Cell wall synthesis inhibitors Part 1

Pharmacology 3

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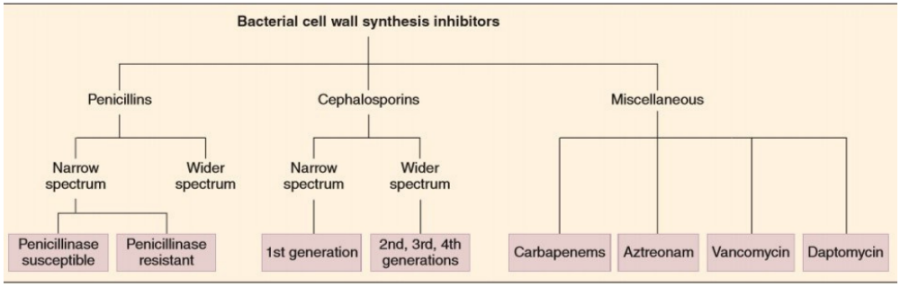
فارما 3
زميلتكم لجين أحمد

لجان النشاط

قال تعالى (يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ)

Inhibitors of Cell Wall Synthesis



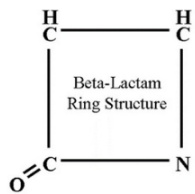
البكتيريا تستطيع مقاومه البنسلين اذا كانت تفرز b-lactamas enzyme

Inhibition of Cell Wall Synthesis

β-Lactam Drugs

- The main group of AB that act on bacterial cell wall is the ‘beta lactams’; so called due to presence of a β-lactamring.
- Irreversibly inhibit enzymes involved in the final steps of cell wall synthesis

- β-lactam drugs include:
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams

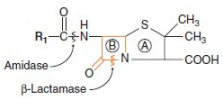


B-lactamas تكسر الحلقه ليصبح البنسلين inactive

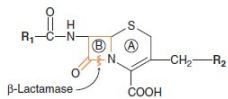
تؤثر على m.o فقط حيث ان خلايا الانسان لاتحتوي cell wall

β-lactam antibiotics

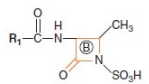
- Basic structures of four groups of β-
- lactam antibiotics and clavulanic acid. The structures illustrate the β-lactamring (marked B) and the sites of action of bacterial enzymes that inactivate these antibiotics (A,
- thiazolidinering). Bacterial lactamse: Enzyme that hydrolyzes B-Lactam ring
- and causes loss of activity (acid does that too)



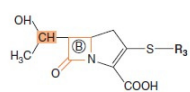
Penicillin nucleus



Cephalosporin nucleus

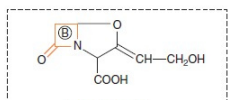


Monobactam nucleus
(β-lactamase resistant)



Carbapenem nucleus
(high resistance to β-lactamases)

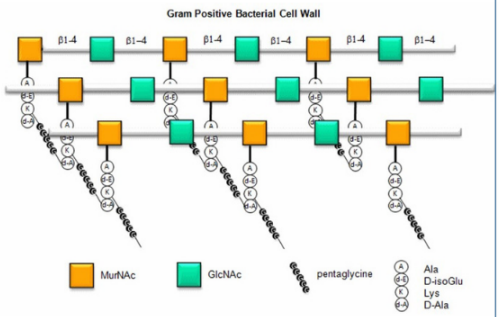
ال Rمهمه لاضافه فاعليه معينه الى الحلقه مثل ان يصبح من الممكن بلعه (oral)



Clavulanic acid
(inhibits many β-lactamases)

Bacterial cell wall

The cell wall is a rigid outer layer that completely surrounds the cytoplasmic membrane, maintains cell shape and integrity, and prevents cell lysis from high osmotic pressure.
The cell wall is composed of a complex, cross-linked polymer of polysaccharides and polypeptides, peptidoglycan.



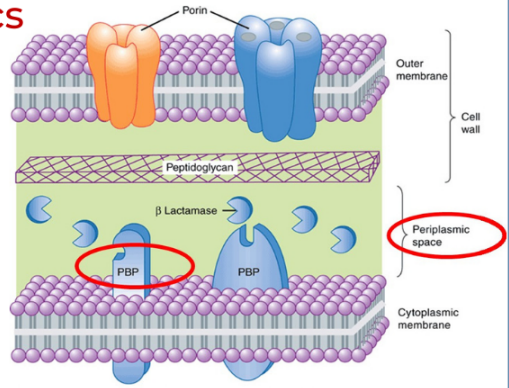
لازم تكون البكتيريا high dividend حتى يقتلها اثناء عمليه صناعه ال wall

Mechanism of action of β-lactam antibiotics

- All β-lactam antibiotics interfere with the last step of bacterial cell wall synthesis, which is the cross-linking of adjacent peptidoglycan strands by a process known as transpeptidation.

- They compete for and inhibit enzymes called transpeptidases (Penicillin Binding Proteins (PBP)).

يرتبط مع TRANSPEPTIDATION. وبالتالي تصبح روابط CELL WALL ضعيفه حيث تدخل السوائل الي داخل الخليه ويحدث لها SWELLING ثم CELL LYSIS وتموت لذلك يسمى BACTERICIDAL



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

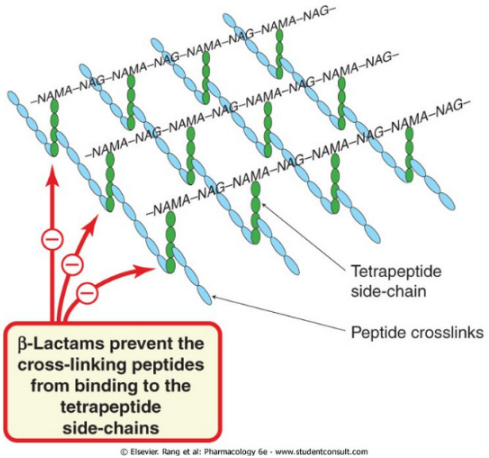
Mechanism of action of β-lactam antibiotics

• β-Lactam antibiotics, structural analogs of the natural D-Ala-D-Ala substrate, covalently bind to the active site of PBPs

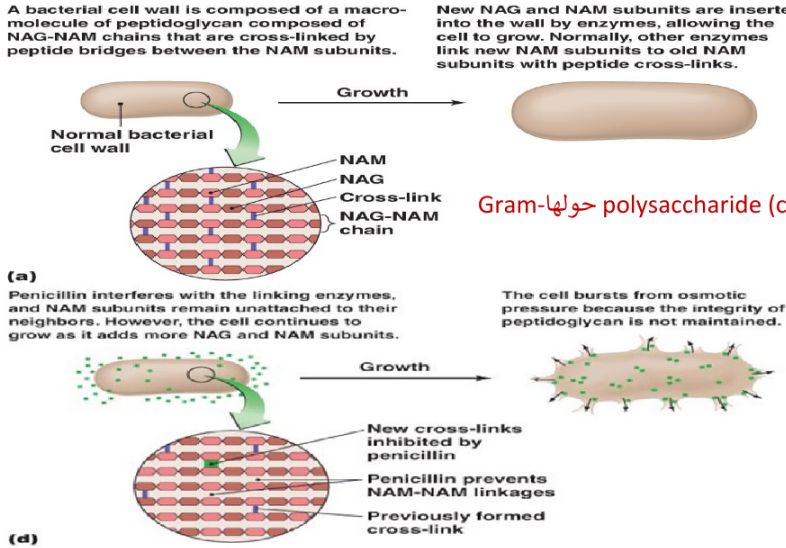
- They interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage)

  اكثر تأثير على gram+ لانه ماعليها capsule

- The result is the formation of a weakened cell wall and ultimately cell death (or this reason, they are regarded as bactericidal).



Mechanism of action of β-lactam antibiotics



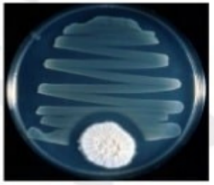
Gram-حولها polysaccharide (capsule)

History: Discovery & Production

- 1928: Scottish biologist, Alexander Fleming discovered that the *Staphylococcus* culture he had mistakenly left growing in open was contaminated with a mould which had destroyed the bacteria.

A. Fleming

- After isolating a sample and testing it, he found that it belonged to the *Penicillium* family.
  Later the mould was classified as *Penicillium notanum*.



- At first, it was difficult to convince people about its potential uses.

The Nobel Prize
Physiology/Medicine 1945

Sir Alexander Fleming
1881 - 1955

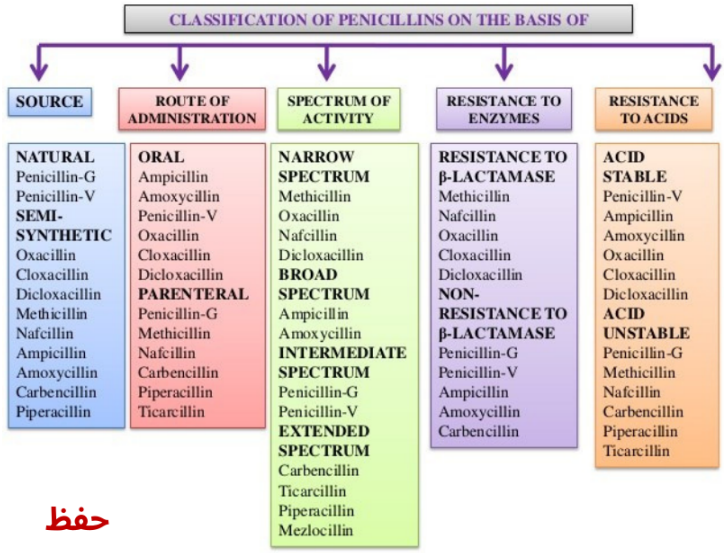
Sir Howard Walter Florey
1898 - 1968

Ernst Boris Chain
1906 - 1979

Alexander Fleming discovered the antimicrobial properties of penicillin in 1928. Twelve years later, Howard Florey and Ernst Chain developed the processes to produce penicillin in sufficient quantity for it to become widely available

Penicillins

- The most widely effective and the least toxic drugs known.(interfere with a site or function unique to the growth of m.o)
- Safe drugs (if we exclude the allergy rxn) حتى على الحوامل
- Mainly excreted by the kidneys.
- Suffix : **cillin**

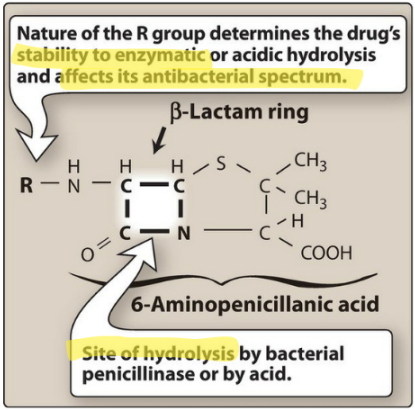

CLASSIFICATION OF PENICILLINS ON THE BASIS OF
SOURCE
NATURAL
Penicillin-G
Penicillin-V
SEMI-SYNTHETIC
Oxacillin
Cloxacillin
Dicloxacillin
Methicillin
Nafcillin
Ampicillin
Amoxycillin
Carbencillin
Piperacillin
ROUTE OF ADMINISTRATION
ORAL
Ampicillin
Amoxycillin
Penicillin-V
Oxacillin
Cloxacillin
Dicloxacillin
PARENTERAL
Penicillin-G
Methicillin
Nafcillin
Carbencillin
Piperacillin
Ticarcillin
SPECTRUM OF ACTIVITY
NARROW SPECTRUM
Methicillin
Oxacillin
Nafcillin
Dicloxacillin
BROAD SPECTRUM
Ampicillin
Amoxycillin
INTERMEDIATE SPECTRUM
Penicillin-G
Penicillin-V
EXTENDED SPECTRUM
Carbencillin
Ticarcillin
Piperacillin
Mezlocillin
RESISTANCE TO ENZYMES
RESISTANCE TO β-LACTAMASE
Methicillin
Nafcillin
Oxacillin
Cloxacillin
Dicloxacillin
NON-RESISTANCE TO β-LACTAMASE
Penicillin-G
Penicillin-V
Ampicillin
Amoxycillin
Carbencillin
RESISTANCE TO ACIDS
ACID STABLE
Penicillin-V
Ampicillin
Amoxycillin
Oxacillin
Cloxacillin
Dicloxacillin
ACID UNSTABLE
Penicillin-G
Methicillin
Nafcillin
Carbencillin
Piperacillin
Ticarcillin

حفظ

Chemically penicillinsconsist of a 6-amino penicillanic acid nucleus with attached side chain (R). Members of penicillin family differ from each other by side chain (R) attached to 6-amino penicillanic acid.

The nature of this side chain affects the:

1.antimicrobial spectrum
2.stability to stomach acid
3.cross-hypersensitivity,
4.susceptibility to bacterial degradative enzymes (β-lactamases).



Classification of penicillin

1-Natural Penicillins

Penicillin G(parenteral)
Penicillin V(oral)

2-The extended Spectrum Penicillins

Aminopenicillins:
- Ampicillin
- Amoxicillin

3- Anti-pseudomonal Penicillins

Piperacillin

4-PenicillinaseResistant Penicillins (anti-staphylococcal)

Cloxacillin.

1. Natural Penicillins

- They are susceptible to inactivation by B-lactamases (penicillinases)
- Narrow -spectrum

(Benzylpenicillin)
Penicillin G

-also called Crystalline penicillin.

-it is powder form.

-can be given IV (bolus or infusion) or IM.

-Has short duration (1-2 h).

Destroyed by gastric juice if it is given orally so, **NOT** given orally.

- It is indicated in the treatment of:
  - Syphilis.
  - acute Tonsillitis.
  - tetanus

sexually transmitted **كان يستخدم ل** disease

(Phenoxymethylpenicillin)
Penicilin V

ospen **مثال تجاري**

- Penicillin V is more acid-stable than penicillin G.
- Given orally (every 4h).
- Oral penicillin .
- It is indicated in the treatment of:

Tonsillitis.
Pharyngitis

upper respiratory tract infection : **لعلاج**

short half life **الثنين**

Derivatives of **penicillin G**

Long-acting forms:-insoluble salt of penicillin G thus slow abs with long duration.

duration of action **ربطوه بواد اخرى حتى يزيد**

1-Procaine penicillin G (12 h) .

2-benzathinepenicillin G(4 weeks) .

- Effective in treatment in syphilis.
- Prophylactic in rheumatic fever patients. auto immune disorders

streptococcus bacteria type A infiction **ناتج عن**

- Both are administered **IM**and serve as depot forms.
- they are **suspension**formulation that is **never given by IV** route.

2. Extended-spectrum Penicillins or Aminopenicillin:

Ampicillin and amoxicillin

They are susceptible to inactivation by B-lactamases (penicillinases)

narrow spectrum

-gram لكن زادت فعاليته على

Ampicillin

- (IV, Oral)isgiven every 6h (4x1).
- It is used in Bacillary Dysentery.

1g for 5 days + fluids.

- Indicated in listeriosis.

- Diarrheais common side effect

WHY????

يسبب اسهال لانه مده امتصاصه طويله يعني انه يبقى في الامعاء لفتره طويله الذي يتسبب بقتل normal floraلذلك يستخدم اذا كان الالتهاب في الامعاء لانه سعطي فاعليه كبيره بسبب بقاؤه مده اطول

Amoxicillin

Oralllyis given every 8h (3x1).

- better absorbed orally than ampicillin with less diarrhea.

حتى يتجنب طبيب الاسنان حدوث cardaitis

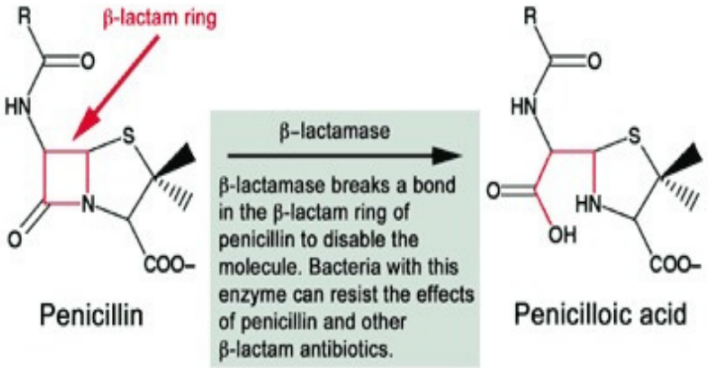
- Is employed ***prophylactically by dentists*** for patients with abnormal heart valves who are to undergo extensive oral surgery.
- used in treatment of peptic ulcer
- to eradicates H.Pylori.
- Otitis media.
- urinary tract infections.

لعلاج : upper respiratory tract infection

Some bacteria produce β-lactamase enzyme that breaks the critical β-lactam ring

Penicillin Resistance

Narrow +extended
يؤثرعليهم ال b-lactamas



مش دائما بكون الحل هو استخدام بنسلين مقاوم لل lactama لانه يعتمد على نوع ال m.o لانه
يوجد انواع لا تستجيب للبنسلين المقاوم للlactamas لذلك الحل هو اضافه ماده اخرى تثبط
ال lactamas نفسه

B-lactamaseinhibitors

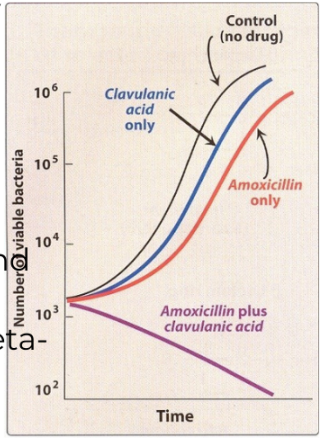
Substance don't have antibacterial activity but they have the ability to inhibit the B-lactamaseenzyme....

Ex. Clavulanicacid

clavulanic acid binds to beta-lactamase and competitively protects amoxicillin

*They potentiating amoxicillin against beta-lactamaseproducing bacteria.

* It is called "suicide inhibitor"



- Formulation with a β-lactamase inhibitor, such as :
  - *amoxicillin +clavulanic acid*
  - *ampicillin +sulbactam.*

المثالين لعلاج staph aureus او anti يمكن استخدم حل ثالث وهو staphylococcus penicillin

- *protects from*
- *enzymatic hydrolysis*
- *extends their antimicrobial spectra.*
- without the β-lactamase inhibitor, MSSA is resistant to *ampicillin* and *amoxicillin.*

antiskin infection3-Anti staphylococcal penicillins

- Also called anti-staph or penicillinase resistance penicillins.

•Ex.Methicillin, **Flucloxacillin, Cloxacillin, Dicloxacillin, Nafcillin.**
•Given IV & **orally**. (every 4-6 hr)
They are restricted to the treatment of infections caused by penicillinase-producing staphylococci (narrow-spectrum).
•Because of nephrotoxicity caused by **methicillin, nowadays this drug is not** used clinically.
•Strains of staphylcoccusresistant to these drug called : methicillin-resistant staphylococcus aureus (MRSA).
•MRSA is a serious source of nosocomial (hospital-acquired) infections.
(MRSA commonly respond to ***vancomycin.)***

4-Anti pseudomonal Penicillins:

- Ex. Piperacillin, Ticarcillin

- Ps.aeruoginosa: G-vebact lacks porins Making these organism resistant to many antimicrobial agents.
- Ps.aeruginose very difficult to deal with & produce resistance easily.
- Given parentally not orally.
- *piperacillin with tazobactam*,
- extends the antimicrobial spectrum to include penicillinase-producin organisms.

Pharmacokinetics of Penicillins

حفظ _>

- Absorption: Penicillins vary in their resistance to gastric acid and therefore vary in their oral bioavailability.
- Examples of compounds relatively stable to gastric acid and suitable for oral administration are penicillin V, dicloxacillin, and amoxicillin.
- Absorption of most oral penicillins(amoxicillin being an exception) is impaired by food (administered at least 1–2 hours before or after a meal).

كلهم على معده فارغه ماعدا amoxicillin

Distribution:

- Most penicillinscross the blood-brain barrier only when the meninges are inflamed.

تعبر المشيمه والحليب لكن لاتعبر bbb الا اذا كان في التهاب (meningitis) لكن يفضل في هذه الحاله استخدام الجيل الثالث (cephalosporin)

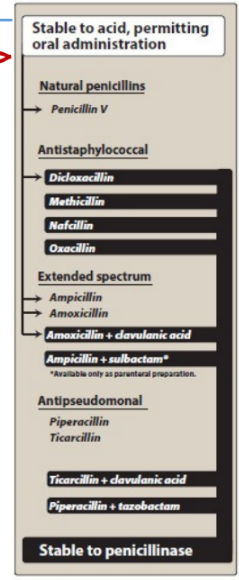
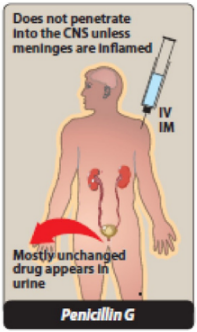


Figure 38.6
Stability of the penicillins to acid or the action of penicillinase.

Pharmacokinetics of Penicillins



- Metabolism and excretion:
- Penicillins are polar compounds usually excreted unchanged in the urine (inhibited by probenecid). دواء نقرص يقلل خروج البنسلين في البول
- Patients with impaired renal function must have dosage regimens adjusted.
- Because nafcillinand oxacillinare primarily metabolized in the liver, they do not require dose adjustment for renal insufficiency.

metabolism and expected by bil هذان النوعان يحدث لهما

Adverse reactions of penicillins

1-Hypersensitivity reaction :

- 5% of population
- Allergic reactions range from a variety of skin rashes to anaphylactic shock (very rare—0.05% of recipients).

الحساسيه اما rush or angioedema وهي انتفاخ بالشفاه واللسان
وغالبا ما يحدث مع ال first generation

- Cross sensitivity with other β-lactam as cephalosporins.
- Should be avoided if history is positive.

Inj. Penicillin induced anaphylactic shock

Perform sensitivity test before administering penicillin Inj.

2-Diarrhea (most common): it is a common problem mainly with (Ampicillin).

Pseudomembranous colitis may occur.

3. **Nephritis:** Penicillins, particularly methicillin, have the potential to cause acute interstitial nephritis. [Note: Methicillin is therefore no longer used clinically.]

Piperacillin-tazobactam, when combined with vancomycin, has been associated with greater incidence of acute kidney injury compared to alternate β-lactam agents.

4. **Neurotoxicity:** The penicillinscan provoke seizures if injected intrathecallyor if very high blood levels are reached.

Resistance to penicillins and otherB-lactams

- Resistance to penicillinsand other β-lactams is due to one of four general mechanisms:

1.Inactivation of antibiotic byB-lactamase (the most common mechanism)

1.Decreased permeability to the drug

- is a greater concern in G-(impermeable outer cell wall)

A.Absence or down-regulation of porins.

B. Presence of an efflux pump, which transport B-lactam antibiotics from the periplasm back across the outer membrane.

3. Modification of target PBPs.

- low affinity for bindingB-lactam antibiotics
- basis of methicillin resistance in staphylococci (MRSA).

penicillin binding sait يغير ال

Thank you