolysins: are bacteriolytic enzymes that digest the cell-wall peptidoglycan of the bacteria that produce the

- The Penicillin drug is an excellent drug that affects specific parts of the peptidoglycan layers in the cell wall.

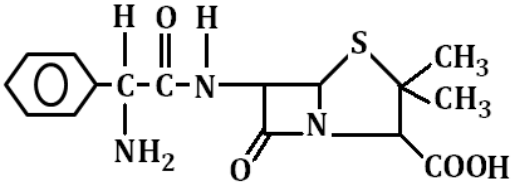
- It disrupts the bonds that keep the cell wall rigid.

- Remember that the cell wall consists of layers of peptidoglycan, the structural unit of this layers NAG (N-acetyl

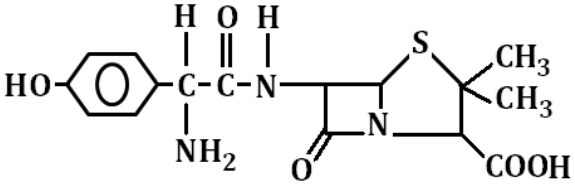
glucosamine) connected to NAM (N-acetylmuramic acid) and the layers are cross linked together by a penta-peptide.



The structure of the penicillin: two rings, the one in the left β-lactam ring (3 carbons and one nitrogen) and Thazolidine ring (presence of sulfur). Note that simple structure can easily be modified to produce various types of penicillin.
Note the “R” group is the one which is modified.
Ex:



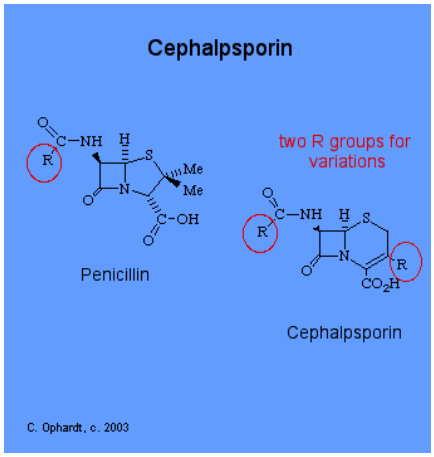
Ampicillin



Amoxicillin

Any modification in the structure especially in relation to B-lactam ring considered as protection for the ring, which means that the enzyme produced by the bacteria against penicillin might not be able to break down the penicillin.

Some modifications may deactivate the B-lactam ring therefore it will not be able to treat the infection. Ex: Penicilloic acid (which has an open B-lactam ring) is not active against bacteria.



Cephalosporin: similar to penicillin but it has a 6-Dihydrothiazine Ring instead of 5-Thazolidine ring in penicillin.

It can be modified also, notice the “R” groups in its structure.

Remember that gram -ve cell wall is simpler than the gram +ve cell wall.(gram +ve have more peptidoglycan layers).

Mechanism of action for penicillin :

There is an enzyme called *transpeptidase* (also known as penicillin binding protein).

Penicillin interact with this enzyme to produce *penicilloyl enzyme*(a complex that prevetns the attachment of the pentapepide to the newly form N-acetyl muramic acid) (in other words it disrupts the formation of cross bridges),so it inhibits the formation of the cell wall,therefore the cell wall becomes weak,as the result of osmotic pressure the cell will get bigger and as there is no cell wall protecting it,eventually the cell lyses.

Gram –ve bacteria have more ability to survive penicillin as it contains fewer amount of peptidoglycan (the rigidity of its cell wall doesn’t only depent on the peptidoglycan as gram +ve does).

So gram –ve is less suspectible to the first generation of penicillin (type g and e) whereas those types have excellent effects against gram +ve.

History of Penicillin :

1-The basic penicillin which discovered in 1941,such as penicillin g :

It has narrow spectrum.

It is not acid stable (we cant take it orally as the acidity of the stomach will inactivate the b-lactam ring).

Penicillin V :a modified penecillin (a carboxyl group is added) so the b-lactam is protected therefore it can stand the acidity of stomach.

Both types affect mainly gram +ve,and rarely to affect gram –ve.

They might affect certain anaerobic bacteria such as bacteroides which found in the intestinal tract (it is gram –ve anaerobic),other than Bacillus and Clostridium.

2-Ampicillin, Amoxacillin :

Gram +ve bacteria have already encoded in their genes (silent genes) a gene which is coding for an enzyme called Penicillinases (ß-Lactamases),and this enzyme can inactivate b-lactam ring (the enzyme cleaves the C-N bond and opens the B-lactam ring).

In labs they added another amino group (in addition to the already added carboxyl group) to produce a new penicillin,which is more stable/effective against gram +ve and certain gram –ve bacteria.

they have moderate specturm,as example it works against some

gram –ve bacteria such as “e-coli” which causes the urinary tract infection.

Ampicillin and Amoxacilln are still similar to the original penicillin and there is no big difference between them,so the bacteria still able to produce another form of penicillinase to inactiave these drugs.

So as the bacterial resistence agaisnt those drugs increases,their uses in the clincial practice decrease.

So the scientists tried to develop a chemical structure that works directly against the B-lactmases and they came out with :

3-A combination of amoxacillin\ampicillin and clavulinic acid :this combination successfully inhibits the action of B-lactamases (the clavulinic acid inhibts the production of the enzymes in large amounts therefore the bacteria won’t be able to resist the drug).

This combination has ***a broad spectrum*** affecing both gram +ve and –ve bacteria.

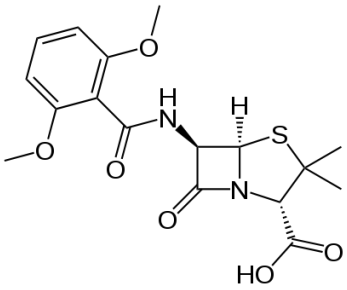
4-The bacteria developed a new type of penicillinases which resist the action of the mentioned combination,so the scientists developed :

a-Oxacillin:penicillin + 2 oxide groups.

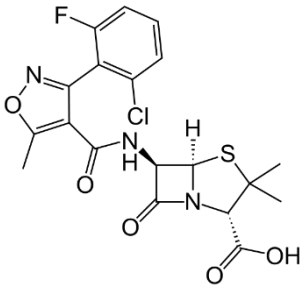
b-Flucloxacillin:penicillin +fluor+oxide group.

c-Methicillin:penicillin + Methyl group.(the first one developed).

Those drugs called “Penicillinase resistant drugs” “Penecillinase-R drugs”



(A)



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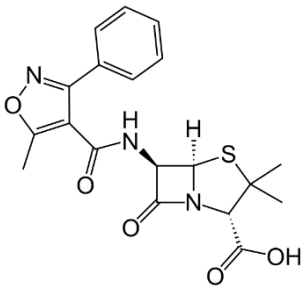

(C)

They were discovered in the 70s and worked greatly (against both gram +ve and –ve) but as usual the bacteria find their way to resist them.

Methicillin-Resistence Staph aureus (MRSA) :this staph resists methicillin and all of previous types of penicillins (G,E,amoxycillin,oxacillin).

Remember that methicillin is no longer used in medicine.

MRSA :it is a serious problem because we cannot use any penicillin against it so we have to develop non-penicillin drugs.

The scientists developd vancomycin and other drugs which work against this MRSA.

The problem with MRSA is a global issue,in our country as example MRSA represnts 70% of the isolated Staph aureus in the clinical specimen (Blood,etc).

Even we developed a drug against it,but notice that vancomycin is very expensive,has to be taken intravenous or intramascular (not orally) and it can be toxic at some extent.

5-Scientists started to focus in developing drugs that are effective specifically against gram –ve or gram +ve or both of them.

A-Drugs against gram –ve:

1-Pseudomonas spp :infection with this organism in the respiratory tract can be serious,and it is not easy to kill it with the avaiable drugs,so they introduce carboxypenicillin (carboxyl group witihin the penicillin drug) in form of **Carbencillin and Piperacillin.**

This drug considered as anti-pseudomonas drug (mainly used against it).(not used against other microbes).

Pseudomonas developed a resistence against that drug also ☹

2-In the 80s They introduced **Monobactam** drug, a modified penicillin,in which the B-lactam ring is alone.

Dveloped in a form of **Aztreonam** and it is effective only against G-ve R-Enteric bacteria.

3-Last type of modified penicillin produced by the pharmacological compaines was **Carbapenem** in a form of ***imipenem*** (billion $ drug)& ***Meropenem***,mainly to traget respiratory and intestinal tracts infetions.

Carbapenem which has a Broad Spectrum, and Highly resistance to most penicillinases, including Extended spectrum beta-lactamases (effective against large number of B-lactamases),Serious Nosocomial Infection, Enteric bacilli, P. aeruginosa, Acinetobacter spp.

The large number of B-lactamaes arises from the silent genes in the bacterial chromsome,these silent genes can be activated during contact with foreign chemical (penicillins,etc).

Extended beta-lactamases are related to certain geographic areas,as example new delhi B-lactamase (developed there),this is important clinically as the travelling became very easy.

By conjugation it is easy for the bacteria to acquire a new type of B-lactamase from another bacteria,(especially e.coli and other intestinal bacteria).

There are no information about how to stop the spreading of such enzymes,we just have to deal with any new type produced by the bacteria over time.

In spite of all the efforts bacteria managed to develop resistence against this drug also.

Cephalosporins:

Mechanism of action similar to that in penicillin.

We have four generations of Cephalosporins,each generation represnted by many types***,(don't memorise them right now).***

Notice that the first and second generation have ***broad spectrum***.

The first generation (Cephalexin) developed by the time of ampicillin and amoxycillin (same spectrum of the 3 drugs),and back then it (1st generation) was taken orally.

The second generation (Cefoxitin, Cefuroxime) (still in used) have same spectrum as the first,at the beginning they weren't available orally,but now they are availble orally and as injectable drug.

The third generation (Ceftriaxone ,Cefotaxime) are important for treatment of serious gram –ve and some +ve bacertia infections.

streptococcus pneumoniae,especially the one related to meningitis (can be fetal),so in case of meningitis an effective drug is needed to cure it.Ceftriaxone,Cefotaxime are excellent drugs to cure meningitis.

The fourth generation (Cefepime) is similar to Carbapenem (same time),now they are not effective and rarely to be used against gram –ve bacteria.

We have large amount of gram –ve bacteria (enteric bacteria) (part of or intestinal flora) (causes various types of infections) (such as Urinary,respiratory tracts infections,blood sepsis,CSF(cerebrospinal fluid) infections also).

The third generaion of cephalosporin and the last generation of penicillin especially Carbapenem are used to control ***the above infections***.

Important feature of imipenem that it cannot be given alone, and if given alone it will be degraded in the kidneys by trans-peptidases, so it must be associated with another compound such as cilastatin, which protects the structure of the imipenem.