Artery Academy

Done By Mariam Yacoub

رجعنالكم اليوم بالبارت الثاني والأخير من الشابتر
بس بدي أنوّه على إشي وهو أسماء البكتيريا المذكورة بسلايدات ليبينكوت حكت الدكتورة إحنا بس مُطالبين بالأسماء الموجودة بالسلايدات و إلّي بتنعاد أكتر من مرة معنا

B-lactam Antibiotics

Pharmacology 3

Dr. Heba Khader

بالمناسبة قبل ما نبلش حابة احطلكم مثال على فحص بيعملوه عادةً ليعرفوا شو
antibiotics resistance or susceptibile

نوع البكتيريا E.coli

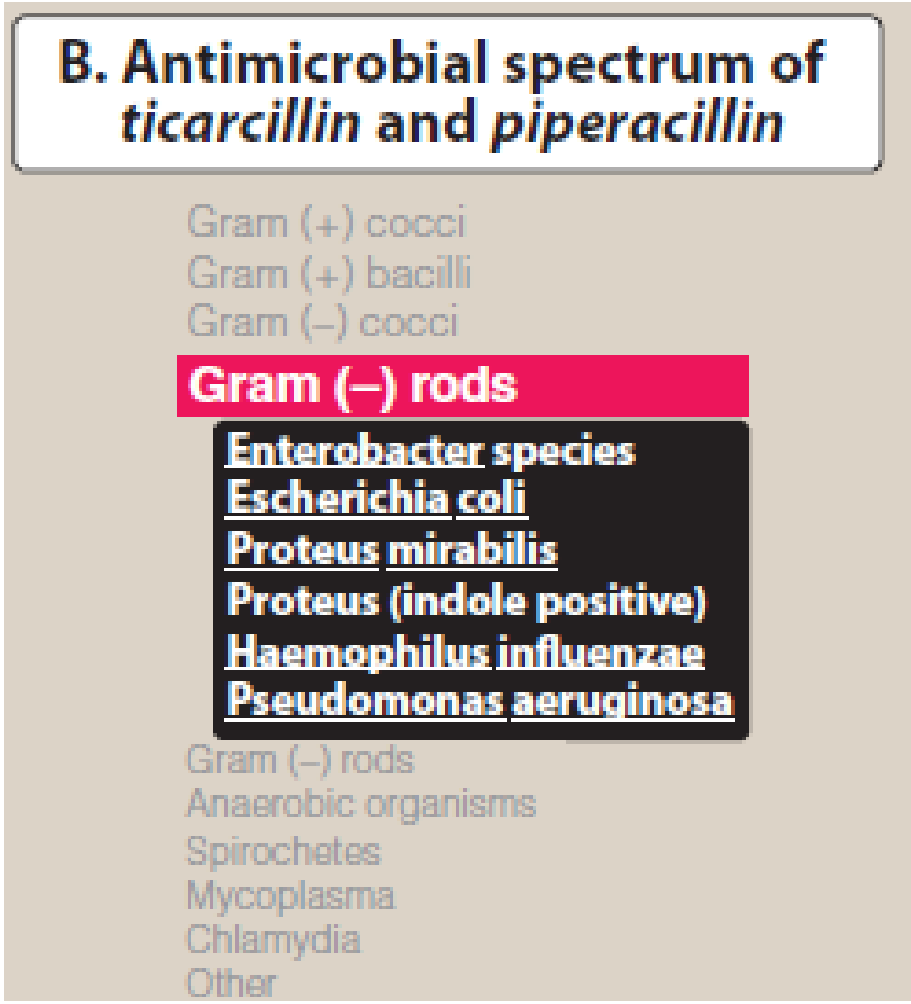
Culture Result:	ESCHERICHIA COLI	
Antibiotic	**Susceptibility:**	**Interpretatio**
AMIKACIN	S	S
AMOXICILLIN/CL	R	R
AMPICILLIN	R	R
CEFEPIME	S	S
CEFOTAXIME	S	S
CEFTAZIDIME	S	S
CIPROFLOXACIN	S	S
ERTAPENEM	S	S
GENTAMICIN	S	S
IMIPENEM	S	S
MEROPENEM	S	S
PIPERACILLIN/T	S	S
TRIMETHOPRIM S	R	R

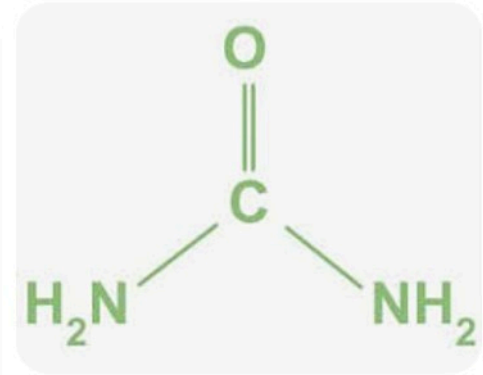
Classification of Penicillins

3. Anti-pseudomonal PNs

- **Piperacillin**
- **Ticarcillin**

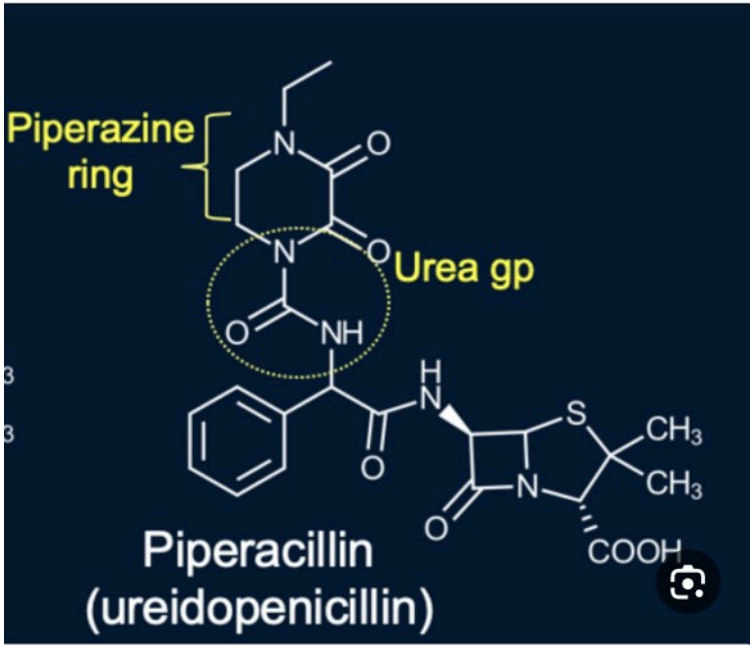
- These agents are available in parenteral formulations only.
- Formulation of ticarcillin or piperacillin with clavulanic acid or tazobactam, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms





التصنيف الرابع معنا بعد ال **natural+ extended+**
antistaph هو : **anti pseudomonal penicillin**
وسبق وحكينا هينت بسيط عنهم إنه بتميزوا بوجود ال
urea group بالستركشر تبعهم حطيتلكم إياه:

متوفرين فقط **parenteral** زي ال **PG** إذا بتتذكروا 🙄
بكون معهم تركيبة تانية وهي :
ticarcillin + clavulanic acid
piperacillin + tazobactam



بنقدر نعتبرهم **stable to lactamase**
inhibitor زي ال **antistaph**

Resistance to penicillins and other B-lactams

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

1. Inactivation of antibiotic **by B-lactamase (the most common mechanism)**
2. Modification of target PBPs.
   - low affinity for binding B-lactam antibiotics
   - basis of methicillin resistance in staphylococci (**MRSA, use Vancomycin).**
3. Impaired penetration of drug to target PBPs.
   - only in G- (impermeable outer cell wall)
   - Absence or down-regulation of porins.
4. Efflux.
   - Gram-negative organisms also may produce an efflux pump, which transport B-lactam antibiotics from the periplasm back across the outer membrane.

حكينا عن ال **mechanism of action** وهسا رح نحكي عن ال **mechanism of resistance**
بمعنى إنه كيف البكتيريا ما رح تستجيب لل **penicillin** وتعمل **resistance** إله
الطريقة الأولى هي الشائعة و إلّي من بداية الفصل بنحكي عنها وهي انزيم ال **lactamase** إلّي
بكسّرلي ال **beta lactam ring** وبالتالي بفقد فعاليته

تاني طريقة هي تعديل بال **penicillin binding protein** بالتالي هون ما رح يقدر ال **penicillin**
يرتبط **as substrate** بدل ال **D-Ala-D-Ala** ويعمل **inhibition of cell wall synthesis** لهاي
البكتيريا
ومن الأمثلة ع بكتيريا بتعمل هيك هي ال **MRSA** ورح يكون شابتر كامل عنها بحيث انه بهاي الحالة
بنستعمللها **vancomycin** وكنسلنا ع كككل ال **beta lactam**

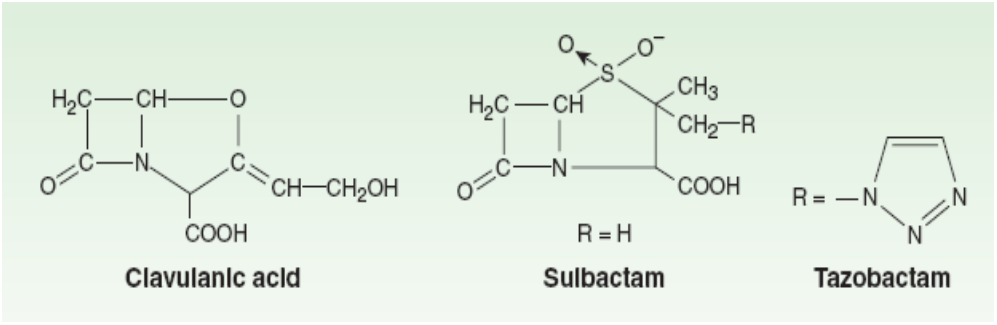
الطريقة التالتة بنشوفها بس بحالة ال **gram negative** لإنه هي عندها بس **outer membrane**
بحيث إنه بتشيل ال **porins** ف بالتالي ما حيقدر ال **antibiotics** يصيرله **penetration** من خلالها

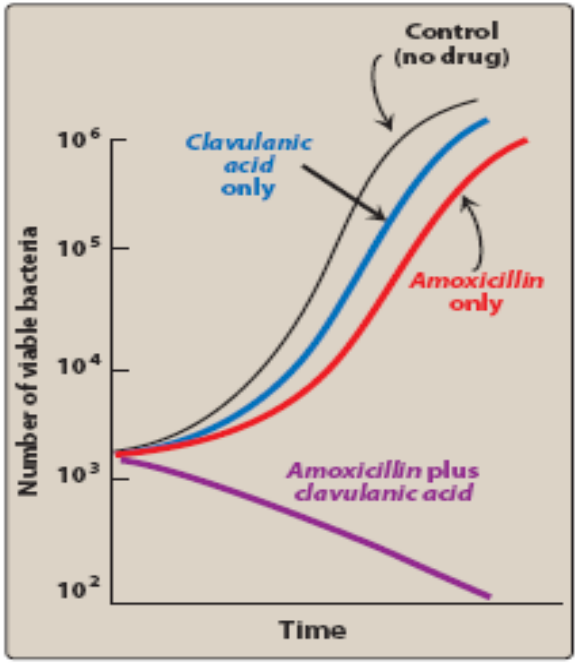
اخر طريقة هي **Efflux** هون بهاي الحالة بكون ال **penicillin** دخل لجوا ووصل ال **periplasmic**
بعدها عن طريق **Efflux pump** موجودة بالبكتريا بتقوم تطلّع ال **penicillin** هاد من جوا لبرا ف ما
بيعمل الأكشن تبعه

لحتى ما تصير ال mechanism الأولى إلّي حكينا عنها بالسلايد الماضي ح نستعمل beta lactamase inhibitor وهمة :

β-LACTAMASE INHIBITORS

- Clavulanic acid, sulbactam and tazobactam
- Contain a β-lactam ring, but do not have antibacterial activity
- Bind to and inactivate β-lactamases
- Formulated in combination with β-lactamase sensitive antibiotics (in fixed combinations)
  - Amoxicillin – Clavulanic acid
  - Piperacillin-tazobactam
  - Ampicillin-sulbactam





in vitro growth of Escherichia coli in the presence of *amoxicillin ± clavulanic acid.*

هاي ال **beta lactamase inhibitor** بكونوا عبارة عن **beta lactam structure** بس ما بكون إله **affinity** على ال **transpeptidase enzymes** وإنما عندهم **affinity** على ال **beta lactamase enzyme** ف بالتالي بضحّوا بحالهم مع هاد الإنزيم لحتى يقدر يدخل ال **penicillin** ويعمل **inhibition of transpeptidation** ويكمل شغله طبيعي
بكونوا **as combination** بأربع تركيبات فقط وهمة :

Amoxicillin – Clavulanic acid
Piperacillin-tazobactam
Ampicillin-sulbactam
Ticarcillin -clavulanic acid

بالمخطط تحت بوضّحلنا نمو ال **E.coli** مع الوقت لما استخدمنا ال **penicillin** لحاله ولما استخدمنا ال **clavulanic acid** لحاله ووقت استخدمناهم سوا **as a combination** وأشهر مثال عال **amoxicillin+ clavulanic acid** هو ال **amoclan** وباقي بدائله مثل ال **moxiclav, curam ...,**

Pharmacokinetics

ضروري جدًا تطلعوا من هاي السلايدة مفرقين بين ال **oral and parenteral penicillin**

إلّي عنده سهم **oral** والباقي **parenteral**

- Absorption:
  - **Oral penicillins**: Penicillin V, dicloxacillin, ampicillin, and amoxicillin are acid-stable and relatively well absorbed
  - Absorption of most oral penicillins (**amoxicillin being an exception**) is impaired by food, therefore they should be given at least 1–2 hours before or after a meal.
  - **Pivampicillin** is a pivaloyloxymethyl ester of ampicillin. It is a prodrug, which is thought to enhance the oral bioavailability of ampicillin because of its greater lipophilicity compared to that of ampicillin

ال **amoxicillin** ما بيتأثر بالأكل عكس الباقي

absorption أعلى =**bioavailability** أعلى = **lipophilicity** أعلى

prodrug of ampicillin هو

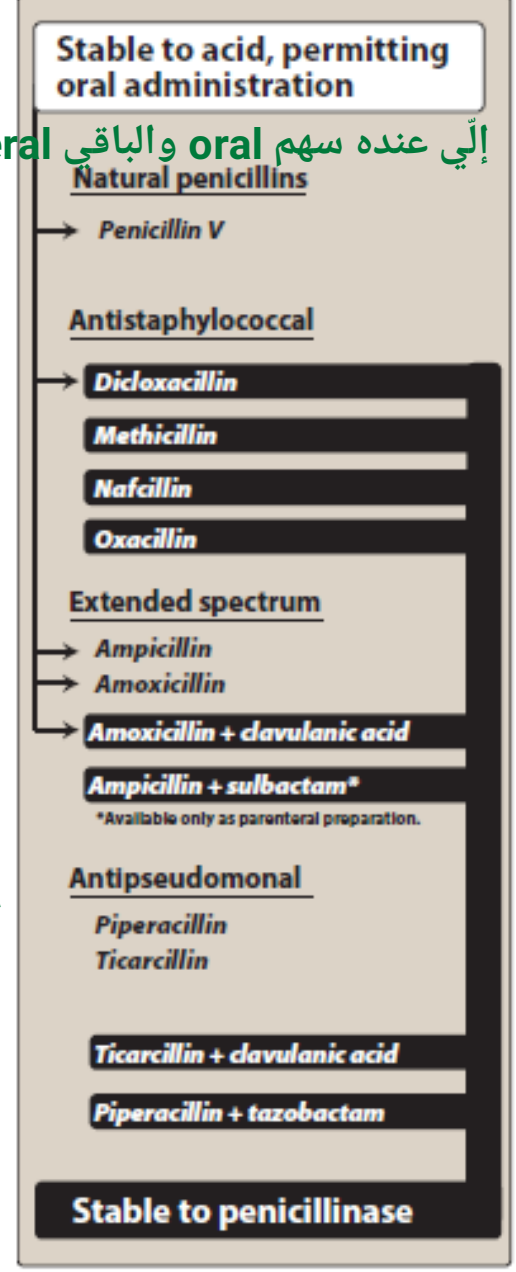


Figure 38.6
Stability of the penicillins to acid or the action of penicillinase.

Pharmacokinetics

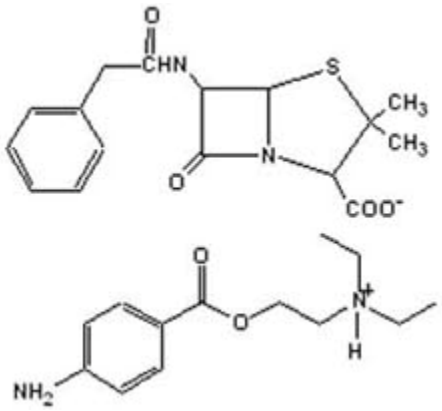
- **Penicillin G**

سبب إنه ال **PG** بنعطيه **IV not IM**

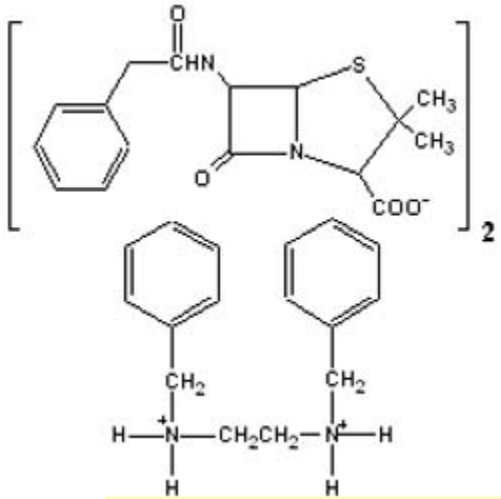
  - IV of is preferred to the IM because of irritation and local pain.

حالة وحيدة بنعطي فيها ال **PG IM** بكون ال **Depot form or sustained** وقت ندمجه مع **benzathine or procaine** فقططط

  - **Depot forms**
  - Benzathine and procaine penicillin G are formulated to delay IM absorption, resulting in prolonged blood and tissue concentrations (3 weeks)



Procaine penicillin



Benzathine penicillin

العلاج حسب الحالة مثلاً إذا إشي **emergency as** بنستعمل **IV meningitis** وفي حالة ال **syphilis** بنستخدم **IM** بكون بتطلب **prolonged treatment** على مدار ٣ أسابيع مثلاً

Pharmacokinetics

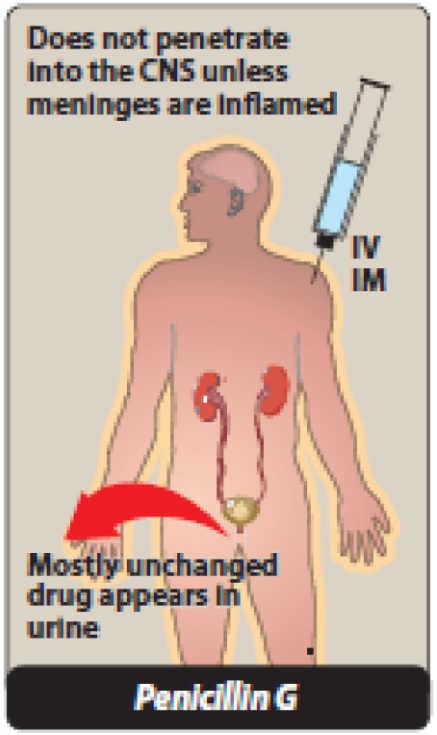
- **Distribution:**
- PNs are widely distributed in body fluids and tissues (but not cerebrospinal fluid unless it is inflamed) .
- All the penicillins cross the placental barrier, but none have been shown to have teratogenic effects…FDA Pregnancy Category B ما بعمل ضرر للجنين ف يُعتبر آمن عالحامل
- Penicillins are excreted in human milk. Caution should be exercised when penicillins are administered to a nursing woman.
- Penicillin levels in the prostate are insufficient to be effective against infections.

Pregnancy Category	Description
A	Appropriate human studies - no risk
B	Insufficient human studies, but animal research suggests safety **or**: Animal studies show issues but human studies show safety
C	Insufficient human studies, but animal studies show problems **or**: No animal studies, and insufficient human studies
D	Human studies, with/without animal research show fetal risks, but the drug is important to some women to treat their conditions
X	Fetal risks are evident; there are no situations where the risk/benefit justifies use

ما في antibiotics مصنف category A لهيك أي دوا category B يُعتبر safer for pregnant

Pharmacokinetics

- **Excretion:**
- The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration.
  - Dose must be adjusted according to renal function
    - Nafcillin cleared by biliary excretion. Oxacillin, dicloxacillin, and cloxacillin are eliminated by both the kidney and biliary excretion; no dosage adjustment is required for these drugs in renal failure subjects.
  - Blood levels of all penicillins can be raised by simultaneous **administration of probenecid** (impairs renal tubular secretion of weak acids such as B-lactam ABs).



probenecid: anti gout

ما إله كتير سايد ايفيكت لهيك بستخدموه العالم كتير

Adverse Reactions to Penicillins

- The penicillins are generally well tolerated, and, unfortunately, this may encourage inappropriate use.
- Most of the serious adverse effects are due to hypersensitivity.
- **Hypersensitivity** (due to penicilloic acid)
  - 5% of population
  - Allergic reactions range from a variety of skin rashes to anaphylactic shock (very rare—0.05% of recipients);
- Large doses of penicillins given orally may lead to **gastrointestinal upset**, particularly nausea, vomiting, and diarrhea.
  - Pseudomembranous colitis from *Clostridium difficile* and other organisms may occur with penicillin use.
- **Nephritis:** Penicillins, particularly *methicillin*, have the potential to cause acute interstitial nephritis. [Note: *Methicillin* is therefore no longer used clinically.]
- **Neurotoxicity:** The penicillins can provoke seizures if injected intrathecally or if very high blood levels are reached.

اغلب الأعراض هاي بتكون عادةً عند الجرعات العالية

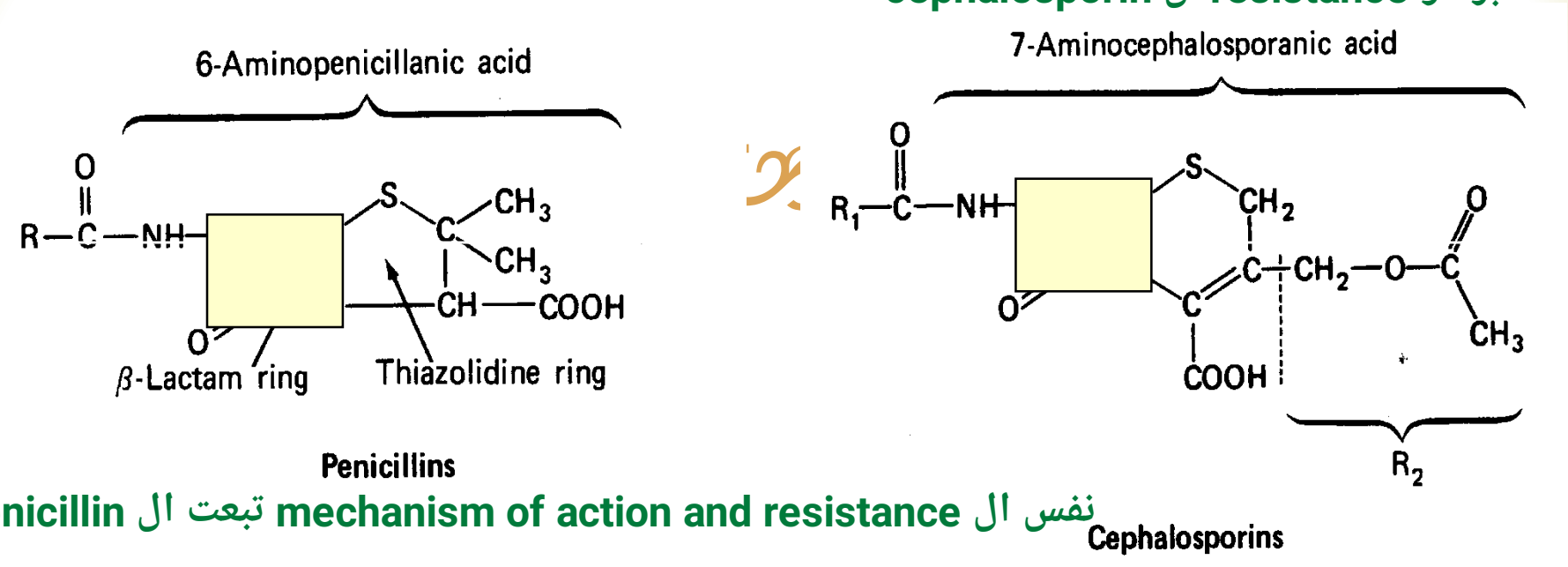
المجموعة الثانية من ال cell wall synthesis inhibition هو :

Cephalosporins

Cephalosporins (CPNs) are Structurally Similar to Penicillins

نفس الستركشر لكن **resistance** أقل ومش شرط إذا البكتيريا **resistance** للبنيسيلين تكون

برضو **resistance** لل **cephalosporin**



mechanism of action and resistance نفس ال **penicillin** تبعت ال

- Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be more resistant than the penicillins to certain β-lactamases.
- But, Methicillin-resistant staphylococci are resistant to CPNs (traditional CPNs).

حكينا أصلاً حنكنسل ع كل ال **beta lactam** بحالة ال **MRSA**

- **Resistance:** ما في اشي جديد هون
- Many bacteria are resistant through the production of other B-lactamases that can inactivate CPNs (extended-spectrum β-lactamases (ESBLs)). نوع الإنزيم إلّي بثبّط **Cephalosporin**
- Resistance can also result from decreases in membrane permeability to CPNs and from changes in PBPs.

Characteristics of CPNs

- Several CPNs were originally isolated from a mold called Cephalosporium (Acremonium chrysogenum). Cephalosporin C is the prototype.
- Cephalosporins inhibit synthesis of the bacterial cell wall (binds to PBP, Bactericidal)
- Absorption, distribution, elimination - similar to penicillins
- Incidence of resistance is lower than penicillins

كله نفس ال penicillin بالخصائص بس الاختلاف إنه ال resistance هون أقل من ال penicillin

بنصنفهم لأربع أقسام حسب ال **activity** الهم عالبكتيريا

Classification of CPNs

- **Four generations** (1^{st},2^{nd} , 3^{rd} , 4^{th}) according to their bacterial activity.

As a general role:

- First-generation CPNs are active predominantly against G+ bacteria.
- Successive generations have increased activity against G- bacteria (often with reduced activity against G+).

- FIRST GENERATION
  - Cefazolin, Cephalexin, cefadroxil, cephradine
- SECOND GENERATION
  - Cefaclor, Cefuroxime
- THIRD GENERATION
  - Cefotaxime, Ceftriaxone
- FOURTH GENERATION
  - Cefepime

بتزيد ال **activity** لل **gram negative** وبتقل لل **gram positive**

ال **generations** الخامس خصائصه مختلفة وممكن يزبط عال **MRSA**

ممكن يساعدوكم بالحفظ

Cephalosporin Generations

1ST Generation

- Cefazoline
- Cefalexin
- Cefalothin
- Cefaloridine
- Cefadroxil

Cef

2ND Generation

- Cefuroxime
- Cefoxitin
- Cefmetazole
- Cefomandole
- ex — Cefaclor

Me
One
Ten

3RD Generation

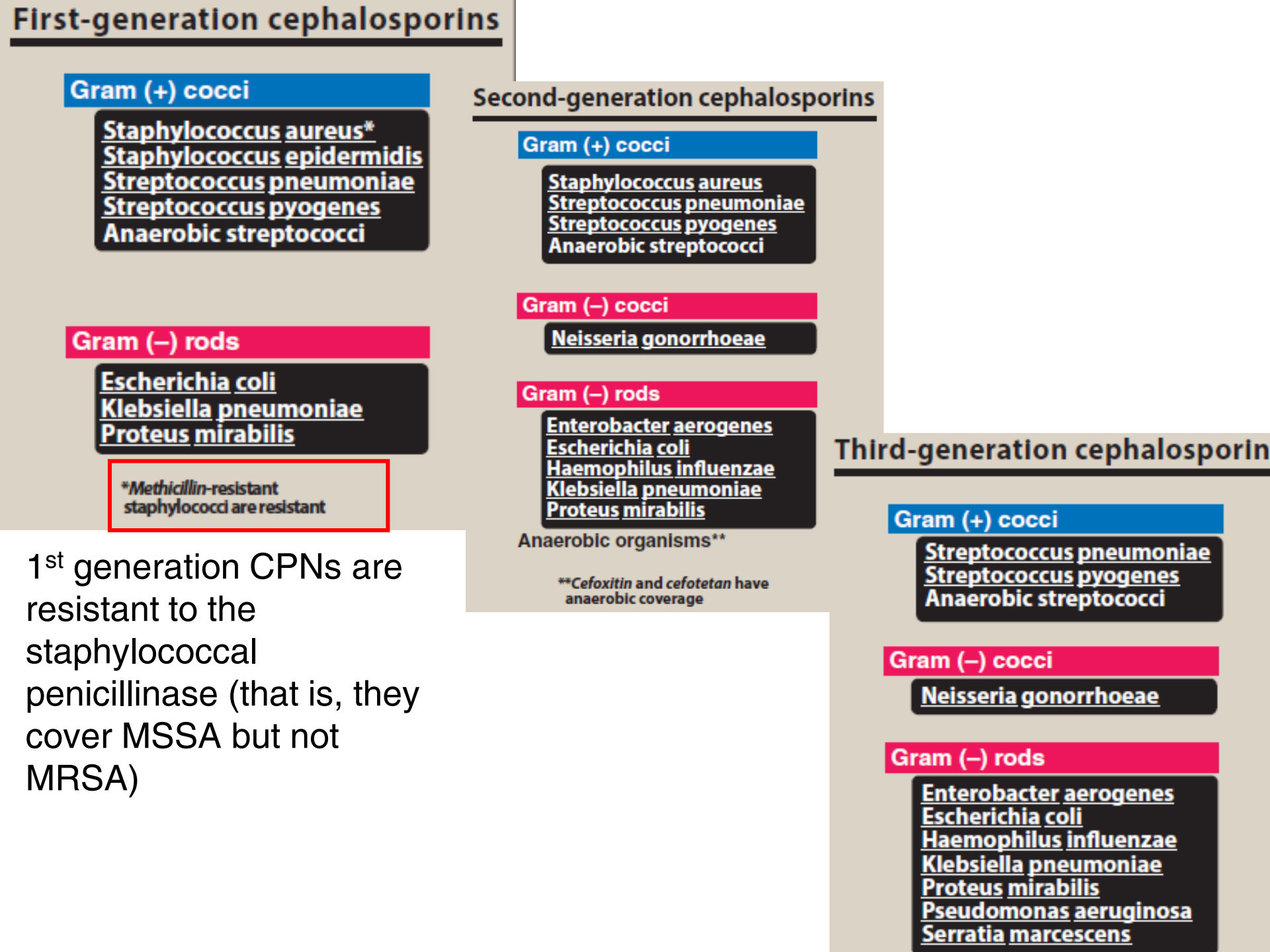
- Cefoperazone
- Ceftriaxone
- Cefotaxime
- Ceftizoxime
- Cefpodoxime
- Ceftazidime
- Ceftibuten
- Cefexime
- Moxalactam

4th Generation

- Cefepime — Pi
- Cefpirome — no 'a'

5th Generation

- Ceftibiprole
- Ceftaroline — NO 'a'



1st generation CPNs are resistant to the staphylococcal penicillinase (that is, they cover MSSA but not MRSA)

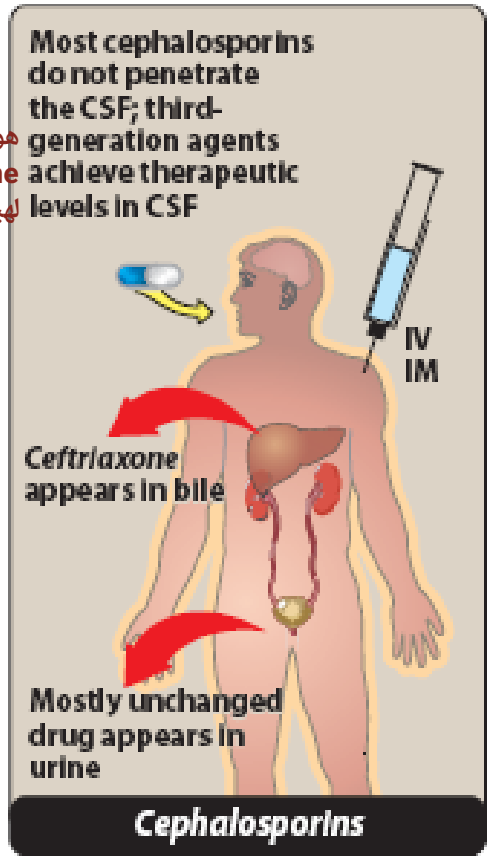
المهم نعرفه هون أكيد ال classification وكمان نميز بين ال oral and IV

Antibiotic (Route of Administration)	Adult Dose	Pediatric Dose[1]	Neonatal Dose[2]	Adjusted Dose as a Percentage of Normal Dose for Renal Failure Based on Creatinine Clearance (Cl_{cr})	
				Cl_{cr} Approx 50 mL/min	*Cl_{cr} Approx 10 mL/min*
First-generation cephalosporins					
Cefadroxil (PO)	0.5–1 g qd–bid	30 mg/kg/d in 2 doses		50%	25%
Cephalexin, cephradine (PO)	0.25–0.5 g qid	25–50 mg/kg/d in 4 doses		50%	25%
Cefazolin (IV)	0.5–2 g q8h	25–100 mg/kg/d in 3 or 4 doses		50%	25%
Second-generation cephalosporins					
Cefoxitin (IV)	1–2 g q6–8h	75–150 mg/kg/d in 3 or 4 doses		50–75%	25%
Cefotetan (IV)	1–2 g q12h			50%	25%
Cefuroxime (IV)	0.75–1.5 g q8h	50–100 mg/kg/d in 3 or 4 doses		66%	25–33%
Third- and fourth-generation cephalosporins including ceftaroline fosamil					
Cefotaxime (IV)	1–2 g q6–12h	50–200 mg/kg/d in 4–6 doses	100 mg/kg/d in 2 doses	50%	25%
Ceftazidime (IV)	1–2 g q8–12h	75–150 mg/kg/d in 3 doses	100–150 mg/kg/d in 2 or 3 doses	50%	25%
Ceftriaxone (IV)	1–4 g q24h	50–100 mg/kg/d in 1 or 2 doses	50 mg/kg/d qd	None	None
Cefepime (IV)	0.5–2 g q12h	75–120 mg/kg/d in 2 or 3 divided doses		50%	25%
Ceftaroline fosamil (IV)	600 mg q12h			50–66%	33%

Cefuroxime axetil (2nd) and cefdinir, cefixime and ceftibuten (3rd) also P.O

Pharmacokinetics

- Administration:
  - Many of them must be administered IV or IM because of their poor oral absorption (however some can be given orally) ميّزناهم بالجدول
- Distribution: ما بعبر لل.CSF إلا إذا كان في inflammation
  - CPNs distribute very well into body fluids but not to CSF.
  - **Cefazolin** penetrates well into most tissues. It is a drug of choice for surgical prophylaxis including orthopedic surgery because of its ability to penetrate bone. هو اكتر واحد بصيرله distribution in bone لهيك بنستخدمه :
  - Only **ceftriaxone** or **cefotaxime** achieve therapeutic levels in the CSF and have become agents of choice for **meningitis.**
  - All CPNs cross the placenta.
- Elimination: نفس ال penicillin
  - Tubular secretion and/or glomerular filtration
  - Doses must be adjusted in cases of renal failure
  - Exception:
    - **Ceftriaxone**, excreted through the bile…..Employed in patients with renal insufficiency هو dose adjustment الوحيد بحتاج



Cephalosporins Active against Methicillin-Resistant Staphylococci (advanced generation; 5th generation)

- **Ceftaroline fosamil**, the prodrug of the active metabolite ceftaroline.
- Ceftaroline has increased binding to penicillin-binding protein 2a, which mediates methicillin resistance in staphylococci, resulting in bactericidal activity against these strains.
- Ceftaroline is currently approved for the treatment of complicated skin and soft tissue infections and community-acquired pneumonia.

كَونه ال **MRSA** عملت **penicillin binding protein 2a** مختلف عن العادي ف العلماء صنّعوا ال **ceftaroline** وسمّوا ال **fifth generation of cephalosporin** بحيث إنه برتبط فيه وبيعمللها **inhibition** لهيك هو يُعتبر **bactericidal**

ولا يُستخدم إلا عند الضرورة عشان نخفف من ال **resistance** ورح احط هايلايتر عالاستخدام :

Adverse Reactions to CPNs

- Allergy (hypersensitivity)
  - ~~The frequency of cross-allergenicity between CPNs and PNs is 5–10% (little)~~
  - ~~Patient with a history of anaphylaxis to PNs should not receive CPNs.~~

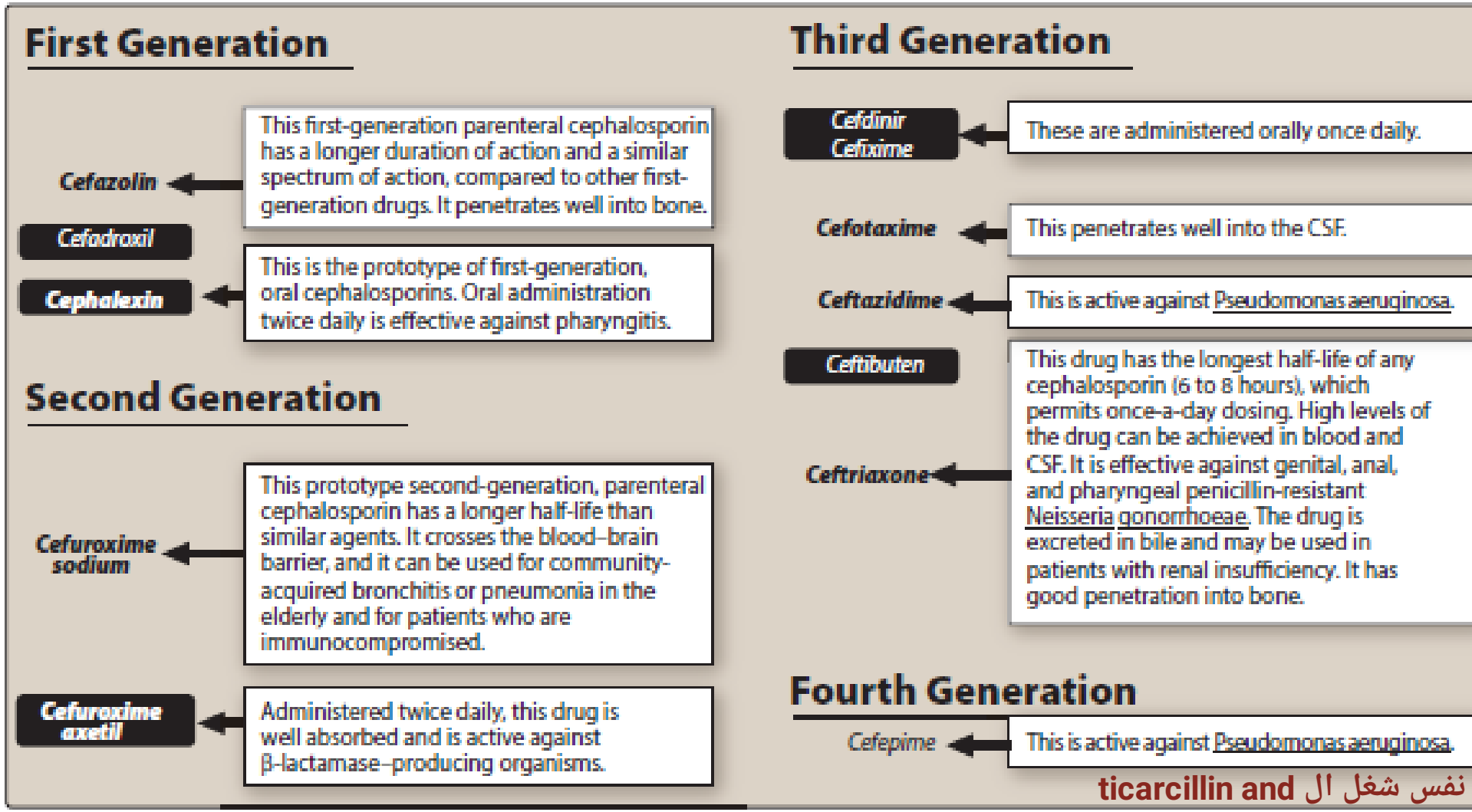
مش بالضرورة شخص عنده حساسية من البنيسلين يكون بتحسس برضو من ال cephalosporin

Overall the frequency of cross-allergenicity between PNs and CPNs is low (~1%)

Patients with a history of anaphylaxis to penicillins should not receive first- or second-generation cephalosporins, while third- and fourth-generation cephalosporins should be administered with caution, preferably in a monitored setting.

يُفضل إذا الشخص عنده حساسية من البنيسلين يبعد عن ال first and second generation من ال cephalosporin والسبب إنه الستركشر تبعهم مُشابه للبنيسيلين تقريبًا والباقي بقدر يستخدمهم بحذر

المكتوب بالغامق هو الأكثر استخدامًا ومطلوب نعرف الاستخدامات الأهم فقط



نفس شغل ال **ticarcillin and**

~~**piperacillin** من ال **penicillin**~~

Figure 38.12

Therapeutic advantages of some clinically useful cephalosporins. [Note: Drugs that can be administered orally are shown in reverse type. More useful drugs shown in **bold**.]. (CSF = cerebrospinal fluid.)

Other CPNs

بس مطلوب المكتوب بالسلايدات الماضية
ومكتوبين هون بالأحمر

- **FIRST GENERATION**
  - **Cefazolin, Cephalexin, cefadroxil,** cephalothin, cephapirin, and cephradine.
- **SECOND GENERATION**
  - **Cefaclor, Cefuroxime,** cefamandole, cefonicid, cefprozil, loracarbef, and ceforanide; and the structurally related cephamycins cefoxitin, cefmetazole, and cefotetan, which have activity against anaerobes.
- **THIRD GENERATION**
  - **Cefotaxime, Ceftriaxone,** cefoperazone, ceftazidime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime proxetil, cefdinir, cefditoren pivoxil, ceftibuten, and moxalactam.
- **FOURTH GENERATION**
  - **Cefepime**

Other B-Lactam Drugs

- Monobactams
- Carbapenem

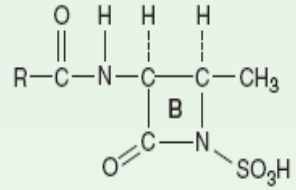
نفس ال mechanism لسا

Monobactams

Monocyclic β-lactam : سبب التسمية

- Disrupts bacterial cell wall synthesis (blocks peptidoglycan crosslinking)
- The only available agent is **aztreonam** : دوا واحد بس وهو
  - Active against the Enterobacteriaceae, P. aeruginosa. **(G-)**
  - Lack activity against gram-positive bacteria or anaerobes (binds the penicillin-binding proteins of Gram+ and anaerobic bacteria very poorly). فقط شغله عال **gram negative**
  - Resistant to the action of most β-lactamases with the exception of the **extended-spectrum β-lactamases (ESBLs).**
- IV or IM هاد الإنزيم إلّي بشتغل عال **Penicillin and cephalosporin** وما بقدر يقاومه ال **aztreonam** كمان
- Penetrates well into the CSF : المميز فيه عن الباقي
- Used for pneumonia, meningitis, and sepsis caused by susceptible G-.
- nontoxic, safe alternative for patients who are allergic and unable to tolerate PNs & CPNs

يُعتبر بديل آمن للناس إلّي عندها **allergy** من أول مجموعتين حكيناهم



Monobactam

Substituted 3-amino-4-methylmonobactamic acid (aztreonam)

broad spectrum يُعتبر ف empiric treatment

Carbapenems

- Difference from PNs : Sulfur (S) atom of the thiazolidine ring has been externalized and replaced by a carbon atom
- **Imipenem**
  - **Plays a role in empiric therapy** because it is active against b-lactamase-producing G- & G+, anaerobes, and P. Aeruginosa
  - Resists hydrolysis by most β-lactamases, but not the **metallo-β-lactamases (carbapenemases).** الإنزيم الوحيد إلّي بحطّم الچروب هاد
  - Administered IV **onlyyyy**
  - Penetrates well into body tissues and fluids, including CSF when the meninges are inflamed.
- Other carbapenems:
  - **Doripenem, ertapenem** and **meropenem.**

penem نهايتهم

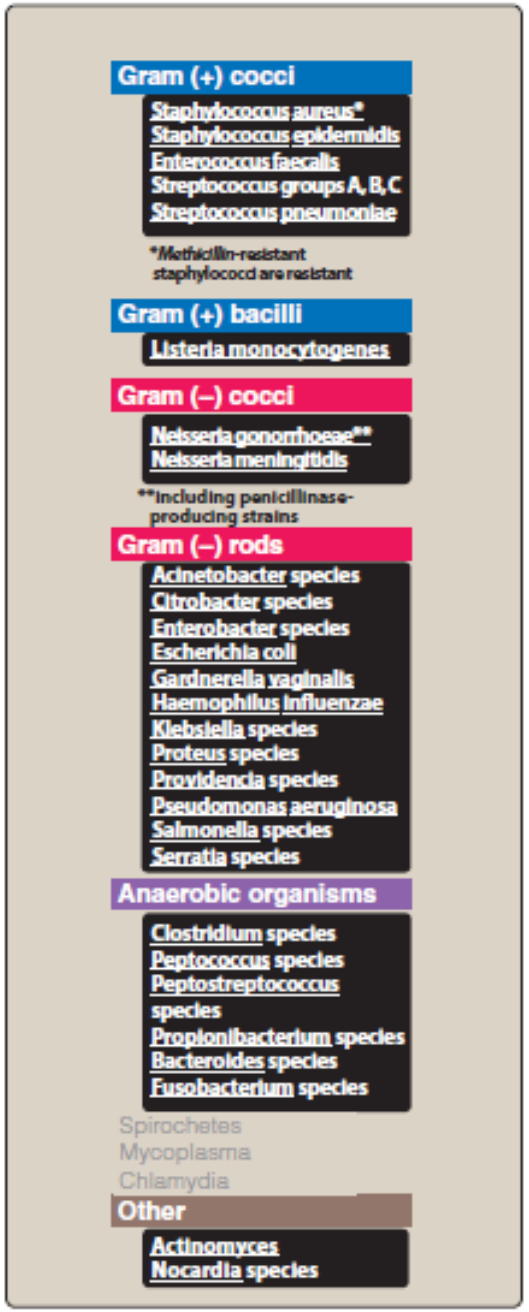


Figure 38.14
Antimicrobial spectrum of *imipenem*.

Carbapenems

- They are excreted by glomerular filtration.
- Imipenem undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. This enzyme forms an inactive metabolite that is potentially nephrotoxic.
- Compounding the **imipenem with cilastatin** (dehydropeptidase inhibitor) protects the parent drug and, thus, prevents the formation of the toxic metabolite.
- The other carbapenems do not require coadministration of cilastatin.

مشكلة ال **imipenem** إنه وقت يوصل ال
proximal renal tubule بصيرله ميتابوليزم
بواسطة **dehydropeptidase** وبحَوله لمادة
nephrotoxic سامة بتعمل
علاج هاي المشكلة إني اضيف **inhibitor** لهاد
الإنزيم وهو ال **Cilastatin**
وهاي المشكلة مُقتصرة فقط على **imipenem**

The End

هيك بكون خلص الشابتر التاني الحمدلله✅