SHEET NO.

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

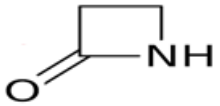
DOCTOR :

Hello and welcome to the 4th lecture of chemotherapy.
(الدكتورة حبّت تأكد على موضوع انه بالنسبة لأسئلة الامتحان الخاصة بمادتها ، رح تكون من السلايدز + الحكي اللي بتحكيه في الريكورد (يعني الشيتات) ، وطبعاً هاد ما بيمنع انه ترجعوا لمراجع ثانية ، ولكن اسئلتها مش رح تطلع عن الشيتات)

As we mentioned before about the antimicrobial agent or antibiotics, it can be cidal or static, and this subject are not absolute, it linked with the concentration and length of the course.
The group of antimicrobial agents, which we goanna to talk about today is:

Beta Lactam Antibiotics:

- In general contain a beta lactam ring, it's the characteristic of all antibiotics from this type of antibiotics, this lactam ring particularly are responsible the activity.
- How they do their job?
  The work to inhibit cell wall synthesis of the bacteria, and that's why they are considered as cidal antibiotics (we talked previously that the subject of cidal linked clearly with concentration used from antibiotics)
  - This structure in the picture, are repeated in all antibiotics linked with or falls under beta lactam antibiotics.



- The **beta lactam ring** is the active functional group where antibiotic activity resides, bacteria produce a lactamase which can break this ring.
- Bacteria might form a kind of resistant against these antibiotics, the things that make the bacteria described as resistance that they can form lactamase
- **What's the function of lactamase**?
  Breaking down these lactam ring, which responsible for the activity of beta lactam.

- So, if the bacteria was able to produce the lactamase, it's goanna be resistant to this kind of antibiotics, so we can't use this type of antibiotics for it.

Type of beta lactam antibiotics:

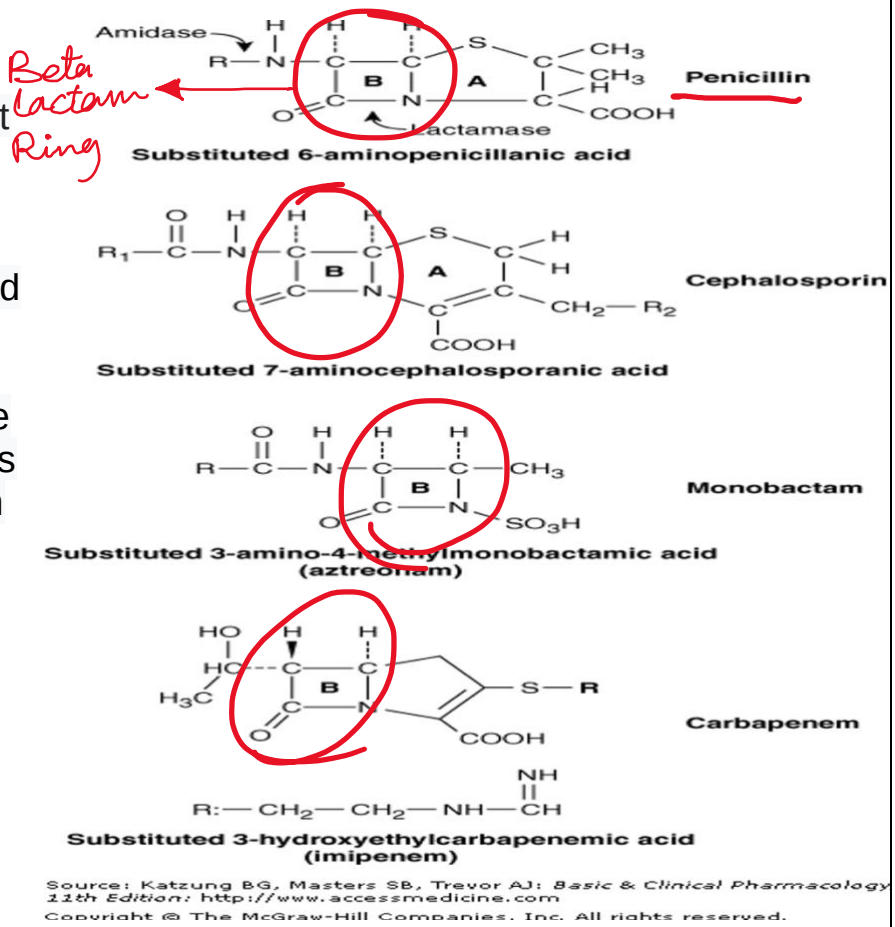
Penicillin G is the **prototype** for all antibiotics and all the *beta lactam antibiotics*, that's mean depend on the structure of penicillin G (which contain beta lactam ring as an essential component) can produce more of structures that either describe synthetic or semisynthetic, it was **oldest antibiotics**, but still growing and new agents are still discovered and added to the group.
The beta lactam antibiotics described as the oldest kind of antibiotics at all.

ملاحظة خارجية صغيرة :
معناها انه هاد الدواء اللي بنحكي عنه هو اشهر واحد للعائلة هاي واللي دائما بناخده Prototype
مثال لحتى نشرحه و الادوية التانية بتنشرح بالمقارنة فيه.

This pic display some examples of antibiotics that falls under *beta lactam antibiotics.*

There are many groups and types of antibiotics, and if you notice that lactam ring repeated in all type and the presence of this ring makes it described as beta lactam antibiotics.

The penicillin G on the basis of which other structures were built that fall under beta lactam antibiotics , the structure that produced can be described as synthetic or semisynthetic.



- Why do we manufacture new structures?

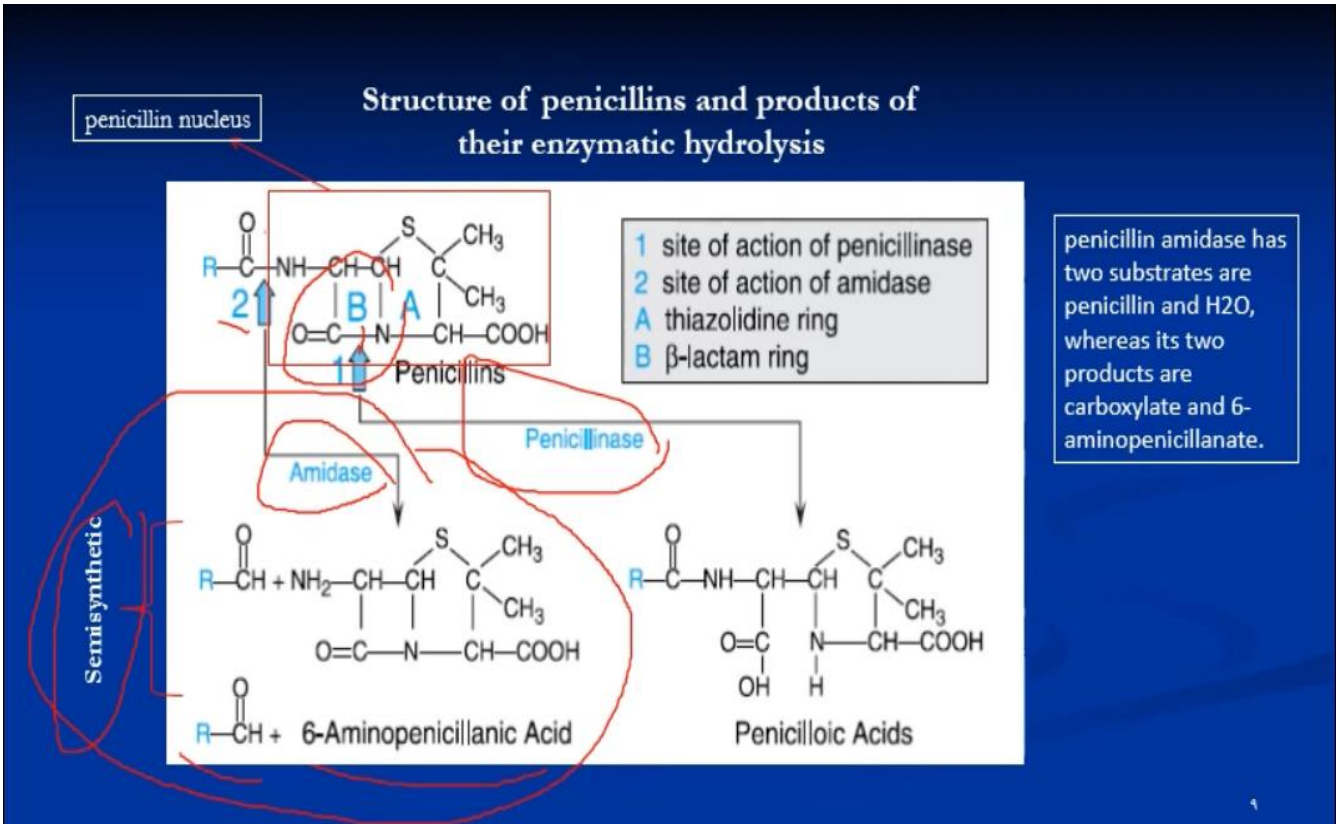
To overcome the problems that's mostly present in the natural product, and the most important one is the *RESISTANT*, so we want to avoid it.

- The *penicillins* considered one of the most famous beta lactam and most widely used.
- Penicillin G was found very effective in treating wide range of bacteria such as important *Gram positive bacteria* like Staph, Strept, Pneumococcus, and many others , but as we said it's use has been discontinued because of **high resistant** which associated with the bacteria that have the ability to produce lactamase.
- Natural produced from the fermentation medium (accidentally found that this medium contain high percentage of **penicillin G** , which leads to kill the bacteria in the betri dish in the laboratory, The goal was **not** to develop penicillium – fungi contamination in the laboratory , it was experiences contain bacteria added for it different materials to see the ability of this material to kill the bacteria , then they found that the bacteria died after the contamination , at the beginning they think that's wrong things happen , but actually was the beginning of the discovery of beta lactam antibiotics.)
- At the beginning, Penicillin G was taken from the medium that already contaminated with **penicillium**, then Isolate and recognize him.

- Penicillin G is the only natural penicillin which is still used until now , and as we said before , there are various manufactures based on penicillin, which leads to produce semisynthetic product (modified natural product, means that it was **not completely manufactured** it was a natural product that underwent some changes to become semi-synthetic) or synthetic product (completely manufactured) , side chains can be added that alter the susceptibility of the resulting compounds to inactivate enzymes (*β-lactamases*)

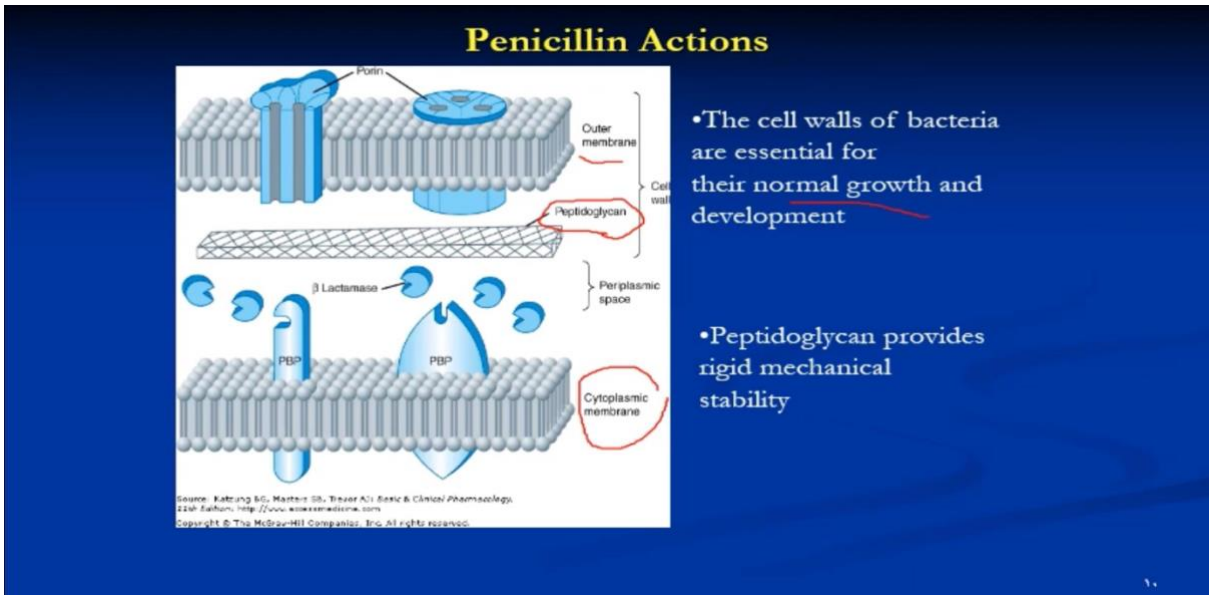
- The good and efficient way **to avoid resistance** facing the penicillin is also to add new products which work with the antibiotics, not only to develop the antibiotics as itself to be more resistant to lactamase , but also do modifications by adding other product with the **same** structure of the drug.
- *Clavulanic acid* one of the most important example of compound that added - combined -with penicillin specifically *ampicillin* to give good combination can do inhibition to enzyme which break the lactam ring (we can call these enzymes *lactamases or penicillinases*) the most popular structure are *"Augmentin"* - and there are various commercial alternatives of this structure – it's a combination of **clavulanic acid** and **ampicillin.**

- This diagram illustrate how **penicillinase work** and **prevent** beta lactam antibiotics from do their work.
- in the normal condition, if we have **penicillins** structure want to enter the bacteria cell , there is an enzyme called *Amidase* break in this point (2) and that leads to produce semisynthetic structure (**active ingredient**) which will make inhibition to the cell wall synthesis and make the affect of antibiotic.
- There are another product (*carboxylate* and *6-aminopenicillinate*) , the part which linked with **amidase** and the process to produce the product that we mentioned before , it supposed to happen when **penicillin** enter the bacterial cell and make it's work , but actually what happen (not always) when there are a type of resistance by the bacteria through the ability of the bacteria to produce the **penicillinase** , then **penicillinase** go and break in this place (1) – site of action of **penicillinase**- and this make the beta lactam ring breaks down , so the product (*amino penicillinase* and *carboxylate* + the semisynthetic product) will not be produced.
- It produce compounds called *penicilloic* acid which **don't** have any efficiency to work against inhibiting the wall synthesis of bacteria.



- This picture show you a cross section to the cell wall of the bacteria, which contain the outer membrane, *peptidoglycan* part of the cell wall and cytoplasmic membrane.

- The cell wall are **essential** for the **normal growth** of the bacteria, and it should be in a normal situation , so this is the main idea that makes us say that penicillin are sidle were it successful in inhibiting the cell wall synthesis.
- *Peptidoglycan* are responsible for forming the **rigidity** in the cell wall of the bacteria, so they are very essential for the cell wall structure.

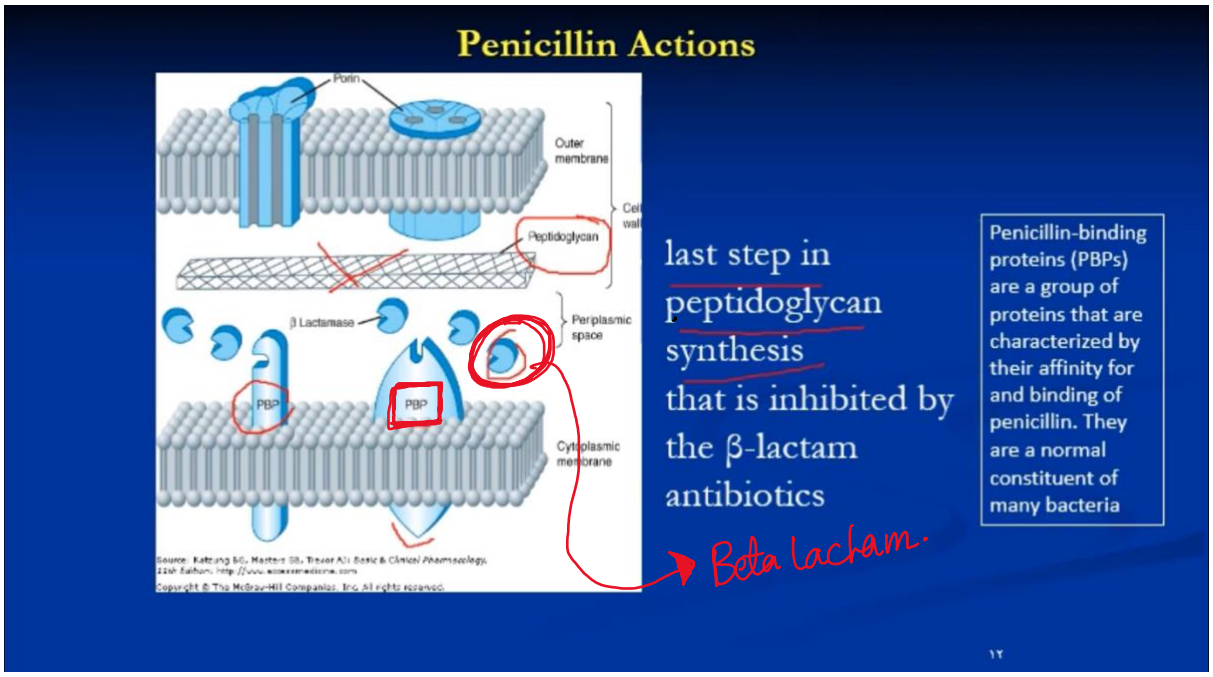


- There is a fundamental difference you need to know it about the differences between *Gram positive* and *Gram negative bacteria* , the **thickness** of the wall are **different** , the **Gram Positive bacteria** thickness of the wall is arrange from **50 – 100** molecules thick , whereas in the **Gram negative bacteria** it's much **less** up to **1 – 2** molecules thick.

- Penicillin specifically inhibits the last step in peptidoglycan synthesis, **remember**: peptidoglycan part of the cell wall is the responsible part about the rigidity of the cell wall, and the **rigidity** of the cell wall is what protect the structure of the bacteria - so if the part that responsible to protect the rigidity of cell wall get damaged, the whole of bacteria will be affected.

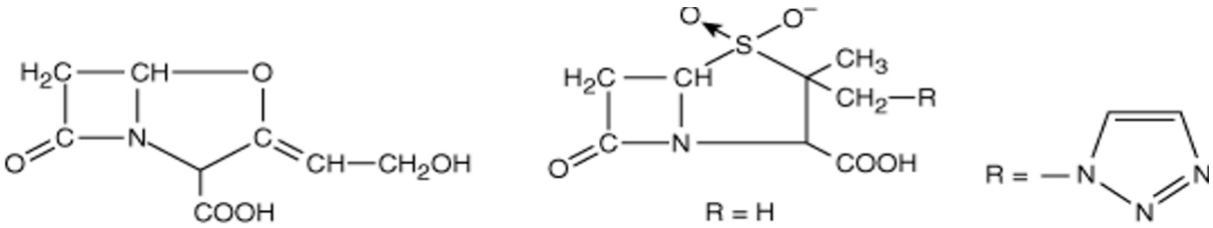
- Beta lactam bind with molecules called *PBPs* (**penicillin binding proteins**) - they are natural product present in the cell wall of bacteria, **not found in the human cell** – then start inhibiting of the last step of peptidoglycan synthesis.

- As we said that *PBPs* found in bacteria but **not** found in human cell, and this explain the selectivity and why **they don't bind to the human cell**.



Beta lactamase inhibitors:

- The one that we mentioned before are *Clavulanic acid* , and there are another example such as *Sulbactam* and *Tazobactam*



Clavulanic acid **Sulbactam** **Tazobactam**

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

**you don't have to memorize the structures **

Some examples of penicillins:

1-Benzyl penicillin (Penicillin G): the only natural product that still used and fall under **penicillins**.

- ✓ It given as **deep IM injection**.
- ✓ It's highly and only effective against sensitive strains of **gram-positive cocci**, But it is no longer efficient for a lot of antibiotics, because of high resistances.
- ✓ hydrolyzed by *penicillinase* are the main problem linked with this type of **penicillins**.
- ✓ ineffective *S. aureus* , but we can say it is the foundation of structures that later it was manufactured that fall under beta lactam antibiotics.

2-Procain benzylpenicillin:

- ✓ Painless, prolonged action to the **penicillin G injection**.

3-Phenoxymethyl penicillin:

- ✓ It is given **orally** - whereas penicillin G given **IM** - because it has been modified the structure to become not able to be destroyed by **gastric juice** , so it still stable with gastric juices inside the **stomach**.

4-Cloxacillin, Dicloxacillin, and Fluclocillin :

Greatly exceeded **penicillinase** resistant, efficient for *Staphylococcus* (which was never affected by **penicillin G**).

* every structure added , have a type of development like routes of administration, the stability and the resistance.**

" لٰكنَّ عَوض الله سيُمحي مُرَّ ما رَأيت ، وما تلَوّعت ، و كُلّ خَيبَة دُقت ، و كُلّ غَصّة عالِقة في صَدرك ، فخُذ بالأسباب و كأنّها كُلّ شَيء و توكّل عَلىٰ الله وكأنّها لا شَيء "