النادي الطبي

Pharmacology

Done by : Johainah Taha

lecture no. 14 - Part 2

Cell wall inhibitors 1

Cell Wall Inhibitors → Bacterocidal

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

Tareq Saleh, MD, PhD

Faculty of Medicine

The Hashemite University

Textbook: Chapter 29 pp 369- 383

● فيديوهات أنصحكم بط لهذه المحاضرة :-

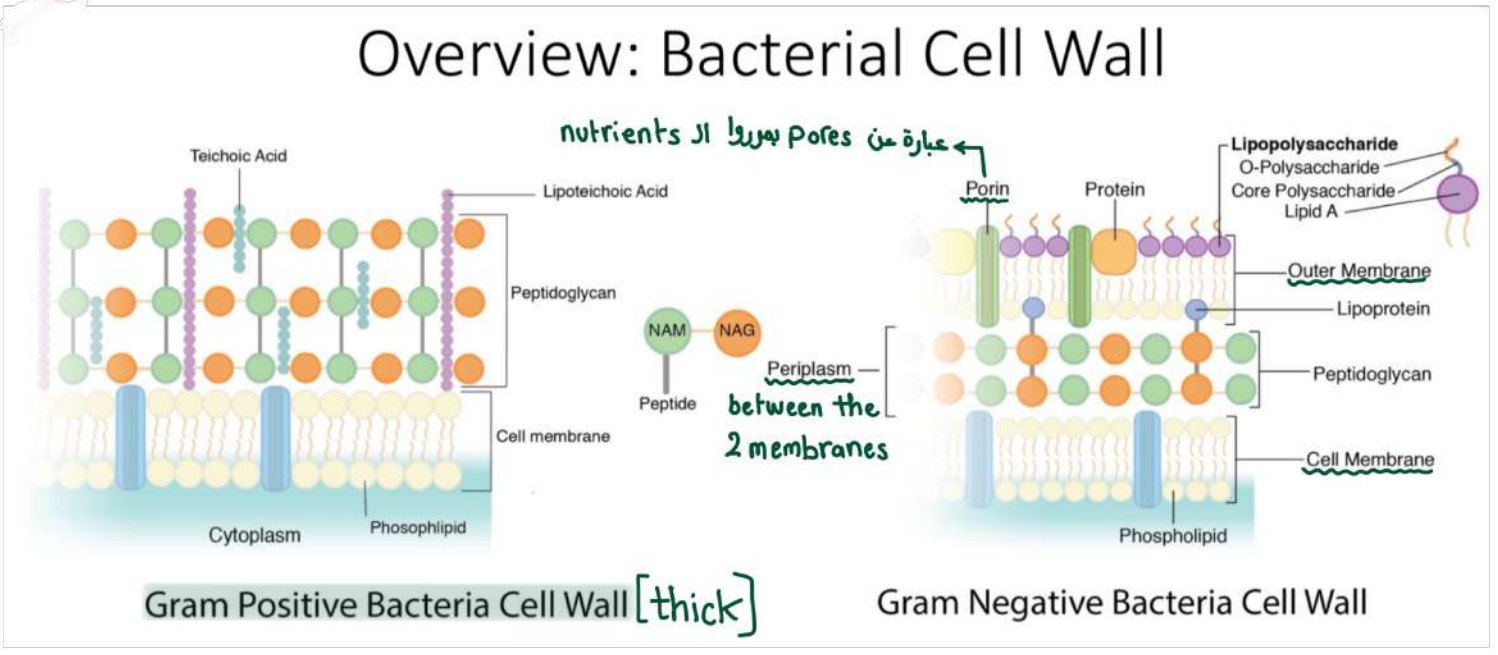
↓

شرح البنسلين اللي حنحكي عنه بالمحاضرة

↓

فيه أساسيات مهم نعرفها قبل ما نبدأ بالموضوع

⊕ مراجعة للمحاضرة الماضية



*Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall a structure that mammalian cells do not possess.

*The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links.
To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms. They have little or no effect on bacteria that are not growing and dividing.

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

*the early cell wall inhibitors have narrow spectrum to the gram positive bacteria and the new classes have wider coverage of the two type of bacteria.

*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.

From the book :

- هم يحكيلي عن عائلات الأدوية اللي بتشتغل عال Cell wall:

*The most important members of this group of drugs are the β-lactam antibiotics (named after the β-lactam ring that is essential to their activity), vancomycin, and daptomycin.

Overview: Synthesis of Bacterial Cell Wall

1. Cytoplasmic Stage:

- Synthesis of glycan precursors: (building blocks)

1. UDP-MurNAc-pentapeptide,
2. UDP-GlcNAc

2. Cytoplasmic membrane Stage:

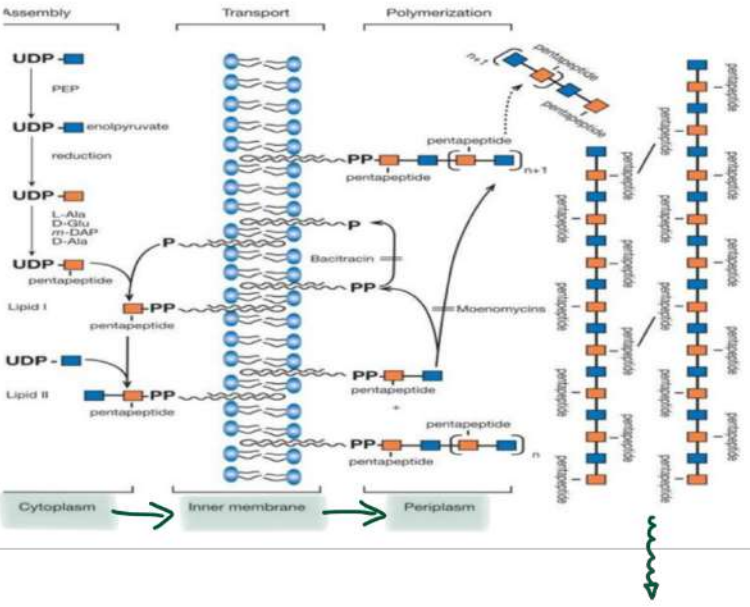
- Transfer to membrane receptors

3. Extracellular membrane stage:

- Transpeptidation via PBP

Pencillin ← Binding → protein

→ the most important Stage.



Glycan → Back bone

Peptide → attach them (أي الصق) → وهاي العملية بسميها

Trans Peptidation وبتصير عبر انزيم اسمه Transpeptidase.

→ or Pencillin Binding protein.

* The third step has another name → Cross Linking.

* حاسة مهم قبل ما نبدأ بالموضوع الجاي انه نلخصها ونتذكر أنواع البكتيريا بالمايكرو :)
حألخصهم بـ Mind Map ♡

Gram - Stain

Posetive

Cocci

- Staphylococcus
  1. S. aureus
  2. S. epidermidis
  3. S. saprophyticus
- Streptococcus
  1. Pyogens
  2. agalactiae
  3. equisimitis
  4. enterococcus
  5. pneumoniae
  6. viridans

Baccili

1. corynebacterium diphtheriae.
2. Listeria monocytogenes.
3. Spore forming
   - Bacillus
     1. Cereus
     2. anthracis
   - clostridia
     1. botulinum
     2. tetani
     3. Perfringenes
     4. difficile

Negative

Cocci

Neisseria

1. gonorrheae
2. meningitidis
3. Catarrh 's

Bacilli

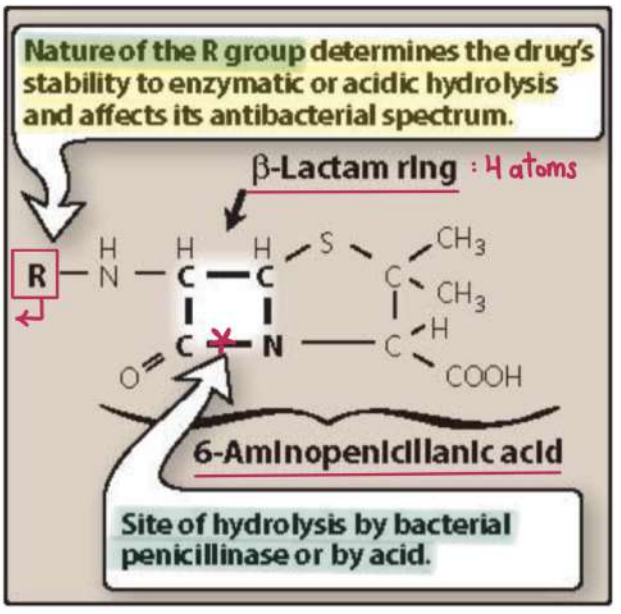
E-Coli

1. Citrobacter.
2. enterobacter.
3. E-sherishia.
4. Proteus
5. Klebsiella.
6. Salmonella
7. Shigella.

Penicillins

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

the side chain that make them different.



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

*Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue.

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

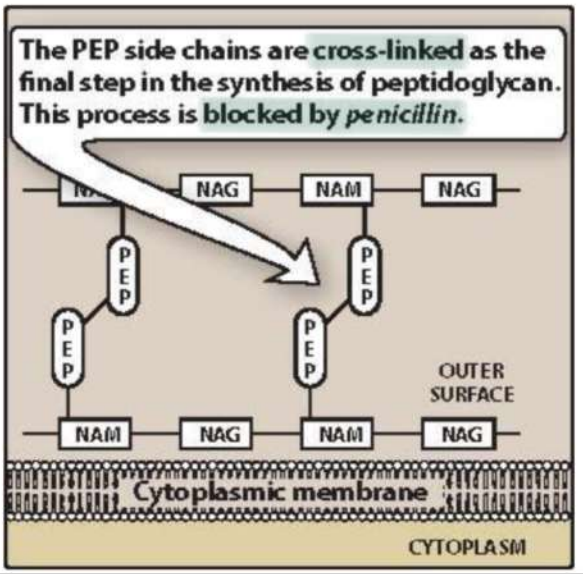
anti-biotic الـ انزيم تطلقه البكتيريا لتكسر الـ β-Lactam ring عن طريق انها بتكسر عليها كبسة C-N وتحديداً بين
الـ اسم آخر Penicillinase

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: PBPs

- 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 انه البنسلين يرتبط فيه .



Mechanism of action: (من الكتاب اقرأوهم لتفهموا الحكاية بعدها انتقلوا للسلايدات)

*The penicillins interfere with the last step of bacterial cell wall synthesis (the 3rd one) (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins.

*These drugs are bactericidal and work in a time-dependent fashion.

*Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall. Consequently, they are inactive against organisms devoid (خالية) of this structure, such as mycobacteria, protozoa, fungi, and viruses.

1. Penicillin-binding proteins:

* penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium.

* Exposure to these antibiotics can therefore not only prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria.

* Alterations in some of these PBPs provide the organism with resistance to the penicillins.

[Note: Methicillin- resistant Staphylococcus aureus (MRSA) arose because of such an alteration]

2. Inhibition of transpeptidase:

Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains. Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity.

3. Production of autolysins: ما انشرحت

Many bacteria, particularly the gram positive cocci, produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall.

In the presence of a penicillin, the degradative action of the auto-lysins proceeds in the absence of cell wall synthesis.

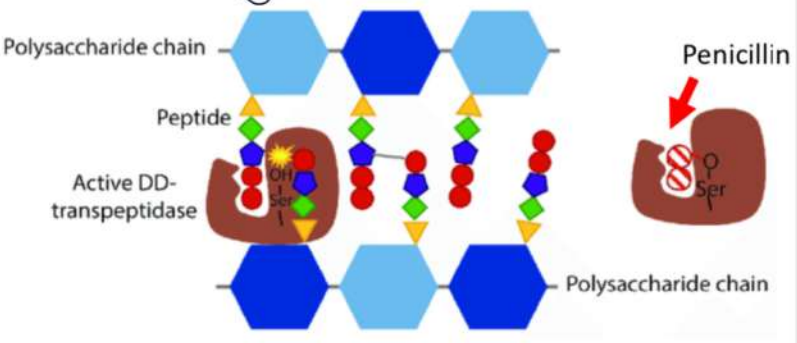
Thus, the antibacterial effect of a penicillin is the result of both inhibition of cell wall synthesis and destruction of the existing cell wall by autolysins.

Penicillins

Mechanism of action

- Inhibit transpeptidation or cross-linkage (*last step* of bacterial wall synthesis) 3rd step
- Prevent cross-linking catalyzed by the PBP transpeptidase

* تأملوا الصورة شوي ؛ البنسلين بتستهدف الانزيم اللي عمل الروابط بين Polysaccharide Chain .



What is the basis of selective toxicity?

What are the *consequences of transpeptidation inhibition*?

- Bacterial cell lysis [cell Burst]
- Bactericidal not Bacteriostatic.
- Time-dependent
- Effective against rapidly growing bacteria → that why I should not give the patient bactericidal with bacteriostatic.

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.**

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

Antibacterial spectrum

1. Natural penicillins:

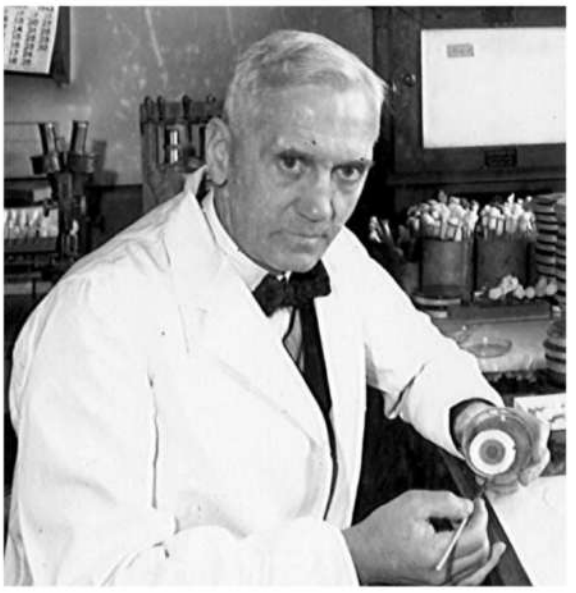
① ②

- Penicillin G, Penicillin V: *Penicillium chrysogenum* → Fungus Species

Cases يوم لأستاذ

Drugs of choice for the treatment of gas gangrene (Clostridium perfringens) and syphilis (Treponema pallidum). ↳ sexually transmited disease.

- Penicillin V is the oral form of penicillin → isn't used in the treatment of Bacteremia.
  ↳ is more acid stable.



*Natural penicillins (penicillin G and penicillin V) are obtained from fermentations of the fungus Penicillium chrysogenum.

حنشرحهم تمان شوي

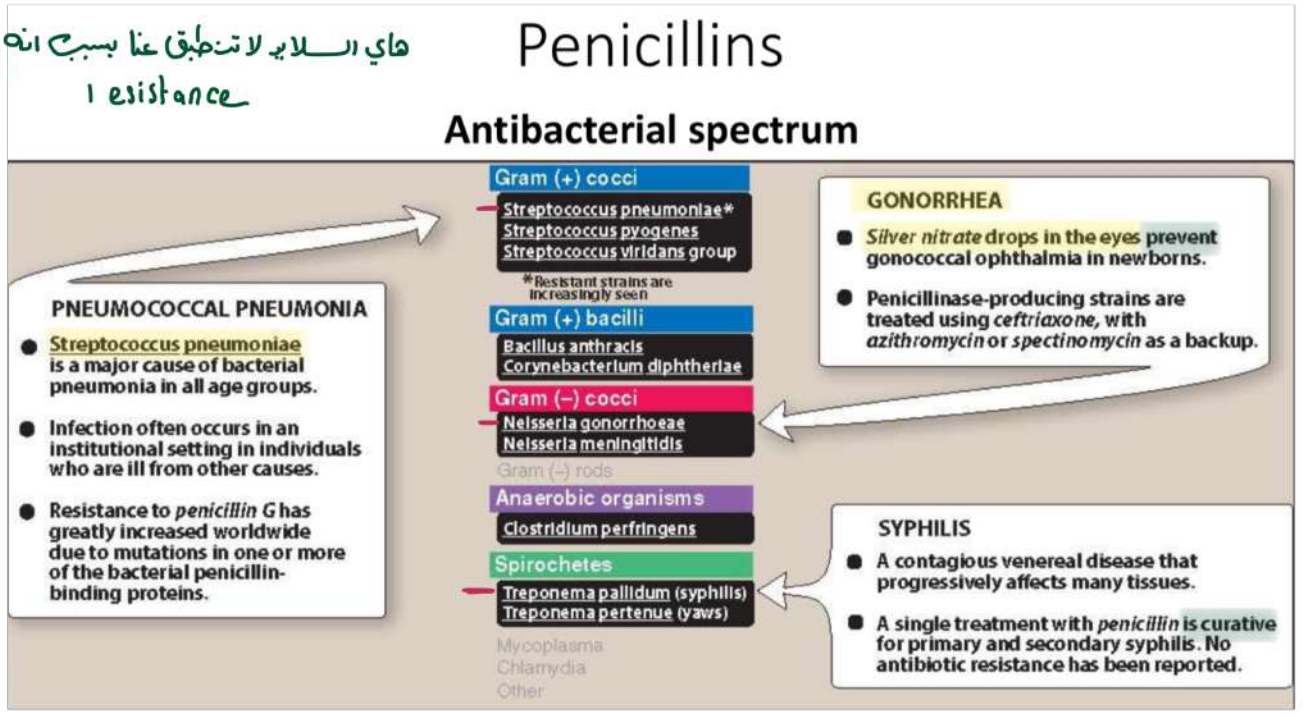
*Semisynthetic penicillins, such as amoxicillin and ampicillin (also known as aminopenicillins), are created by chemically attaching different R groups to the 6-aminopenicillanic acid nucleus.

Penicillin G (benzyl-penicillin) is the cornerstone of therapy for infections caused by a number of gram-positive and gram-negative cocci, gram-positive bacilli, and spirochetes. Sexually transmited diseases وهم Saphilis Gonorrhea وعلى فكرة مش كلهم ؛ بس نوعين

Penicillins are susceptible to inactivation by β-lactamases (penicillinases) that are produced by the resistant bacteria.

* Penicillin G is given by injection.
* Penicillin V is given orally. بعدين طورنا منه

هاي السلايد لا تنطبق عنا بسبب انه في resistance



Antibacterial spectrum:

2. Extended-spectrum penicillins:

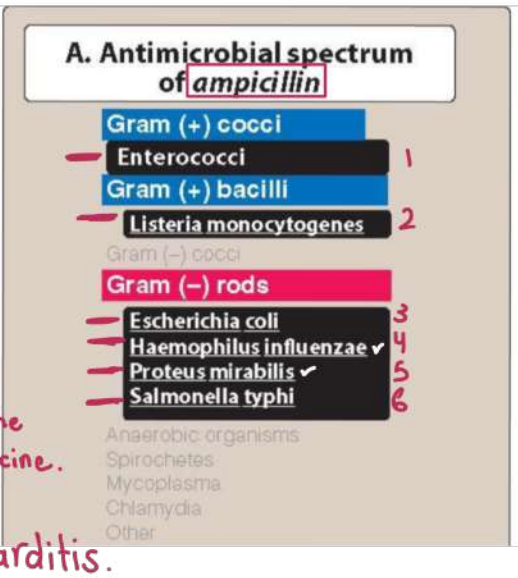
هي شرحنا هاد للمصطلح

- Semisynthetic: ampicillin, amoxicillin ① ②
- Spectrum: extended to include gram-negative bacilli → Pores بيقدروا يمروا من

❑Ampicillin: **drug of choice** for gram-positive bacillus *L. monocytogenes, enterococci,* resp infections → with or without the addition of gentamicine.

❑Amoxicillin: dental prophylaxis

↳to prevent Bacterial endocarditis.



Extended-spectrum penicillins:

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

*Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated penicillinases.

*[Note: Escherichia coli and Haemophilus influenzae are frequently resistant.]

. Resistance من لتحميهم β-Lactamase لـ inhibitors مع بنعطيهم -

*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.

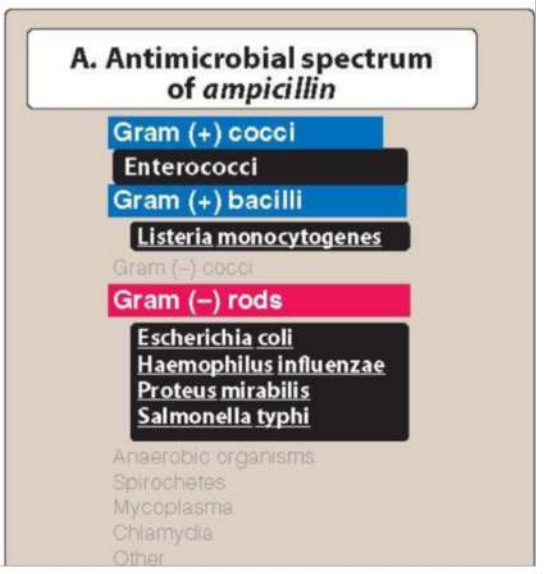
Penicillins

Antibacterial spectrum:

2. Extended-spectrum penicillins:

- Combined with β-lactamase inhibitors → Resistance ال مشكلة لنحل

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



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) → toxic to kidney [لريك ننتبه لل Case وانما نقرأها]

Antistaphylococcal penicillins:

***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
] ولو البكتيريا agar ال على methicillin بستخدم *

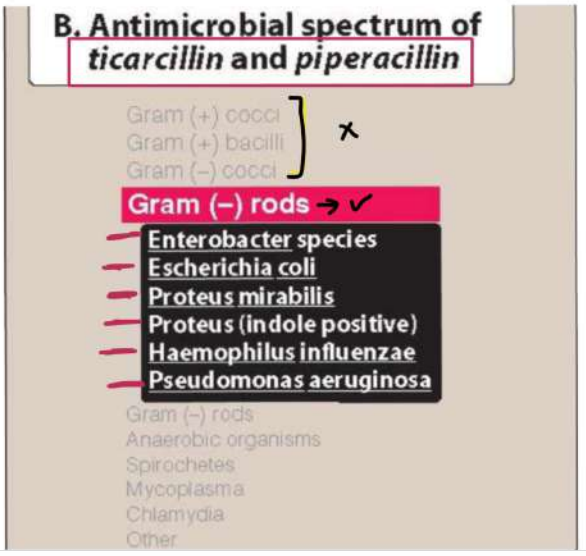
Penicillins

Antibacterial spectrum:

4. Antipseudomonal penicillins:

- Piperacillin (1) + ticarcillin (2)
- Effective against gram-negative bacilli (but not against *Klebsiella*) → because of its constitutive Penicillinase
- Common combinations:

Piperacillin + tazobactam



Antipseudomonal penicillins:

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

***These agents are available in parenteral formulations only.**

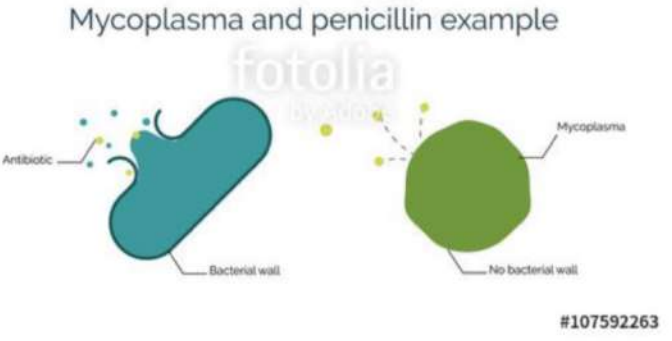
***Formulation of ticarcillin or piperacillin with clavulanic acid or tazobactam, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms (for example, most Enterobacteriaceae and Bacteroides species).**

β-lactamase بتخمي من

Penicillins

Mechanisms of resistance

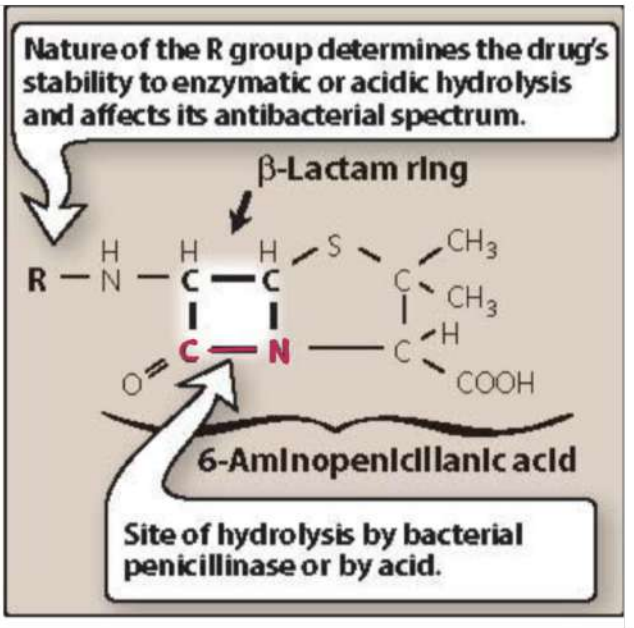
- **Intrinsic Resistance:**
  - Microorganisms that lack peptidoglycans cell walls e.g., *M. pneumoniae* Atypical (Mycoplasma)
  - Microorganisms that have impermeable cell walls to the drugs. (جدار خلية غير مُنفذ)



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 → Before penicillin attack cell wall.
   - **Gram-negative**: periplasmic β-lactamases → inactive it in periplasmic space.



*β-Lactamases either are constitutive, mostly produced by the bacterial chromosome or, more commonly, are acquired by the transfer of plasmids.

*Some of the β-lactam antibiotics are poor substrates for β-lactamases and resist hydrolysis, thus retaining their activity against β-lactamase–producing organisms.

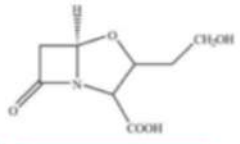
*[Note: Certain organisms may have chromosome-associated β-lactamases that are inducible by β-lactam antibiotics (for example, second and third generation cephalosporins).]

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

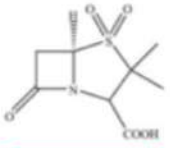
How is this problem solved?

By using inhibitors, such as ↓

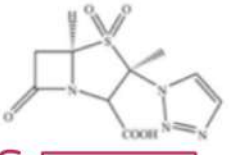
β-Lactamase Inhibitors



① Clavulanic acid

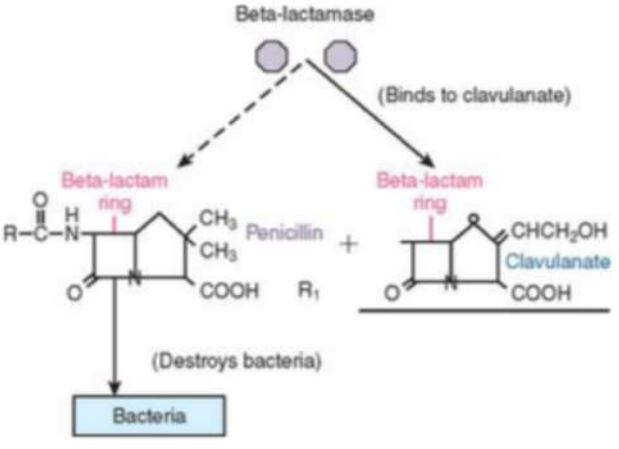


② Sulbactam



③ Tazobactam

↑ Lamoxiclave



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

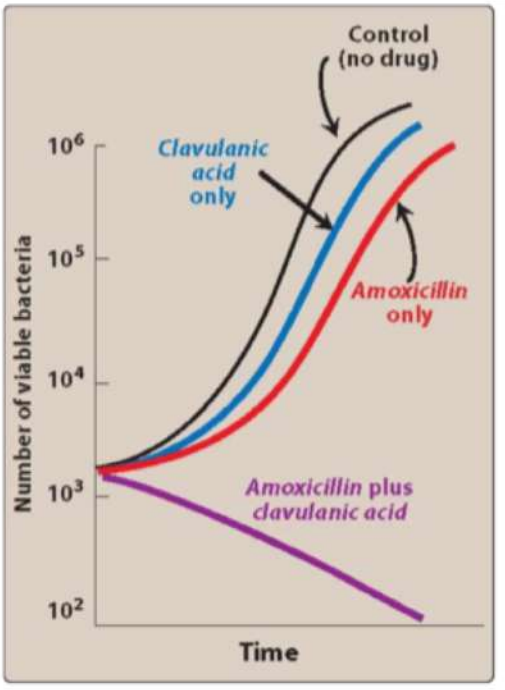
② Sulbactam: combine with ampicillin.

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.....?

حكينا فوق



Penicillins

Mechanisms of resistance

- **Acquired Resistance:**

2. Decreased permeability to the drug:

- Reduced permeability e.g., *Pseudomonas aeruginosa*
- Efflux pump e.g., *Klebsiella pneumoniae*.→ بتشوف drug molecule فتقول الـ pump للخارج

3. Altered PBPs:

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

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

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.

Penicillins

Pharmacokinetics

- **Routes of administration**

By IV injection

- **IV, IM only:** ampicillin+sulbactam, piperacillin+tazobactam, nafcillin, oxacillin

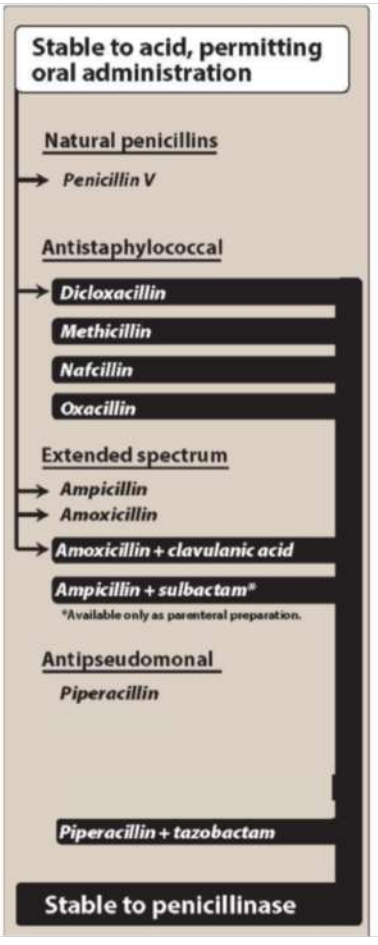
↳ very common in hospitals.

- **Oral only:** Penicillin V, amoxicillin, amoxicillin+clavulanic acid, dicloxacillin

injection ↓

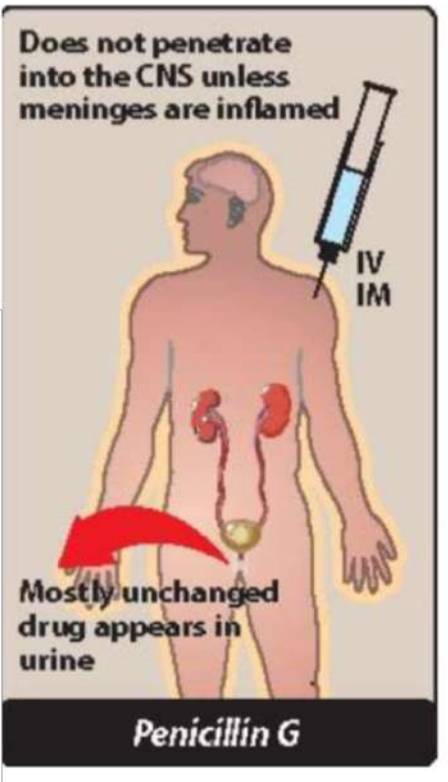
- **Depot forms:** Procaine penicillin G and benzathine penicillin G (IM) ↓

They are slowly absorbed into the circulation and persist at low levels over a long time period



Pharmacokinetics

- **Absorption** *Poorly absorbed in GI tract
- Most penicillins are incompletely absorbed after oral administration
- Empty stomach? ↓



*they reach the intestine in sufficient amounts to affect the composition of the intestinal flora.

*Food decreases the absorption of all the penicillinase-resistant penicillins because as gastric emptying time increases, the drugs are destroyed by stomach acid.

*Therefore, they should be taken on an empty stomach.

- **Distribution**

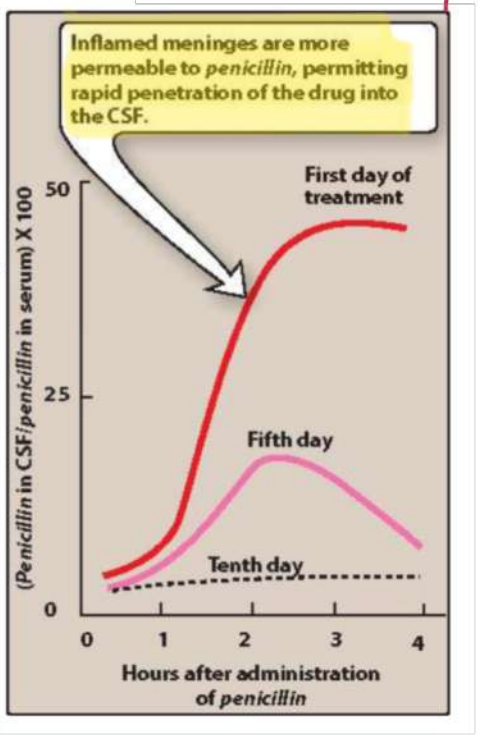
- Good distribution e.g., cross placenta (but no teratogenic effect)
- Insufficient penetration to bone or CSF (unless inflamed)

The β-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none have been shown to have teratogenic effects. However, penetration into bone or cerebrospinal fluid (CSF) is insufficient for therapy unless these sites are inflamed.

[Note: Inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the drug in the CSF compared to the serum.]

Penicillin levels in the prostate are insufficient to be effective against infections.

بقسم نسبة البنسلين في CSF/Plasma إذا كانت النسبة عالية إذاً يوجد inflamation.



* إذاً هو يوصل الـ fetal ولكن هو كبنسلين ما بعمل مشاكل، ويعتبر الـ drug choice للمرأة الحامل ← السبب انه ما عنده Transpeptidase والبنسلين بس برتبط ب transpeptidase تبع البكتيريا.

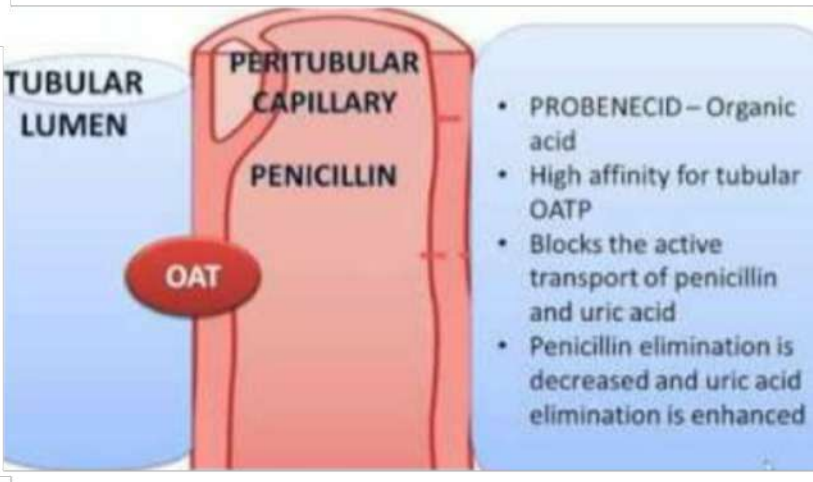
Pharmacokinetics

- **Metabolism**
- Insignificant metabolism
- Exceptions?

*Nafcillin and oxacillin are primarily metabolized in the liver and are excerted in bile to feces and do not require dose adjustment for renal insufficiency.

↓

Hepatic insufficiency بقدر أعطيهم للمرضى اللي عندهم



- **Excretion:**
- Renal: tubular secretory system
- *Probenecid* is an inhibitor of renal tubular excretion of penicillin

بستخدمه لو بدي أخلي البنسلين يطول حسب أكثر بالـ Blood Stream لأزيد الـ effect

uricosuric agent:

يعني بزيد الـ excertion لـ uric acid في الـ urine

لعلاج الـ Gout ؛ لهيك مرات بحطلهم أقل من جرعة البنسلين.

*The penicillins are also excreted in breast milk.

Penicillins

Adverse effects

1. Hypersensitivity:

- 5-10% percent of patients (simple rash to angioedema to anaphylaxis)
- Cross-allergy
- Always inquire (استنس) about penicillin allergy

2. Diarrhea:

- Caused by intestinal flora imbalance
- More with extended-spectrum agents

Hypersensitivity

Diarrhea

1. Hypersensitivity:

*Approximately 5% percent of patients have some kind of reaction, ranging from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis.

↳ very Severe

*Cross allergy: المريض عنده حساسية من دوية بنس المجموعة

*Cross-allergic reactions occur among the β-lactam antibiotics.

*To determine whether treatment with a β-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.

2. Diarrhea:

It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum.

Pseudomembranous colitis from Clostridium difficile and other organisms may occur with penicillin use.

Adverse effects

3. Nephritis:

- Methicillin: no longer used because of this

4. Neurotoxicity: → injection in spinal cord.

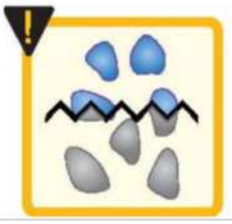
- If injected intrathecally

5. Hematological toxicities

- Decreased coagulation
- Cytopenias → ↓ Blood Cell type, such as RBCs, WBCs, Platlets.

Nephritis → kidney damage

Neurotoxicity



Hematologic toxicities

4. Neurotoxicity:

The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached.

Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

5. Hematologic toxicities:

Decreased coagulation may be observed with high doses of piperacillin, ticarcillin, and nafcillin (and, to some extent, with penicillin G).

Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.

Quick Revision

- Name a penicillin that is effective against penicillinase-producing S. aureus (MSSA)? 1. Nafcillin / Oxacillin / dicloxacillin
  2. ampicillin + Sulbactan.
- Name a penicillin that is effective against penicillinase-producing S. aureus (MRSA)? x