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micro sheet No.9

19-10-2014

In this lecture we will continue talking about antibiotics:

**Modes of antimicrobial action:**

It depend on the nature of antibiotic structure and degree of affinity to certain target sites within bacterial cells, and these sites are:

1- the cell wall.

2- the cell membrane.

3- the ribosomes.

4- the DNA and RNA.

5- the metabolic pathways which are essential for the survival of the bacterial pathogens.

We will start talking about **drugs that inhibit cell wall synthesis:**

They act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls, the peptidoglycan layer is important for cell wall structural integrity.

Peptidoglycans produced by enzymes, these enzymes are actually proteins which are present in some bacteria and able to bind penicillin so they are called penicillin binding proteins (PBP) and they are enzymes responsible for the synthesis of peptidoglycans as we said.

We have large group of antibiotics known as **beta\_lactam antibiotics** and they are four groups:

**1- penicillins.**

**2- cephalosporins.**

**3- carbapenems.**

**4- monobactams**.

And they have a common beta\_lactam ring and it’s a square\_shape ring.

the monobactams have only one ring which is beta\_lactam ring and if we see another ring beside beta lactam ring the structure will be cephalosporin or carbapenem or penicillin and these extra rings are different in all these antibiotics.

**\*\* Who we differentiate between the beta\_lactam antibiotics?**

By the ring which is next to beta\_lactam ring also the addition of different side chains will give different antibiotics with different properties.

\* The penicillin (6 aminopenicillanic acid) composed of beta\_lactam ring and next to it there is thiozolidine ring in addition to side chains.

\* The cephalosporins (7\_aminocephalosporanic acid) composed of beta\_lactam ring and next to it there is dihydrothiazine ring in addition to side chains.

Let's start talking about **Penicillins**:

the first penicillin to be used was **penicillin G** it is acid sensitive so if you swallow it, it will be destroyed by gastric acid so it can't be given by mouth it must be given by injection either intravenously or intramuscularly.

it has high activity against gram positive bacteria but is really in low activity against gram negative bacteria because the gram negative bacteria in its outer membrane has porins which does not allow to penicillin G to pass inside it.

it's very safe antibiotic it has been present for many many years and does not have many toxic effect but some people may be allergic to penicillin but do not reach the level of toxicity so it is not toxic to kidney or liver and so on….

so penicillin G cheap and very safe and (ebn nas kwis :p) and that’s why it’s the first penicillin to be used but as we said you can't take it by mouth because it is unstable in the highly acidic stomach and remember it's not effective against gram negative bacteria.

Penicillin G is produced by (penicillin producing fungus), so it's natural.

Now back to slides to see the structure of penicillin G:

The side chain which have a pink color it’s the side chain of natural penicillins if you add the side chain below (the CO CH2O) with this ring, this will get another penicillin which is really synthetic manufactory.

The second type of penicillins is **Penicillin V:**

Called also phenoxymethylpenicillin it's with different side chain but has similar properties of penicillin G but it can be given by mouth because it's stable in gastric acid juices.

Note: when I read from Wikipedia this what I understood:

Penicillin V has a range of antimicrobial activity against gram positive bacteria that is similar to that of penicillin G and a similar mode of action, but it is substantially less active than penicillin G against gram negative bacteria, so you may have to ask the doctor to be sure.

The third type of penicillins is **Ampicillin:**

To get broader range of action of penicillin they added an amino group next to the side chain and they end up with ampicillin.

so it has border range of action, it can penetrate the gram negative bacteria, it's effective and it's acid stable it can be taken by mouth also it can be taken by injection or can be as form of capsules.

The fourth type of penicillins is **Carbenicillin:**

also if we change the side chain we can end up with carbenicillin,acid stable, it's active against gram negative bacteria such as Pseudomonas and Proteus but not will absorbed by intestine.

When they use these penicillins at the beginning, some bacteria actually develop resistance against it and express plasmid-encoded an enzymes known as beta\_lactamase or penicillinase according to its name they destroy the penicillin or beta\_lactam ring.

all the penicillins that we have mentioned are affected by beta\_lactamase and destroyed by it, so they developed a new drug which is resistant to beta\_lactamase and they called it penicillinase resistant, it's less active than penicillin G but whatever because its resistance to penicillinase is very effective, it is unstable in acid so it can be taken only by injection.

So all bacteria are resistant to penicillin G, penicillin V and ampicillin because of production of beta\_lactamase or penicillinase.

some of bacteria actually change genetically the penicillin binding proteins so penicillin will not be able to bind these enzymes anymore, so it's not matter if it's penicillin' ampicillin or even methicillin (which is resistant to beta lactamase) they will not work because penicillins not able to bind to the penicillin binding proteins which are enzymes responsible for the synthesis of peptydogycans of the bacterial cell walls.

\*\* MRSA are staphylococci (they are hospital acquired infection) which are resistant to the methicillin because they change their own penicillin binding protein and they are known as Methicillin Resistant Staphylococcus Aureus (MRSA).

the only antibiotics that can kill these MRSA are Vancomycin and Teicoplanin which work on the cell wall but at a later stage; they work on the bridge formation of the peptidoglycans, and they only used in hospital because wrong use make the bacteria resistance to them also.

We finish talking about first group of beta\_lactam antibiotics which are penicillins.

Now the second group of beta\_lactam antibiotics which are **Cephalosporins**

cephalosporins have four generations (no need to know the names of generations),when we have bacterial resistance against generation they produce other generation which is stronger until they reach to fourth generation ,so the fourth generation is more stronger than others.

cephalosporins have these two advantages:

1- Broader acting spectrum than penicillins.

2- More resistant to beta\_lactamase.

So they are active against both gram positive bacteria and gram negative bacteria.

 Unfortunately some bacteria became even worst and produce beta\_lactamase enzymes which are stronger than other beta\_lactamase , so they called these enzymes Extended Spectrum Beta\_Lctamase (ESBL),they have the ability to destroy all of the penicillin and many of the cephalosporins.

The antibiotics which are effective against (ESBL) are carbapenems

Know the third group of beta\_ lactam antibiotics which are **Carbapenems:**

They are effective against (ESBL) but don't use it as first line antibiotic except for (ESBL) infections.

Some bacteria called Klebsiella Pneumoniae they have ability to resist carbapenem and they have enzymes called Klebsiella pneumoniae Carbapenemase, but carbapenems are still used as very strong antibiotics.

Tthe fourth group of beta\_ lactam antibiotics which are **Monobactams:**

monobactams are most and only effective against aerobic gram negative bacteria such as Neisseria and Salmonella.

There is also group of **Beta\_lactamase inhibitors** such as clavulinic acid and sulbactam, these are not really antibiotics, they inhibit beta\_lactamase, so if you give them with products of penicillins (which are sensitive to beta\_lactamase) as a combination they will suppress the beta\_lactamase and allow to the antibiotic (penicillins) to work against bacteria

Examples of these combinations:

1- Amoxicillin with Clavulanate give (Augmentine):

Active against most respiratory and some GI tract gram negatives.

2- Ampicillin with Sulbactam give (Unasyn):

Very good activity against respiratory and GI tract gram negatives.

 3- Piperacillin with Tazobactam give (Zosyn):

Excellent activity against respiratory and GI tract gram negatives, including Pseudomonas Aeruginosa.

**Other drugs:**

**Vancomycin** and **Tiecoplanin** which are complex glycopeptides that works on cell wall.

 1- They disrupt cell wall synthesis in growing gram positive bacteria at a later stage.

2- They also work against MRSA (Methicillin Resistant Staphylococcus Aureus).

3- They are effective against some anaerobic bacteria like clostridium difficle.

**Remember:**

**\*** The **penicillin binding proteins (PBP)** are enzymes involved in synthesis of peptidoglycans of cell wall and they called (PBP) because they are the site where penicillin is bind.

Examples of (PBP):

transpeptidase, transglycosylates, carboxypeptidases and endopeptidases.

**\*** **penicillins** are highly effective with extremely low toxicity.

Classes of penicillins:

1- Natural penicillins: such as Pen G,Pen V ,benzathine and procine and they are produced by penicillin's fungus naturally.

benzathine and procine forms are very long acting antibiotics ,instead of having penicillin injections every 6 or 8 hours you can take procine every 24 hours which is enough.

2- Amino penicillins : such as ampicillin and amoxicillin, they have enhanced gram negative coverage due to amination ,but they are highly susceptible to beta lactamases.

3- Antistaphylococcal penicillins : such as methicillin, oxacillin, dicloxacillin…

They are more stable to beta\_lactamases, due to modification near beta lactam ring but have poor entry into gram negatives.

4- Antipseudomonal penicillins : such as carbenicillin, ticarcilline, pipracillin …

They enhanced gram negative coverage due to extensive side chain addition but they are highly susceptible to beta\_lactamase.

**\* caphelosporins** they are more stable to beta lactamase hydrolysis and have a wider antimicrobial spectrum.

First generation active against gram positives, E.coli, Klebsiella.

Second generations are more effective against gram negative bacteria such as H-influenza, enterobacter, serratia, citrobacter and some anaerobes.

Third generations are effective against most enterobacteriacae and P.aerugenosa.

Fourth generations are very effective against enterobacter( which are difficult to be destroyed) and citrobacter.

Note: you don't have to remember the bacteria but you should remember the properties of generations of caphelosporins.

**\*** The **semi synthetic penicillins** which are carbapenems and monobactam and we said that are penicillinase resistant penicillins.

**\* carbapeneme** have extremely broad activity including S.aureus and other gram positives, Pseudomonas and anaerobic organisms.

But it cause toxic side effect, hypersensitivity and seizures.

**Resistance to beta\_lactams:**

How bacteria become resistance to beta\_lactam??

1- Degradation by beta\_lactamases:

Nearly all S.aureus destroy beta\_lactam antibiotics by the beta\_lactamases.

2- The porins in outer membrane of gram negative bacteria have different sizes so they prevent the entry of some antibiotics, by this way the bacteria decrease the permeability.

Example: most gram negative bacteria refractory to penicillin G.

3- Bacteria may can modified the antibiotic by change the binding site of the antibiotic or by adding side chains or amino groups or whatever.

4- By alter the penicillin binding proteins in the bacteria themselves.

Example: methicillin even its resistance to beta lactamase but it does not work against staphylococcus aureus because S.aureus alter the (PBP).

5- Some bacteria can pump the antibiotics outside after the antibiotics is already enter the bacteria inside.

**\*** refer to slide to see who the beta lactamase or penicillinase works:

The beta\_lactamase split the squar of beta lactam ring of penicillins and result in penicilloic acid.

If there is any question do not feel hesitate to ask me

GOOD LUCK

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