Athar Batch

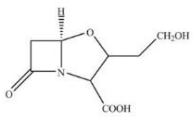
Pharmacology

Lecture: 28

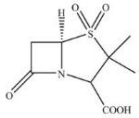
Done By : Saja Alnajjar

النادي الطبي

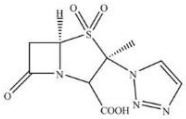
β-Lactamase Inhibitors



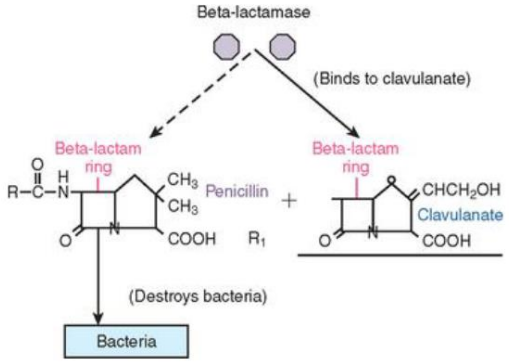
Clavulanic acid



Sulbactam



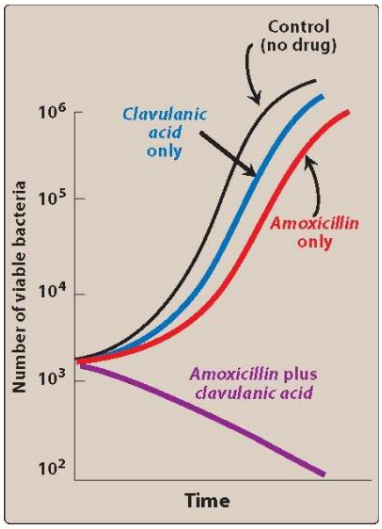
Tazobactam



- B-lactamase inhibitors: Beta-lactamase inhibitors are a class of medicine that block the activity of beta-lactamase enzymes (also called beta-lactamases), preventing the degradation of beta-lactam antibiotics.
- Clavulanic acid mostly common combine with amoxicillin →amoxiclan or الاموكلان→- oral formulation ...this means we take it orally
  -most prescribed drug → high resistance.
- Sulbactam mostly common combine with ampicillin
- Tazobactam with piperacillin

β-Lactamase Inhibitors

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



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

هون بالسلايد هاد بحكيلنا انو هاي المثبطات لو اخدتها لحالها ما رح يكون الها تأثير على البكتيريا يعني ما رح تقتل البكتيريا ولا تعمل تثبيط لنمو البكتيريا .

هم بحد ذاتهم مش مضادات حيوية ولا بشتغلو شغل المضادات الحيوية .

-B-lactamase inhibitors only stop the function of B-lactamase produced by the bacteria as a way of resistance to the cell wall inhibitors antibiotics,

- we can prove this by monitoring bacterial cell culture >> measure the viable bacteria over time.

-If you look at the figure above: 1- in control state (no drug) the bacteria is capable of growing , dividing and proliferating >> this mean the number of bacteria increase over time .

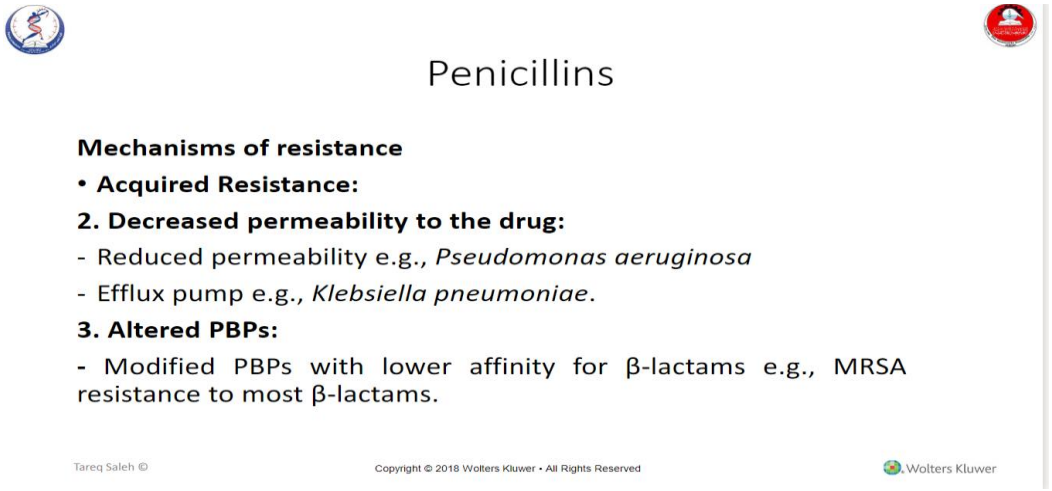
2- if we admit the B-LACTAMASE INHIBITOR alone with out the cell inhibitor antibiotic(amoxicillin) → NO SIGNIFICANT reduction in the number of viable bacteria ... this means no antibacterial activity.

- If the bacteria is resistance to amoxicillin as E.coli → if we admit amoxicillin alone we will see very little reduction in bacterial cell viability because E.coli can secrete many B-lactamases that can hydrolyze and cleave amoxicillin .

  3- if combine amoxicillin with clavulanic acid → this well block the action of B-lactamases produced by E.coli thus the amoxicillin will do its function properly and will reduce the number of bacteria .(amoxicillin will restore its bactericidal effect) .

  -amoxicillin + clavulanic acid → not effective against MRSA

  - amoxicillin + clavulanic acid→Active against MSSA



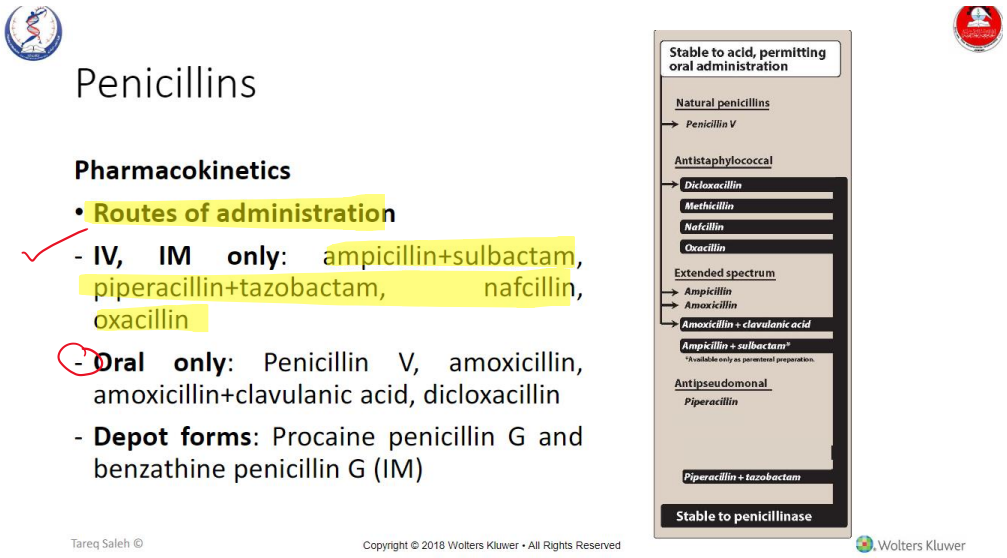
-AS we said targeting G (-) bacterial cell wall by cell wall inhibitors is more difficult than targeting G (+) bacteria.

-the drugs that work against G(-) bacteria will have to go through the porins (outer channels on the outer cell membrane of g(-) bacteria) SO→ certain

bacterial types will be able to change the permeability of outer membrane in a way that it will prevent further diffusion of cell wall inhibitors to the interior .

DO NOT FORGET THAT WE STUDY ABOUT ONE DRUG THAT IS ACTIVE AGAINST P. AERUGINOSA → ***Piperacillin*** .

- P. AERUGINOSA >> GRAM NEGATIVE BACTERIA SO IT HAVE OUTER CELL MEMBRANE THAT PREVENT THE DIFFUSION OF PENICILLINS TO THE PERIPLASMIC AREA
- Klebsiella pneumonia is resistance to piperacillin because of the efflux pumps.
- (3)- we know the main target of penicillin is PBPs (penicillin binding proteins→ important in transpeptidation process) so some bacteria alter the structure of PBPs as a way of resistance to cell wall inhibitors → so it make them less affinity to bind to B-lactam drugs .



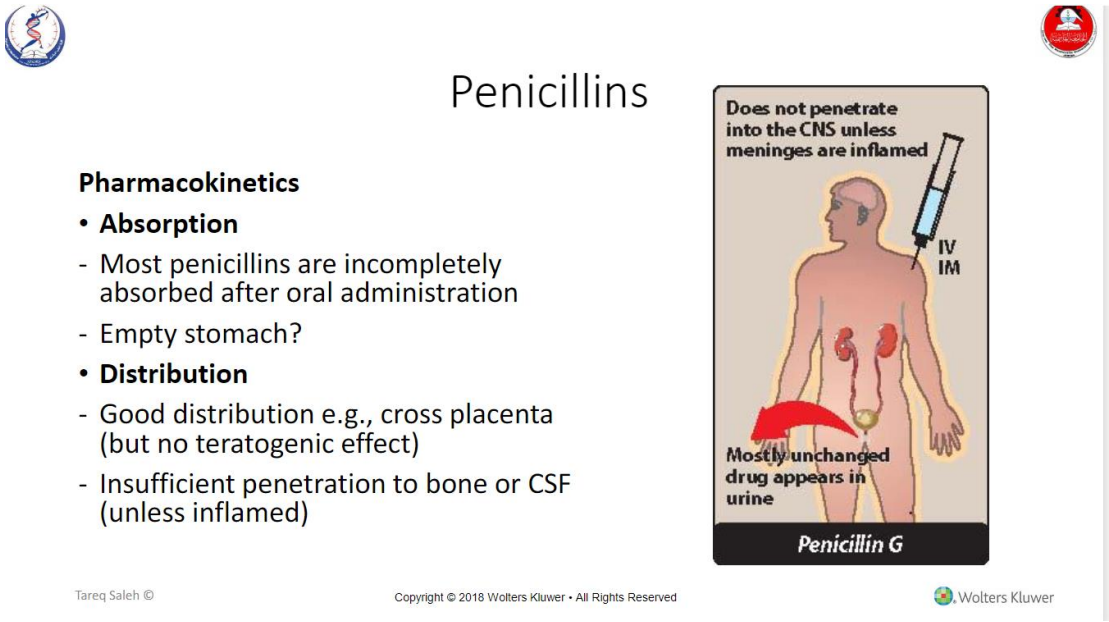
1. Administration: The route of administration of a P-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.

-rout of administration notes:

-Penicillin v: is only given in minor infections → ear, chest , throat and skin infections

-depot forms of drug (slow releasing form): They are slowly absorbed into the circulation and persist at low levels over a long time period.

Procaine penicillin G → penicillin G is given by IM rout → it causes pain if we give it alone to the patient so we can combine it with local anesthetic (procaine).

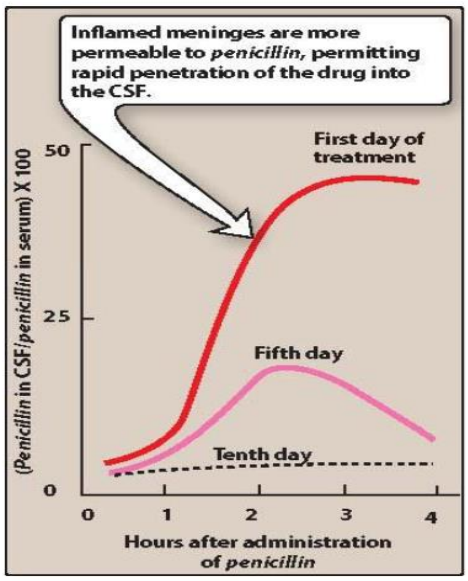


Food decreases the absorption of the penicillins ,Therefor should be taken on an empty stomach.

Penicillin can pass the BBB to CSP ONLY IF the BBB is inflamed.

THIS figure represent the passage of penicillin by the inflamed BBB or meninges>> in the first day >> severely inflamed BBB so the permeability increase thus enhancing the entry of penicillin so the concentration of in CSF increases rapidly

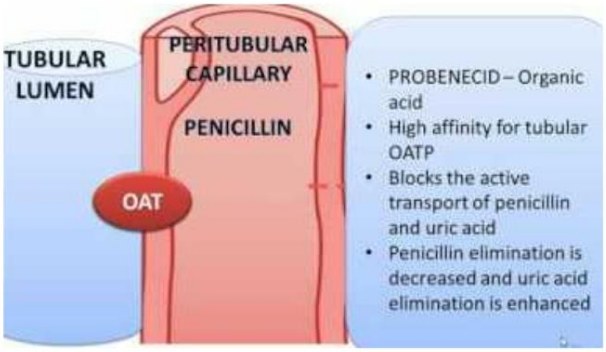
بعد هيك وبمرور الايام بخف الالتهاب وبيلش كمية البنسيلين تقل تدريجيا لحد ما يروح الالتهاب كليا وبنرجع للوضع الطبيعي الي بكون فيه حرفيا ممنوع دخول البنسيلين لجوا ف بصير تركيزو جدا قليل زي ما ملاحظين بالخط المخطط بالرسمة



Penicillins

Pharmacokinetics

- **Metabolism**
- Insignificant metabolism
- Exceptions?
- **Excretion:**
- Renal: tubular secretory system
- *Probenecid* is an inhibitor of renal tubular excretion of penicillin



-most of penicillins do not metabolize in the liver.

-Nafcillin and oxacillin are exceptions to the rule and are primarily metabolized in the liver .

The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration but mainly / heavily depend on the tubular secretory system.

- *Porbenecide inhibit tubular excreation of penicillin so the penicillin concentration will increase → we should decrease the doses to prevent toxicity.*
- *Patients with impaired renal function must have dosage regimens adjusted.*
- *Because nafcillin and oxacillin are primarily metabolized in the liver, they do not require dose adjustment for renal insufficiency.*

Penicillins

Adverse effects

1. Hypersensitivity:

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

2. Diarrhea:

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

Hypersensitivity

Diarrhea

-Penicillins are among the safest drugs. However, adverse reactions may occur.

Reactions range from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis.

بالنسبة للنقطة هاي .. هلا هاي معناها الحساسية الي بتطلع من ادوية بكونو من نفس المجموعة يعني الهم علاقة ببعض .. فمثلا لو مريض عندو حساسية من البينيسلين معناتو في احتمالية

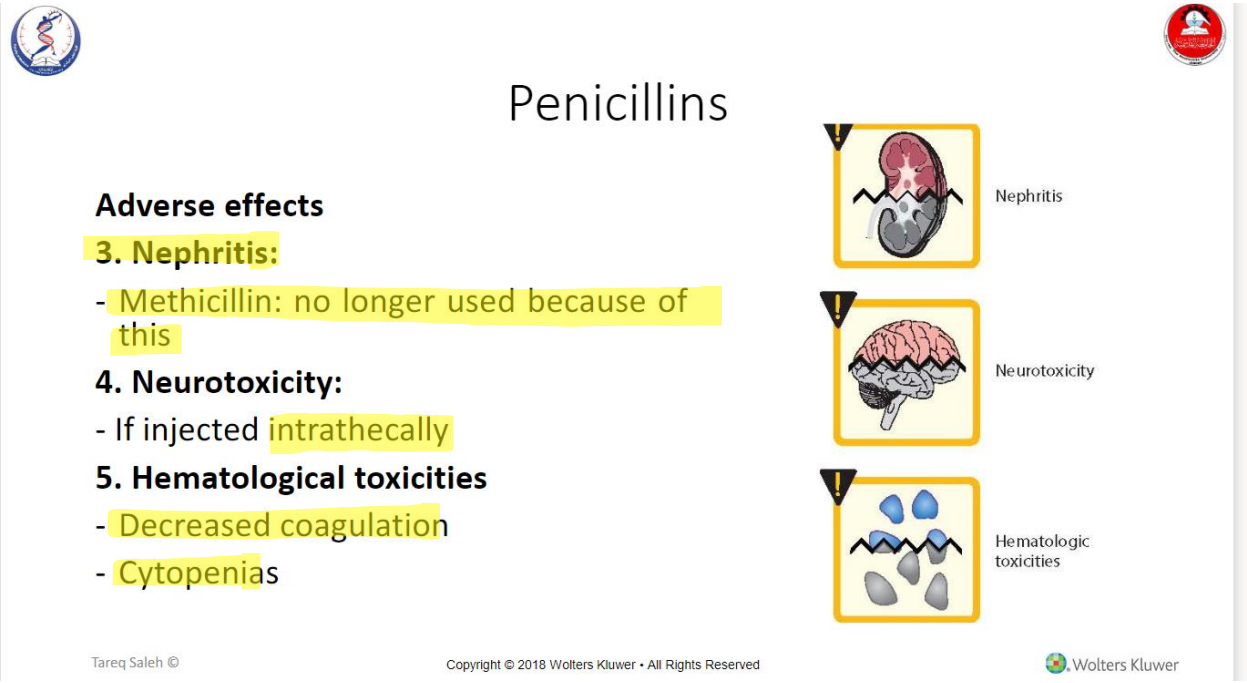
كبيرة يكون عندو حساسية من الادوية الي من نفس المجموعة عشان هيك لازم نكون حذرين بالتعامل مع هاي الادوية وكمان ضروري ناخد الهيستوري تبع المريض بخصوص الادوية وهكذا..

2- diarrhea: Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms.

- greater extent with those agents that have an extended antibacterial spectrum.

Such as ampicillin and amoxicillin.

- Pseudomembranous colitis from Clostridium difficile→ long term use of antibiotics reduces the normal flora in the intestine and trigger the C.difficile overgrowth in intestine .



Methicillin causes sever kidney inflammation

- *Intrathecally rout of administration: Intrathecal administration is a route of administration for drugs via an injection into the spinal canal.*

Quick Revision

- Name a penicillin that is effective against penicillinase-producing S. aureus (MSSA)? _____

- Name a penicillin that is effective against penicillinase-producing S. aureus (MRSA)? _____

Answers:

1-naficillin / oxacillin

2- unfortunately there is no penicillin that is active against MRSA.

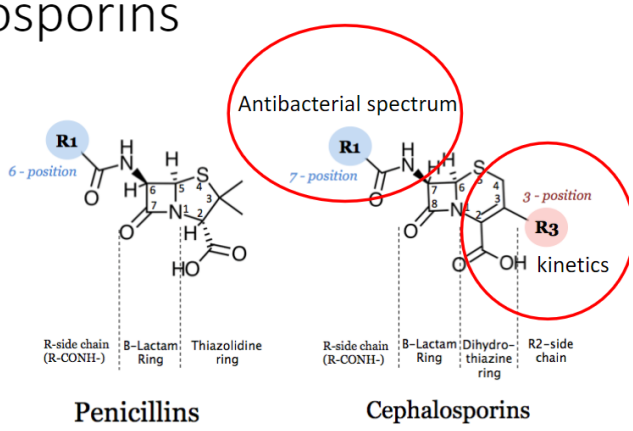
S,ALNAJJAR .

Cephalosporins

-The second category of the B-LACTAMS (CELL WALL INHIBITORS)

Cephalosporins

- β-lactams
- Structurally/functionally related to penicillins
- Semisynthetic
- More resistant to certain β-lactamases



* B-lactams → means that they have LACTAM ring in their structure

* The have 2 side chains attached to 7-nocephalosporanic → in 7 position the have R1 →Structural changes on the acyl side chain at the 7-position alter antibacterial activity
* variations at the 3-position (R3) modify the pharmacokinetic profile
* their function is similar to penicillin function which is inhibiting the last step of the cell wall synthesis (interferes the transpeptidation process catalyzed by PBPs transpeptidase)
* most of cephalosporines are semisynthetic.

Cephalosporins

- Classified into generations:

-first

-second

-third

-fourth

-advanced

CEPHALOSPORINS
Cefaclor CECLOR
Cefadroxil DURACEF
Cefazolin KEFZOL
Cefdinir OMNICEF
Cefepime MAXIPIME
Cefixime SUPRAX
Cefotaxime CLAFORAN
Cefotetan CEFOTAN
Cefoxitin MEFOXIN
Cefprozil CEFZIL
Ceftaroline TEFLARO
Ceftazidime FORTAZ
Ceftibuten CEDAX
Ceftizoxime CEFIZOX
Ceftriaxone ROCEPHIN
Cefuroxime CEFTIN
Cephalexin KEFLEX

الجدول عاليمين مش للحفظ بس في شغلات رح تمر علينا بالامثلة بالسلايدات الجاي مطالبين فيها .

- The classification based largely on their bacterial susceptibility patterns and resistance to B-lactamases.

Cephalosporins

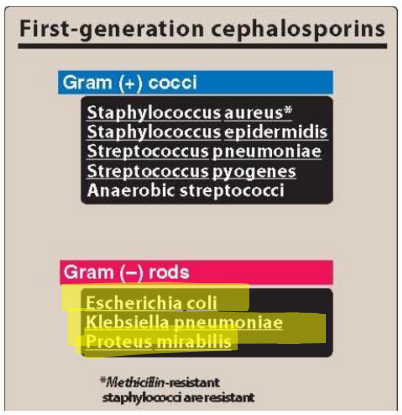
Antibacterial spectrum

- **First-generation cephalosporins:**

- penicillin G substitutes

- They cover MSSA (resistant to penicillinase) but not MRSA

Cefazolin
Cephalexin
cefadroxil



*Not MRSA

- 1st generation cephalosporins act as penicillin G substitutes.
- They have activity against penicillinase producing bacteria such as MSSA (methicillin resistant staphylococcus aureus (*BUT NOT MRSA*).
- Cefazolin →can be used out clinic sittings.
- Cephalexin→ for mild infections
- Cefadroxil

Cephalosporins

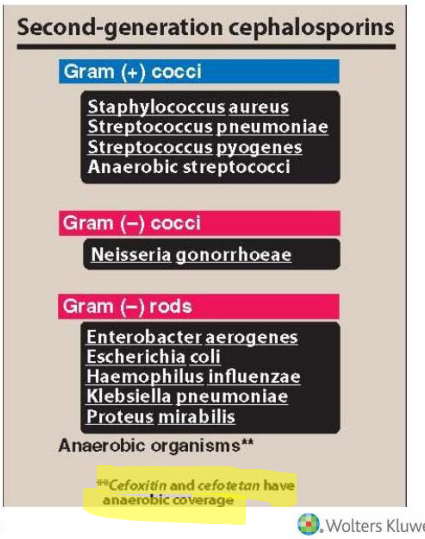
Antibacterial spectrum

- **Second-generation cephalosporins:**

- Wider gram-negative spectrum: *H. influenzae*, *Klebsiella*, *Proteus*, *Moraxella catarrhalis*, and some *Neisseria* species

Cefotetan
Cefuroxime
Cefoxitin
Cefprozil

Non are first line

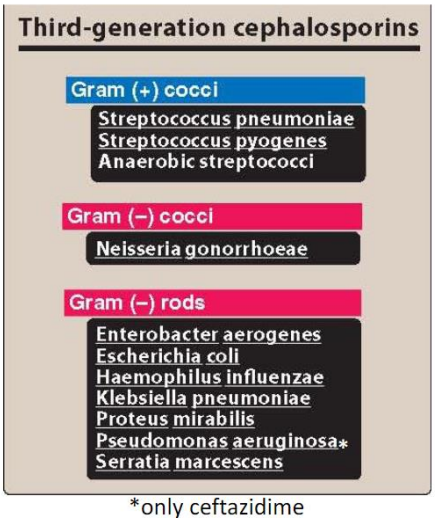


Cephalosporins

Antibacterial spectrum

- **Third-generation cephalosporins:**
- Greater activity against gram-negative bacilli (broad-spectrum)
- Drugs of choice for the treatment of meningitis
- Must be used with caution "collateral damage"

Ceftriaxone
Cefotaxime
Ceftazidime
Cefdinir



*only ceftazidime

- 3rd generation cephalosporins are first line drugs →effective treatment that has limited side effects /The first line medication is the favored treatment.
- They have broad spectrum so we can use it for empirical treatment.
- Major changes happen because of 3rd generation.
- Ceftriaxone and cefotaxime → the drugs of choice for treatment of pneumonia and meningitis.
- Ceftazidime→ activity against pseudomonas aeruginosa.
- pseudomonas aeruginosa * → means there is a resistance increasing
- from the book →cephalosporins must be used with caution, as they are associated with significant "collateral damage," including the induction of antimicrobial resistance and development of Clostridium difficile infection.

Cephalosporins

Antibacterial spectrum

- **Fourth-generation cephalosporins:**
  - Broad-spectrum
  - Active against strep and staph species (not MRSA)
  - Active against aerobic gram-negative species including P. aeruginosa

Cefepime

Tareq Saleh ©

Wolters Kluwer

Antibacterial spectrum

- **Advanced-generation cephalosporins:**
  - Broad-spectrum
  - Only β-lactam that is active against MRSA
  - Indicated for complicated skin MRSA infections and pneumonia
  - How about pseudomonas? ESBL?
  - *What are the limitations for using ceftaroline?*

Ceftaroline

Wolters Kluwer

Answer: The twice-daily dosing regimen also limits use outside of an institutional setting.

Quick Exercise

Which of the following cell wall synthesis inhibitors is effective against MRSA?

-amoxicillin
-ampicillin
-amoxicillin/clavulanate
-cefazolin
-cephalexin
-ceftriaxone
-cefepime
-ceftaroline

Tareq Saleh ©

Wolters Kluwer

Answer: ceftaroline → advanced generation

Cephalosporins

Mechanisms of resistance

- Similar to penicillins

Susceptible to

1. Penicillinases (*staph*)
2. Extended spectrum beta-lactamase ESBL (*E.coli, Klebsiella*)

ESBL

a group of plasmid-mediated, diverse, complex and rapidly evolving enzymes which share the ability to hydrolyze third-generation cephalosporins and aztreonam

Rawat et al, 2010

Cephalosporins

Pharmacokinetics

- **Administration:**

* like Penicillin ← - Poor oral absorption, mostly given IV, IM

- **Distribution:**

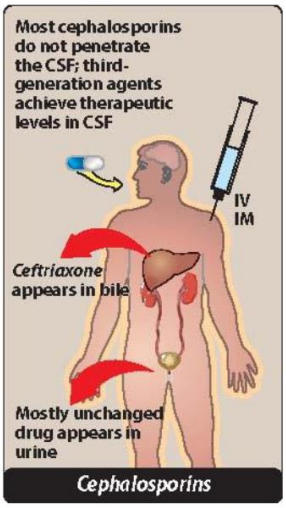
* 3rd generation

Drug of choice for ← 1. - To CSF: ceftriaxone and cefotaxime are effective in the treatment of neonatal meningitis caused by *H. Infuenzae* 2.

-cefazolin can penetrate bone

- **Elimination:**

* like penicillin ← -Renal tubular secretion (except ceftriaxone, eliminated in bile)



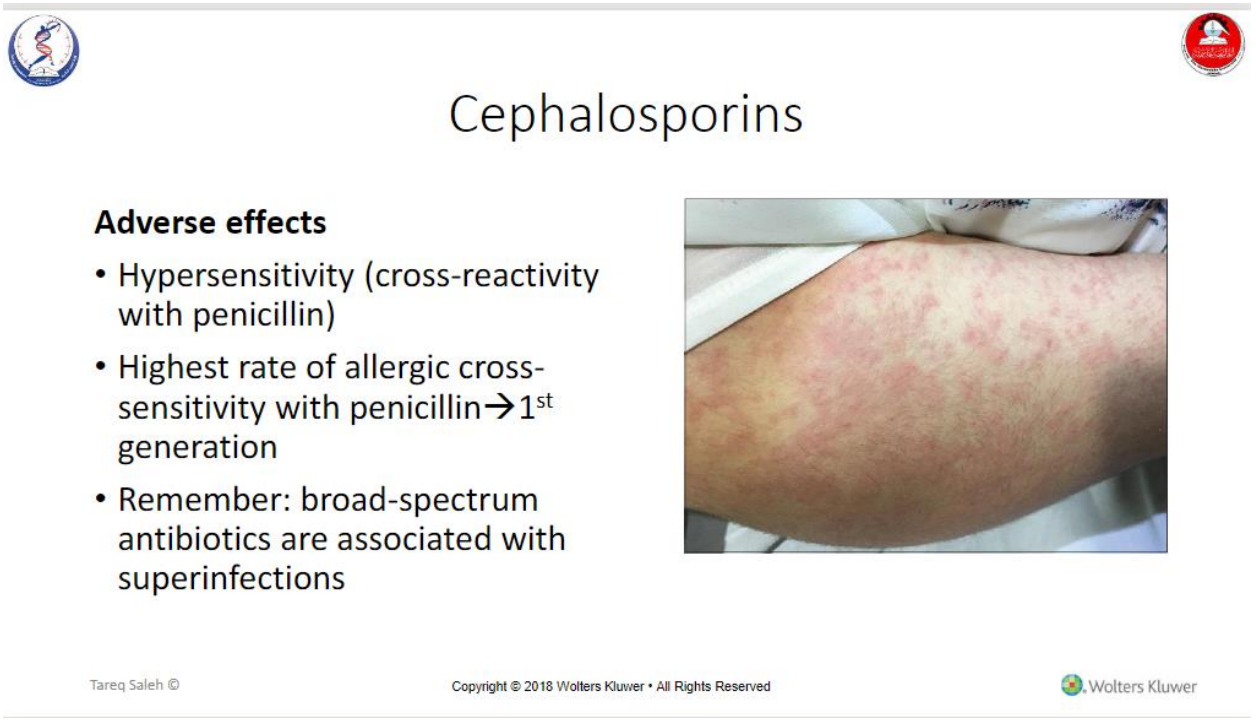
-ceftriaxone and cefotaxime can achieve high therapeutic concentrations in the CSF so they used for treatment of CNS infections.

-cefazolin can be used for infections in bone

Most of cephalosporins do not undergo hepatic metabolism so they execrated unchanged in the urine. (very good to patients of hepatic failure)

-ceftriaxone, which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

المعلومة من الكتاب ما ذكرها الدكتور بس اغلب اسئلة الدكتور كيسز ف ممكن ننسأل عنها عادي .. لو عندي المريض عندو مشاكل بالكلى يفضل ما اعطيه ادوية بتم التخلص منها عن طريق الكلى ف بستخدم السيتفرياكسون لانو الجسم بتخلص منو بطريقة لا تعتمد على الكلى .

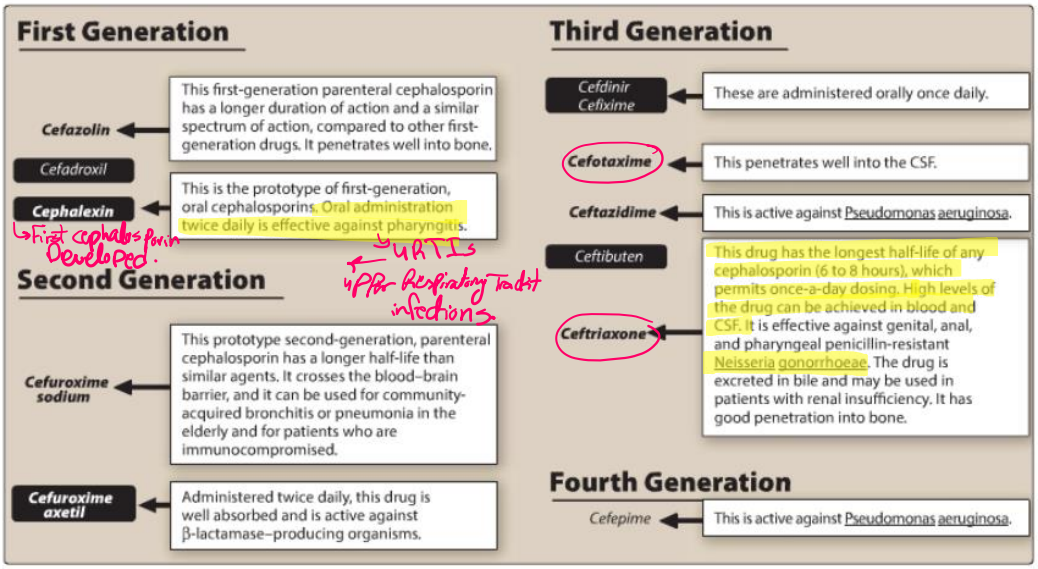


As we said even if the drug is safe the side effects may occur.

Cephalosporins and penicillin are related to each other in structure and function so if the patient has an allergy from penicillin, he might have allergy from cephalosporins.

-superinfections→ mainly with 3rd , 4th and advanced cephalosporins → because of their broad spectrum activity → they may kill the normal flora allowing the growth of pathogenic bacteria , example (Clostridium difficile) → cause pseudomembranous

Colitis.



Very important

اقرأوه كلو واعرفوه لانو جدا مهم وهون بعض الاضافات الي ضافها الدكتور .

Cefuroxime axetil → given orally / can be used in family medicine clinics

We said the penicillin G can be used for treatment of Neisseria gonorrhea but the resistance increased to penicillin G so → the drug of choice now to Neisseria gonorrhea is ceftriaxone.

In cephalosporins we have 2 drugs active against pseudomonas aeruginosa →

1-cefepime

2-cefotaxime (3rd generation)

In penicillin we have piperacillin active against pseudomonas aeruginosa.