Pharmacology

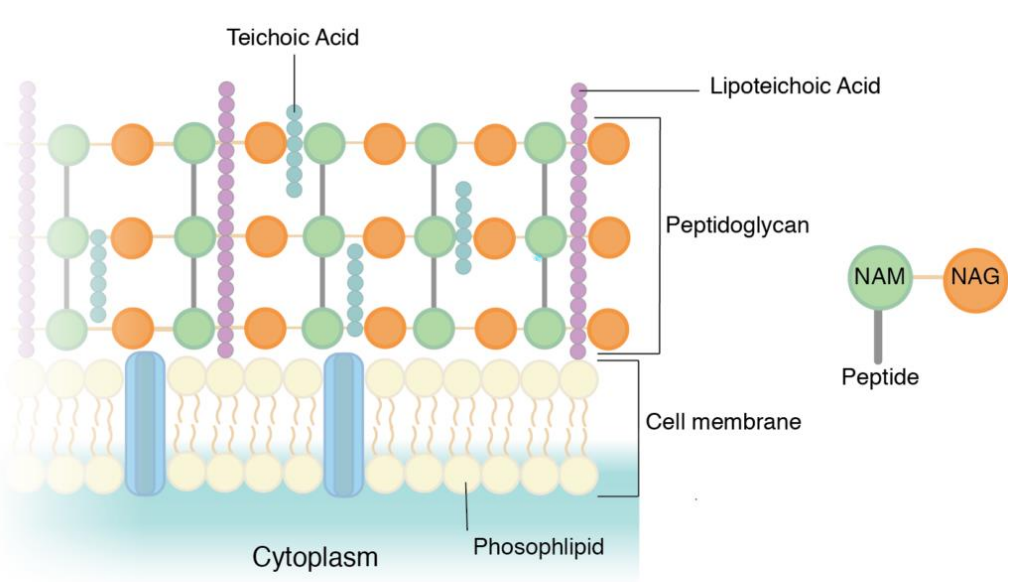
Subject :

Lec no : 23

Done By : Raneem Azzam

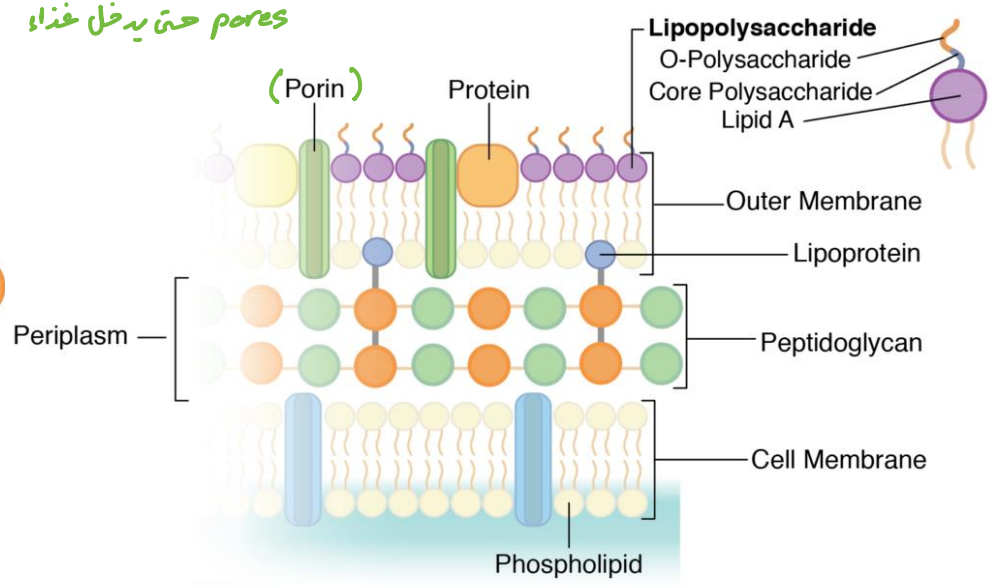
وَقُل رَّبِّ زِدْنِي عِلْمًا

Overview: Bacterial Cell Wall



Gram Positive Bacteria Cell Wall

pores حتى يدخل غذاء



Gram Negative Bacteria Cell Wall

Tareq Saleh ©

Wolters Kluwer

هسا كل البكتيريا عندها cell wall، شو بختلف تاعها عن تاع البني ادم انو احنا بالاصل ما عنا cell wall ،،،من هون منعرف فائدة استخدام ال antibiotic انها بتستهدف ال cell wall of bacteria لانو لو انا عندي cell wall كان المضاد هاجمني زي ادوية الكانسر

البكتيريا ليه عندها cell wall حتى تحميها وخصوصا من ال anti
*طب مين ال antibiotics لي بتأثر على ال cell wall ؟
1)B lactams
2)vancomycin
3) daptomycin

كل البكتيريا محاضرة Micro الي في ال

Gram-positive cell walls | Gram-negative cell walls

الفروقات بينهم : ايضا في فرق باللون بسبب الصبغة

• Thick peptidoglycan → 3 layer	• Thin peptidoglycan 1 layer
• Teichoic acids في بس ببتيدوغليكان	• No teichoic acids
• No outer membrane	• Outer membrane
• No periplasm	• Have periplasm +

Selective Toxicity:

"The ability of an agent to injure or kill an invading microorganism without harming host cells"

Minimal effect of toxicity

Mean that's antibiotic target bacterial with minimal effect on human

الدكتور بالبداية ذكر في محاضرة

*Both types of bacteria have a layer of cell wall that outline the cell membrane which is responsible of regulationg the permeability of substances in and out the cell.

هسا بسبب اختلاف ال cell wall من ناحية الخمل و وجود ال outer membrane بين ال + و - رح تختلف عندي تأثير ال antibiotic

مثل

ال penicillin بشتغل better على ال gram positive bacteria than negative bacteria

*it is difficult to target gram negative cell wall because of the structure of the outer cell membrane

The major challenge For successful Antimicrobial Therapy is to eradicate gram negative bacteria specially multi resistant of gram-negative bacteria → in treatment

بينما ال ⊖ difficult to kill

+ منو بطلع د معلومة انو ⊕ dependent on cell wall to kill

Overview: Synthesis of Bacterial Cell Wall

Made of peptidoglycan (in bacteria)
- Polymer of disaccharide N-acetylglucosamine (NAG) & N-acetylmuramic acid (NAM)
- Linked by polypeptides

1. Cytoplasmic Stage:

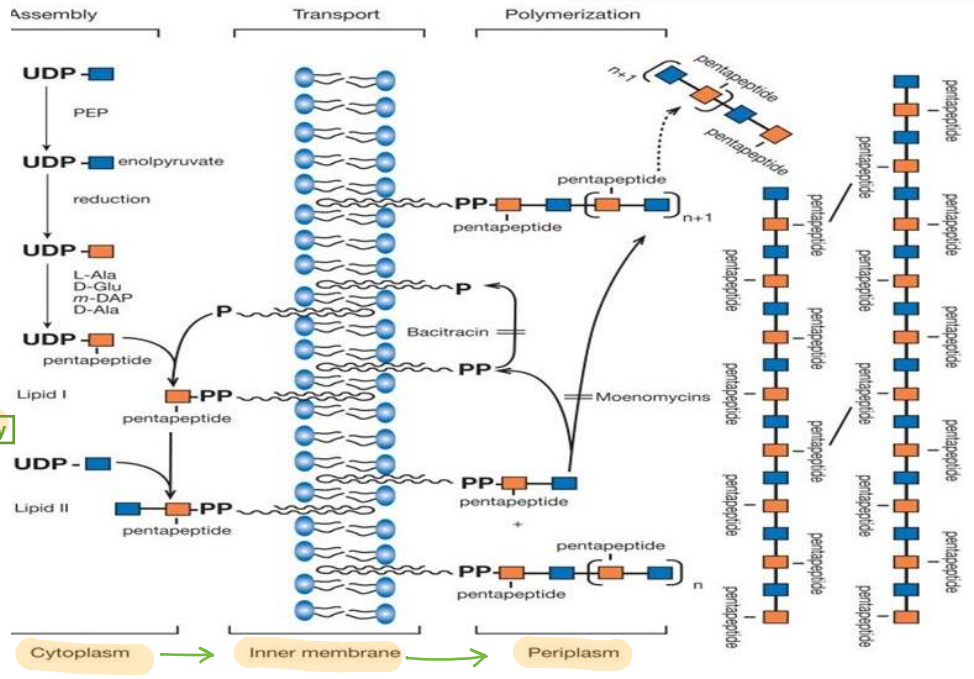
- Synthesis of glycan precursors: UDP-MurNAc-pentapeptide, UDP-GlcNAc

2. Cytoplasmic membrane Stage:

- Transfer to membrane receptors

3. Extracellular membrane stage:

- Transpeptidation via PBP

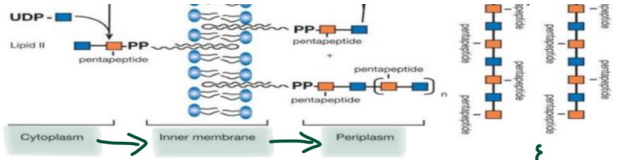


3. Extracellular membrane stage:

- Transpeptidation via PBP

Pencillin ← Binding → protein

→ the most important Stage.



Glycan → Back bone

Peptide → attach them (أي الصنع)

Trans Peptidation وبتحبس عبر انزيم اسمه Transpeptidase. → وهاي العملية بسميها

or Pencillin Binding protein.

* The third step has another name → Cross Linking.

Penicillins

*The penicillins are among the most widely effective and the least toxic drugs known, but increased resistance has limited their use.

Penicillins

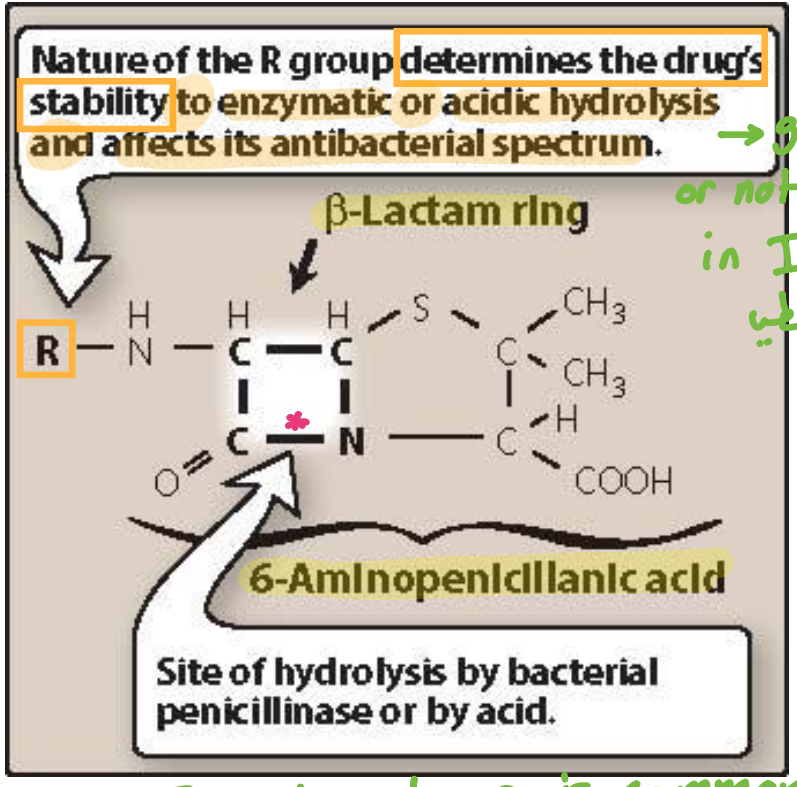
PENICILLINS

- *Amoxicillin* AMOXIL
- *Ampicillin* PRINCIPEN
- *Dicloxacillin* DYNAPEN
- *Nafcillin*
- *Oxacillin*
- *Penicillin G* PFIZERPEN
- *Penicillin V*
- *Piperacillin*
- *Ticarcillin*

Members of this family differ from one another 6-aminopenicillanic acid residue.

سبب تنوع واختلاف R

first one →



بعد :- give itoral or not / injection in IM or IV أو الأحسن اعطيه oral

*The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, cross-hypersensitivity, and susceptibility to bacterial degradative enzymes (β-lactamases)

anti-biotic الكسر لبكتيريا تطلقه انزيم → β-Lactam ring عن طريق انها بتكسر → عليها تجمة C-N وتحديداً بين

الاسم آخر → Penicillinase

This structuer is common on all penicilline drug *

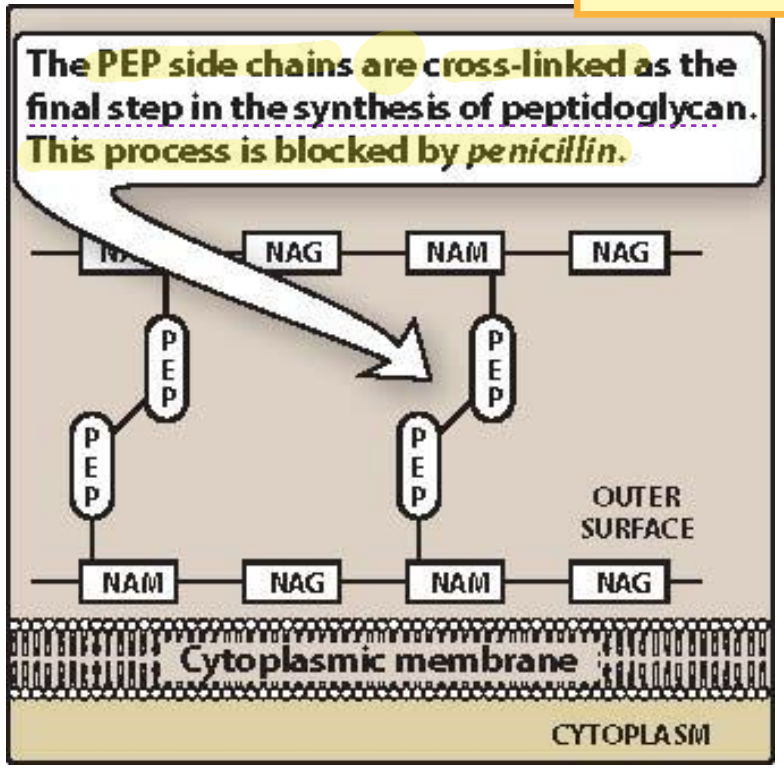
Quick Microbiology Reminder

A group of enzymes that are responsible to mediate the third step of cell wall synthesis "the cross-linking"

Penicillin-binding proteins:

- Penicillins bind and inactivate bacterial cell membrane proteins called: penicillin-binding proteins (PBPs).
- Bacterial enzymes involved in cell wall synthesis
- Variable among different species
- Involved in resistance

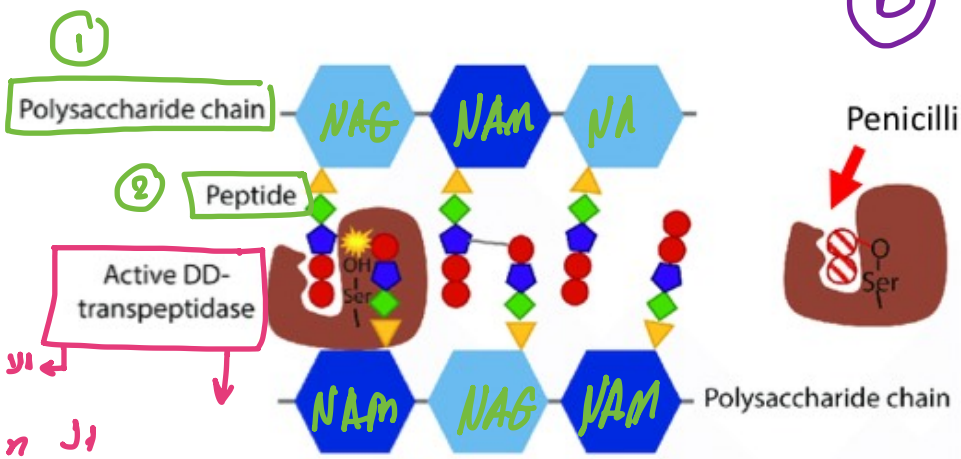
غير قابل انو يرتبط فيه Penicilline



هسا كيف البنسلين بستهدف ال cell wall ؟

نتذكر تركيبة ال cell wall

A



الانزيم اللي بربط
1 Pebtide chain ال
مع الجدارين (Poly disclm)
2

الاسم الثاني الـ PbPs

B

Penicillir → بيجي ال B - Lactams

وبعمل bind

مع هذا الانزيم اللي كان يربط الـ p.chanin

مع polysaccharide

شو النتيجة؟ يمنع تكوين ال cell wall

فالبنسلين بدخل من الثقوب الموجودة على cell wall / تعمل rupture للخلية تطول

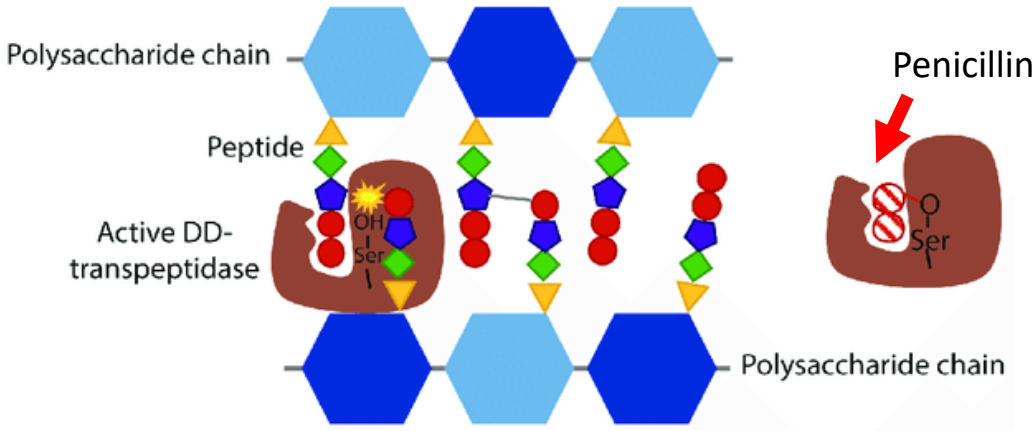
فلما اعاد ابسط البنسلين بفوت ويدمر الخلية ، فهاد البنسلين قاتل او لا ؟

قاتل آكيد

Penicillins

Mechanism of action

- Inhibit transpeptidation or cross-linkage (*last step* of bacterial wall synthesis)
- Prevent cross-linking catalyzed by the PBP transpeptidase



What is the basis of selective toxicity?

Penicillins

What are the consequences of transpeptidation inhibition?

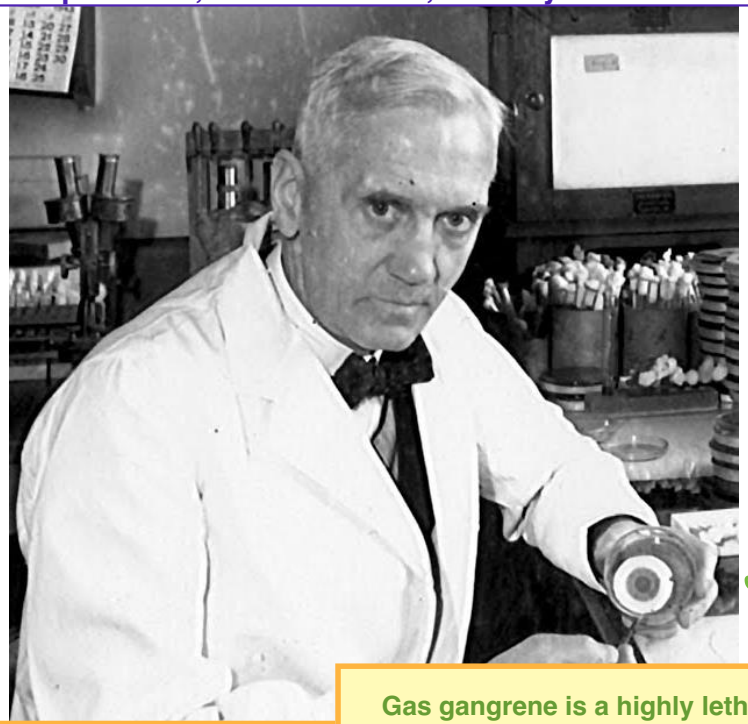
- Bacterial cell lysis — because of → cell wall became weak
- Bactericidal — قاتل — البنسلين قاتل للبكتيريا
- Time-dependent
- Effective against rapidly growing bacteria — worked better when↑

→ that why I should not give the patient bacteriocidal with bacteriostatic.

طيب، هسا بدنا نحكي أنواع البنسلين [مهم للـ Cases]، مهم نعرف النوع، الأمثلة، الاستخدام، الفرق بين كل مثال والثاني واللي بكون عبارة عن كلمة وحدة 😊.

Penicillins

في جملة شهيرة اول قالها :
I didn't invent penicillin,nature did that , I'm only discovered by accident



Antibacterial spectrum

1. Natural penicillins:

- Penicillin G, Penicillin V: *Penicillium chrysogenum*
- Drugs of choice for the treatment of gas gangrene (Clostridium perfringens) and syphilis (Treponema pallidum).
- Penicillin V is the oral form of penicillin

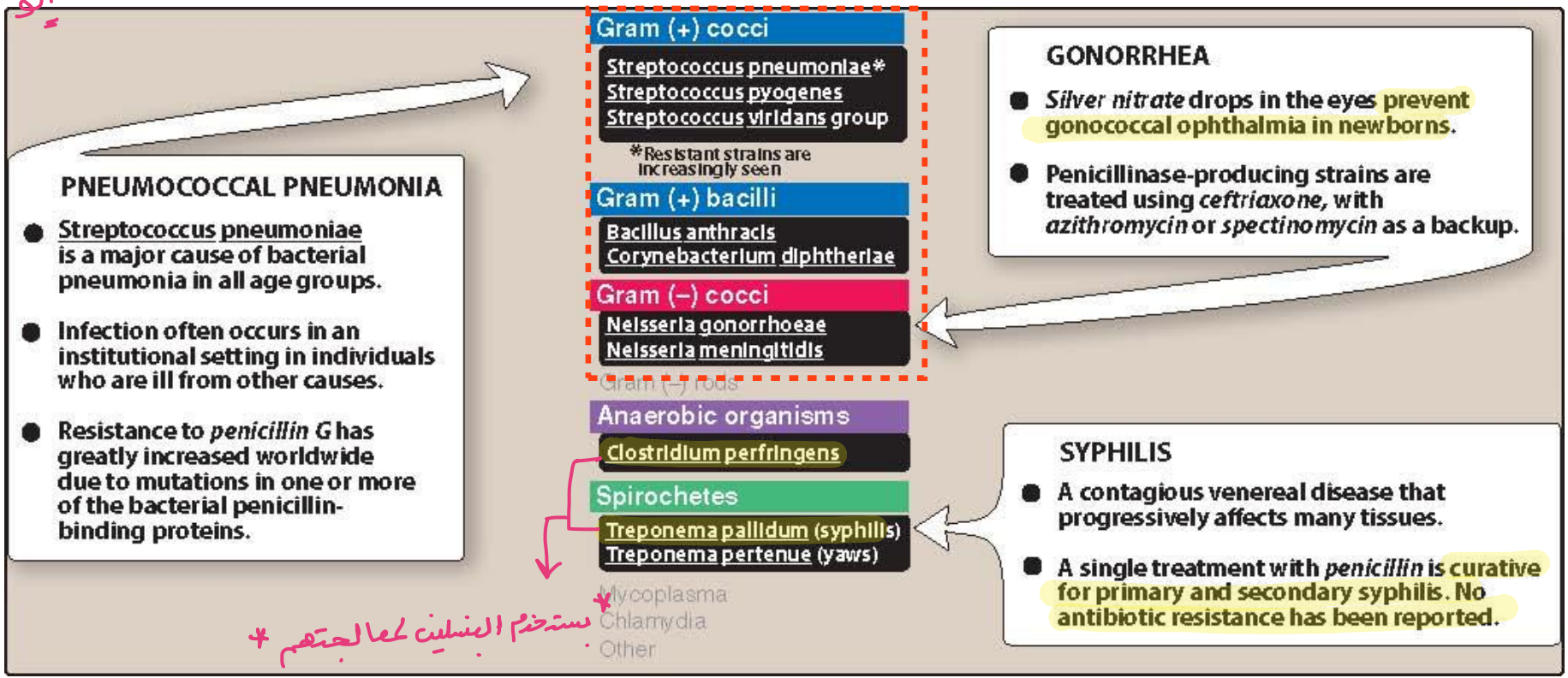
كلام الدكتور ، مش عشان في كثير resistant طلع بعد استخدام البنسلين انو مارح نستخدمو ابدا لا بالعكس لسا بنستخدم في بعض ال particular still helpful + available in clinic ولسا of infection

Syphilis is a sexually transmitted infectious (STI) disease caused by the bacterium Treponema pallidum

Gas gangrene is a highly lethal infection of soft tissue, caused by Clostridium species, with Clostridium perfringens being the most common

Penicillins

Antibacterial spectrum



من الكتاب

Antibacterial spectrum:

*The antibacterial spectrum of the various penicillins is determined, by their ability to cross the bacterial peptidoglycan cell wall to reach the PBPs in the periplasmic space.

*Factors that determine the susceptibility of PBPs to these antibiotics include : the size, charge, and hydrophobicity of the particular β-lactam antibiotic.

*In general gram-positive microorganisms have cell walls that are easily traversed by penicillins

: classification of penicillin طب شو هي ال +

1. **Natural penicillins:** → ..... إلي أكتشفها العالم من عفن الخبز ← إلي جاي من الشياد طبيعية

لـ كان عيبها انها ضيقة المدى (الطيف) ← كان معظمها g+ و واحدة g- هاي Neisseria gonorrhoeae

2. **Extended-spectrum penicillins:** ..... Ampicillime ضمار اسمو penicillime على a.a هون ضافو

*Semisynthetic penicillins, such as amoxicillin and ampicillin (also known as aminopenicillins), are created by chemically attaching different R groups to the 6-aminopenicillanic acid nucleus.

وهاد واسع الطيف أو المدى

3. **Antistaphylococcal penicillins:**

4. **Antipseudomonal penicillins:**

Wider Than the original penicillin + able to kill different types of gram +/-

Ampicillin and amoxicillin have an antibacterial spectrum similar to that of penicillin G gram-negative bacilli.

Penicillins

Antibacterial spectrum:

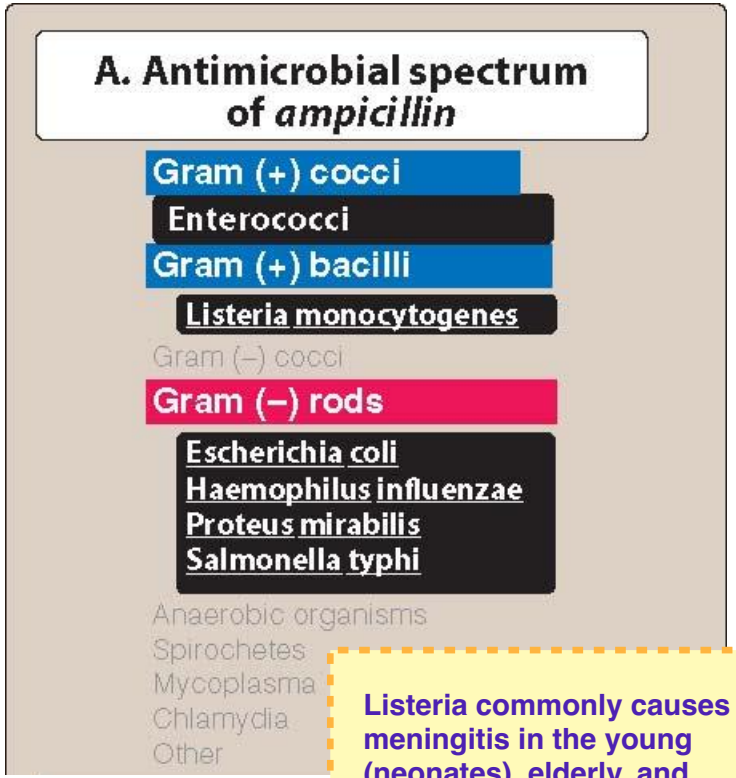
2. Extended-spectrum penicillins:

- Semisynthetic: ampicillin, amoxicillin
- Spectrum: extended to include gram-negative bacilli

❑ Ampicillin: **drug of choice** for gram-positive bacillus *L. monocytogenes*

**Also for *enterococci*, resp infections

❑ Amoxicillin: Ear, nose, and throat infections, dental prophylaxis



Listeria commonly causes meningitis in the young (neonates), elderly, and immunocompromised patient population.

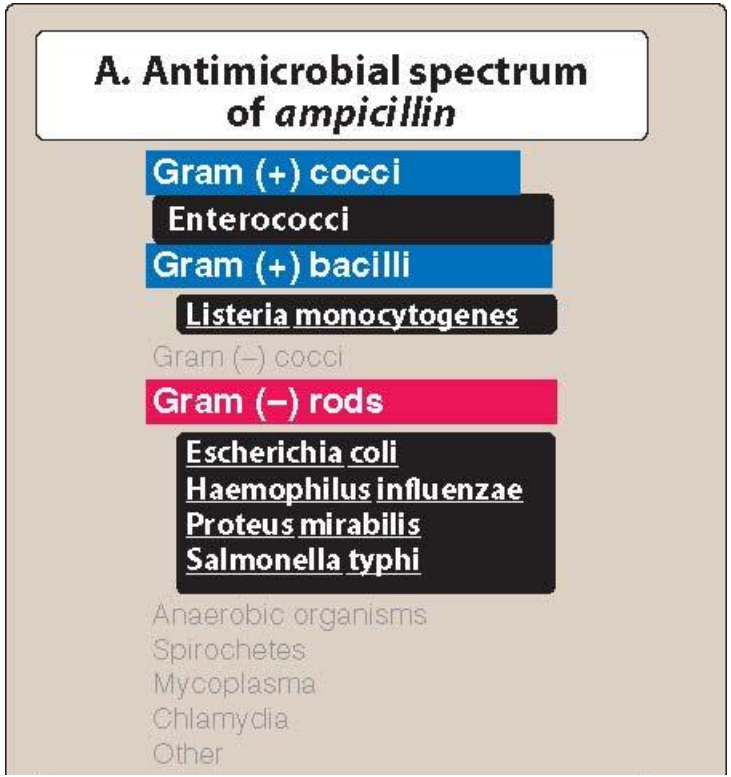
Penicillins

Antibacterial spectrum:

2. Extended-spectrum penicillins:

- Combined with β-lactamase inhibitors

e.g., MSSA is resistant to ampicillin and amoxicillin IF given without a β-lactamase inhibitors



. Resistance لتحييم من β-Lactamase لـ inhibitors مع بشكل-

*Formulation with a β-lactamase inhibitor, such as clavulanic acid or sulbactam, protects amoxicillin or ampicillin from enzymatic hydrolysis and extends their antimicrobial spectra. مهم جداً جداً

*Amoxicillin → Better ↔ distribution. absorption.

Penicillins

Antibacterial spectrum

3. Antistaphylococcal penicillins:

- Methicillin, nafcillin, oxacillin, dicloxacillin
- Effective against penicillinase-producing staphylococci (MSSA)
- Minimal activity against gram-negative
- Methicillin not used clinically (toxic)

Antistaphylococcal penicillins:

مجموعة 3

*are β-lactamase (penicillinase)-resistant penicillins.

*[Note: Because of its toxicity (interstitial nephritis), methicillin is not used clinically in the United States except in laboratory tests to identify resistant strains of S. aureus. MRSA is currently a source of serious community and nosocomial (hospital-acquired) infections and is resistant to most commercially available β-lactam antibiotics.]

MSSA ← مانت
MRSA ← ماماتت
بستخدم * methicillin على الـ agar ولو البكتيريا

+ resistant to all penicilline
لـ بس استثناءات مع وجود خطر للمرض

4-) Antipseudomonal penicillins:

خاص بالمجموعة 4

*Piperacillin and ticarcillin are called antipseudomonal penicillins because of their activity against Pseudomonas aeruginosa .

Blactamase اغلبها من

*These agents are available in parenteral formulations only.

*Formulation of ticarcillin or piperacillin with clavulanic acid or tazobactam, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinaseproducing organisms (for example, most Enterobacteriaceae and Bacteroides species).

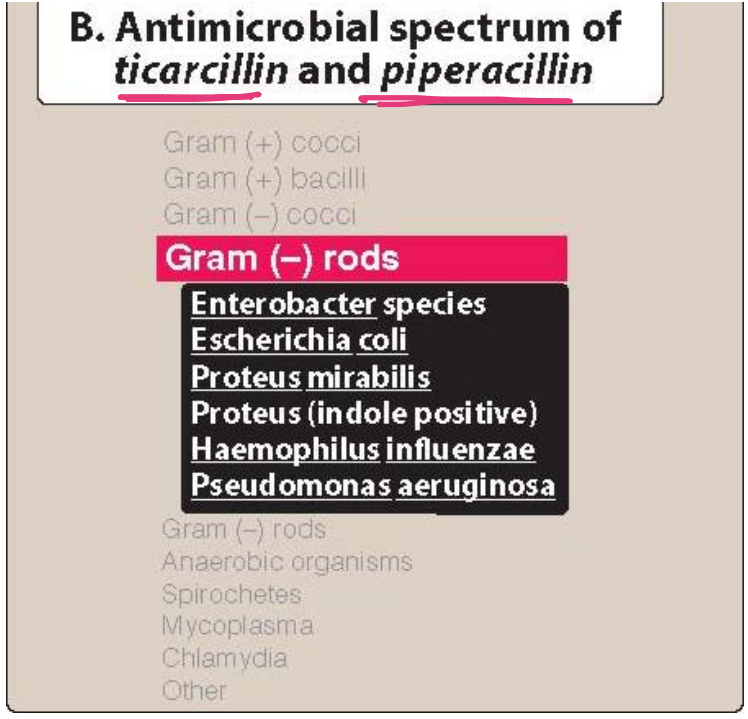
Penicillins

Antibacterial spectrum: New

4. Antipseudomonal penicillins:

- Piperacillin
- Effective against gram-negative bacilli (but not against *Klebsiella*)
- Common combinations:

Piperacillin + tazobactam



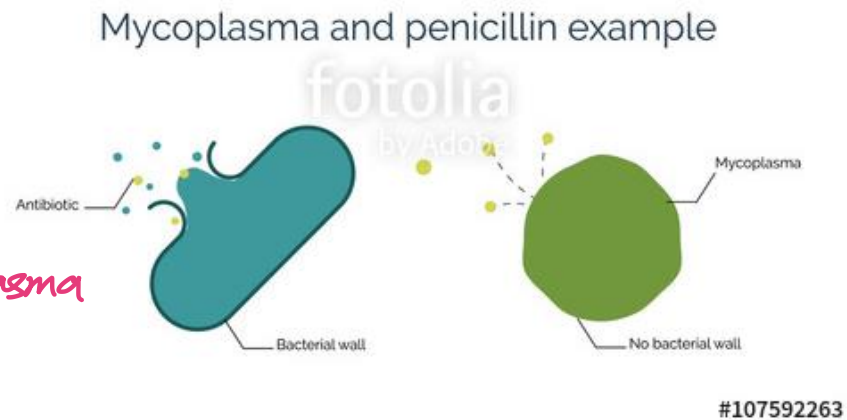
Penicillins

Mechanisms of resistance

- **Intrinsic Resistance:**

- Microorganisms that lack peptidoglycans cell walls e.g., *M. pneumoniae*

- Microorganisms that have impermeable cell walls



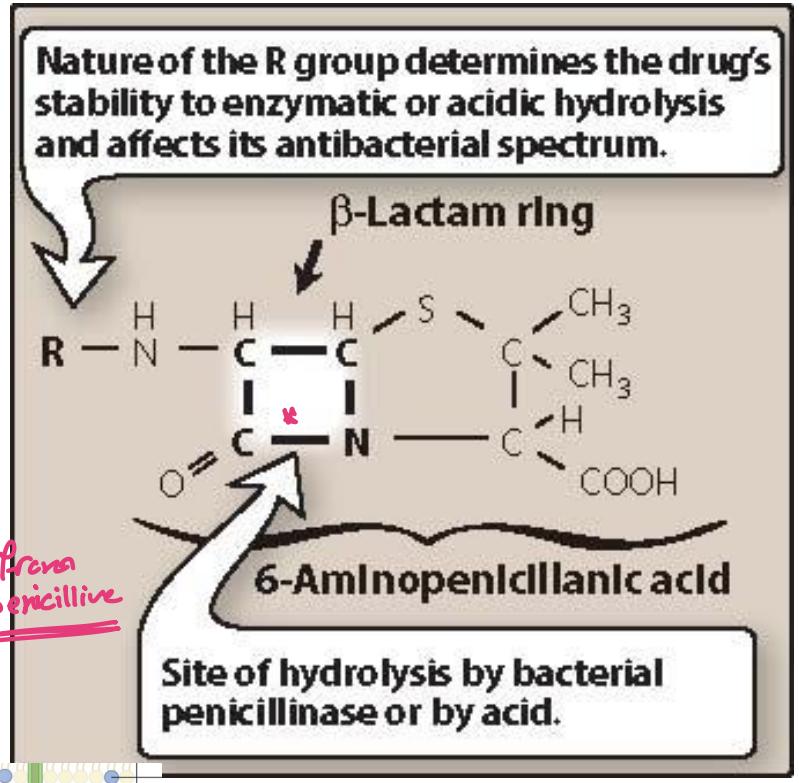
Penicillins

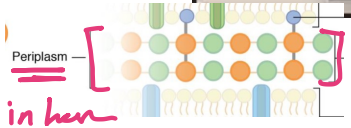
Mechanisms of resistance

- **Acquired Resistance:**

1. β-Lactamase activity:

- Enzymes that *hydrolyze* the cyclic amide bond of the β-lactam ring
- Mostly acquired (plasmids)
- **Gram-positive**: secrete β-lactamases extracellularly out cell to protect the cell wall from penicillins
- **Gram-negative**: periplasmic β-lactamases





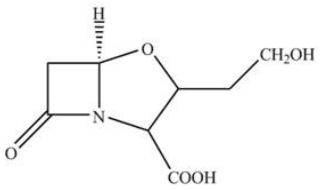
Production of β-Lactamases is the main resistance mechanism against β-Lactams.

How is this problem solved? by use β-Lactamase Inhibitors

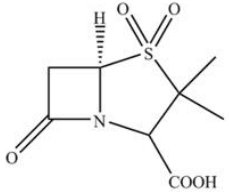
كلام الدكتور ←

On their own, this chemical don't have antibiotic affect they don't kill bacteria if they used in their own, their only use to interfere with the action of the B-lactamase enzyme produced by the bacteria, in order to protect the the penicillin from the resistant mechanism

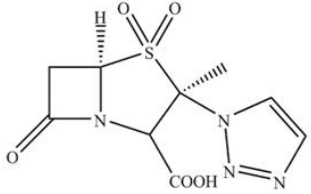
β-Lactamase Inhibitors



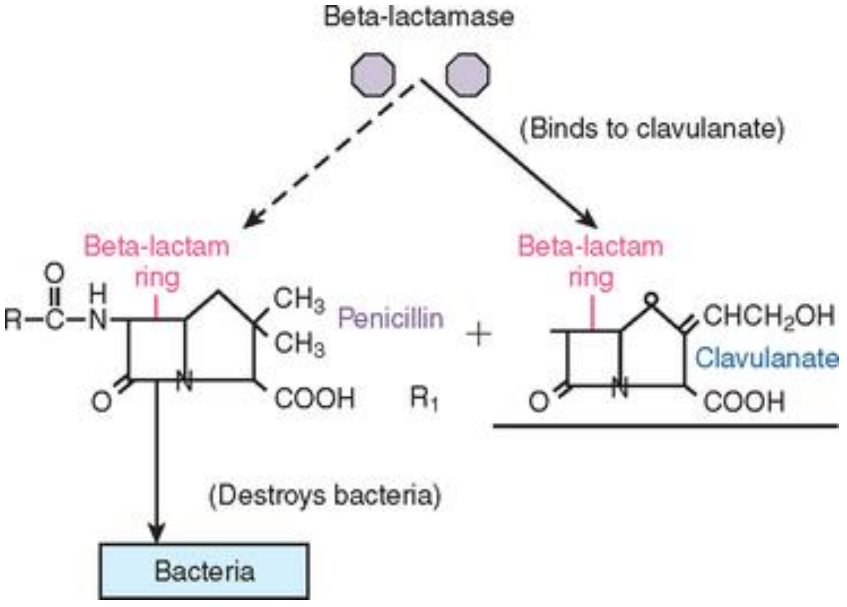
Clavulanic acid



Sulbactam



Tazobactam



كلام الدكتور

① Clavulanic acid: Combine mostly with Amoxocillin to produce amoxiclave, which is administered orally only.

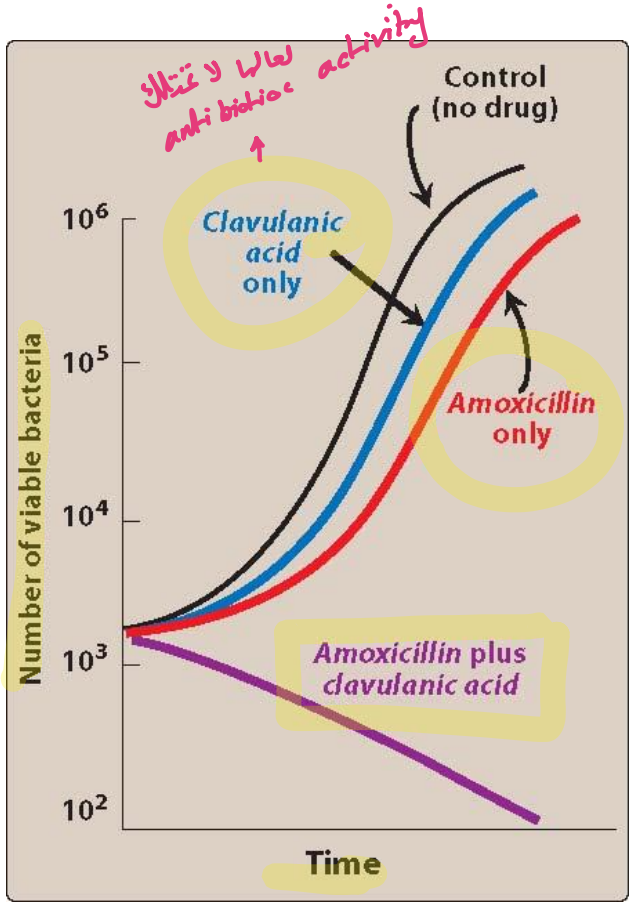
② Sulbactam: Combine with ampicillin.

③ Tazobactam: Combine with piperacillin.

β-Lactamase Inhibitors

- Contain β-Lactam rings
- BY THEMSELVES, no antibacterial activity
- Protect antibiotics that are normally substrates for β-Lactamases
- Example……?

إلي فوق بالسلايد



The in vitro growth of Escherichia coli in the presence of amoxicillin, with and without clavulanic acid.

Penicillins

Mechanisms of resistance

- **Acquired Resistance:** Prevent reach penicillin to the target cell wall

2. Decreased permeability to the drug:

Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPs

- Reduced permeability e.g., *Pseudomonas aeruginosa*
- Efflux pump e.g., *Klebsiella pneumoniae*.

The presence of an efflux pump can also reduce the amount of intracellular drug (for example, Klebsiella pneumoniae).

3. Altered PBPs:

بتشوف البنسلين مثلا وبتعملو pump لبرا حتى ما يوصل ل periplasmic

- Modified PBPs with lower affinity for β-lactams e.g., MRSA resistance to most β-lactams.

البكتيريا بتعمل mutates of gen للبنسلين كود بروتين ف بتعمل
change in structure which make it reduce the affinity to binding b lactams , penicillin now don't bind to penicillin bind protein as should be

3. Altered PBPs:
Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. This explains MRSA resistance to most commercially available β-lactams.

These modified PBPs change the active site, causing the β-lactam agents to lose or diminish their affinity with the target protein, promoting resistance