passion ACADEMIC team.

- YU-Medicine

Sheet #17

Lec. Date : 3.NOV.2019

Lec. Title: Cell wall inhibitors

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PHARMACOKINETICS (penicillins)

- Absorption: decrease by food in the stomach, must be administered 30 min before meals or 2 to 3 hours postprandial
- Route of administration:
  - Penicillin V, amoxicillin, and amoxicillin combined with clavulanic acid are oral preparations
  - Ticarcillin, piperacillin, and the combinations of ampicillin with sulbactam, ticarcillin with clavulanic acid, and piperacillin with tazobactam, must be administered intravenously (IV) or intramuscularly (IM).
  - Depot forms: Procaine penicillin G and benzathine penicillin G are administered IM and serve as depot forms

PHARMACOKINETICS (penicillins)

- Distribution:
  - Cross Placenta (not teratogenic)
  - Bone, CSF (in inflammation only)
  - Prostate (insufficient)
- Clearance :
  - Renal tubular secretion.
  - Impaired renal function, dose adjustment?
  - ***Probenecid*** inhibits the secretion of **penicillins** by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels

Adverse reactions: Penicillins

- **Hypersensitivity**; penicilloic acid (5%) varies from rash, angioedema to anaphylactic shock.
- **Diarrhea**: for extended spectrum, *pseudomembranous colitis* from *clostridium difficiles*
- **Nephritis**: methicillin \ Withdrawn from market
- **Neurotoxicity**: seizures if injected intrathecally
- **Hematologic toxicities**; ex. Piperillicin decreased coagulation

β-Lactamase Inhibitors

- Hydrolysis of the β -lactam ring, by β -lactamase destroys the antimicrobial activity of a β -lactam antibiotic
- β-Lactamase inhibitors, do not have significant antibacterial activity, they inactivate β -lactamases, so, protecting antibiotics
- Formulation with a β-lactamase inhibitor, such as *clavulanic acid or sulbactam, protects amoxicillin* or *ampicillin, respectively, from enzymatic hydrolysis and extends* their antimicrobial spectrum.
- For example, without the β -lactamase inhibitor, MSSA is resistant to *ampicillin and amoxicillin*

- When we talked about cell wall inhibitors and all of them has the same mechanism of action, almost have the same binding site, and this binding site is penicillin binding protein (the first target receptor).

- They found that this protein has types: X,α,2X, etc...
- So activity starts to change from generation to another, EX: natural group of penicillin are sensitive to penicillase (it is a ß-lactamase penicillase enzyme that opens ß-lactam ring), and this penicillase is excreted from the bacteria and it degrades the antibiotic by opening ß-lactam.

- When the natural group of penicillin is sensitive to ß-lactamase, that means it can't use for those who secrete ß-lactamase,
- EX: staphylococcus aureus and klebsiella are very resistance, why?

  Because they prevent the drug from accumulation inside.

- First, we have apreplem that penicillin was most active against normal gram (+) without staphylococcus aureus

- Penicillin group is the first line for:

1) Gonorrhea
2) Syphilis

Sexual transmitted disease

3) Pneumonia (Pneumococcal Pneumonia)
4) Prevention endocarditis staphylococcus aureus

- If staphylococcus aureus is developed that means there is methicillin resistance and methicillin is sensitive to staphylococcus aureus
- Ampicillin and amoxicillin ⟶ there are amino group on penicillin for broading the spectrum and this spectrum becomes against H.pylori, anaerobic (for example: for treatment and prevention endocarditis, listeria (not common), and staphylococcus aureus (the sensitive one not the resistance).
- Now, we made special group from penicillin that are selective toxicity, two types of drug, one is anti-staphylococcal penicillin (it's very narrow spectrum) it's only against MSSA (methicillin sensitive staphylococcus aureus) which is resistance to penicillin, so it is higher activity and very narrow spectrum.

- These drugs are:

1) Nafcillin
2) Oxacillin
3) Dicloxacillin

- And the master of these drugs (prototype) is methicillin, but it's withdrawn because it's nephritis, so we have 3 drugs for staphylococcus aureus.

- For now, we haven't talked about any penicillin that treat pseudomonus, because it's target is gram (+), but we made a specific composition that made it most against pseudomonus.

these drugs are:

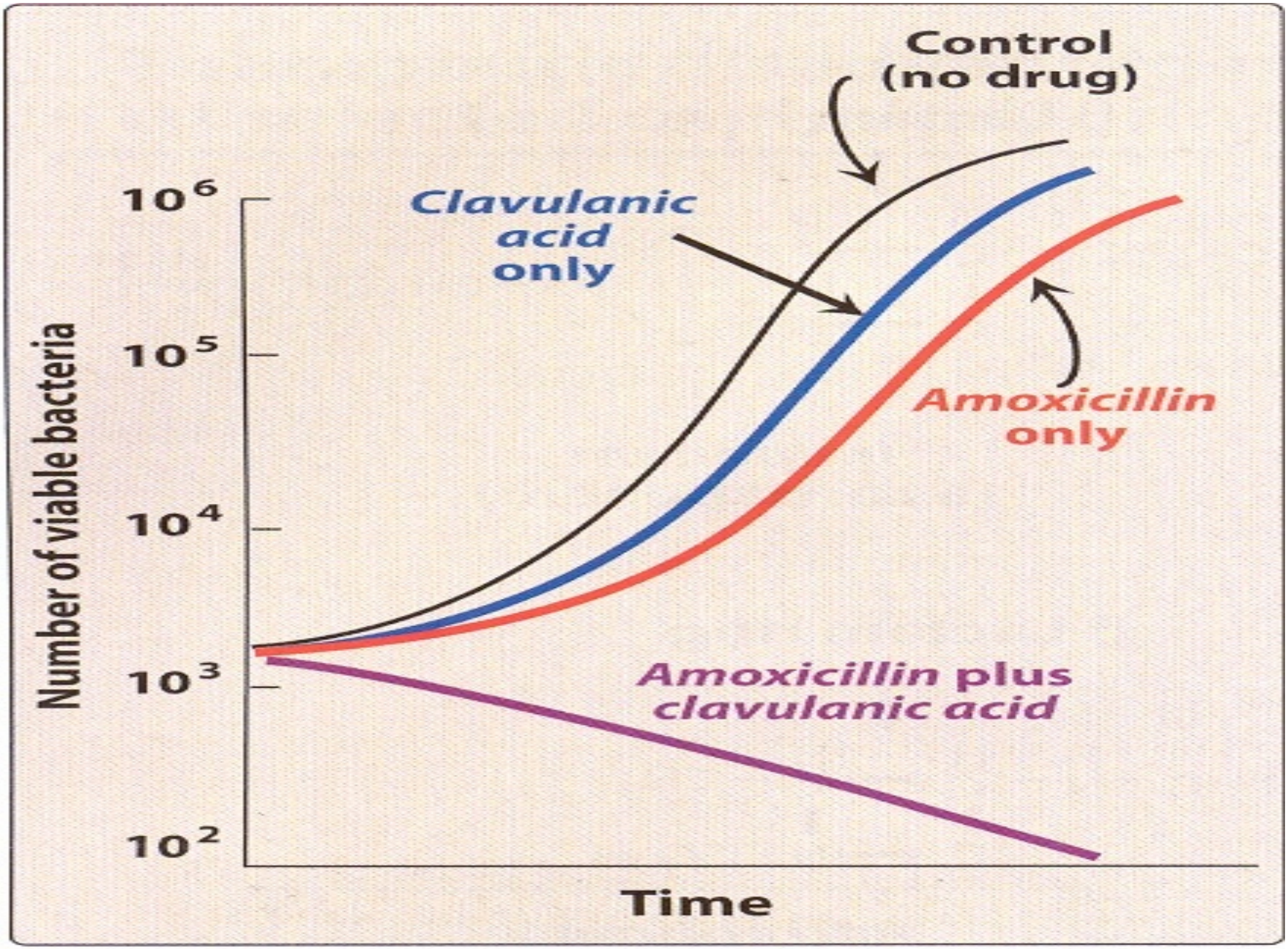
1) Plaperacillin
2) Carbenicillin
3) Ticarcillin

- The all four groups which we mentioned previously can be combined with ß-lactamase inhibitors

- Clavulanic acid, sulbactam, and Tazobactam → these drugs aren't antibiotics, but when you mix them with antibiotics it will extend the spectrum, because they in degredation of ß-lactamase so the antibiotic will be active against all mithicillin resistance, all klebsiella, all bacteria that secrete ß-lactamase.
- 1+0 > 2 (synergism)

  1 : antibiotic

  0 : ß-lactamase inhibitor


Control
(no drug)
Clavulanic
acid
only
Amoxicillin
only
Amoxicillin plus
clavulanic acid
Number of viable bacteria
10^6
10^5
10^4
10^3
10^2
Time

- When there is no drug, the number of bacteria increase with time.
- When we used only clavulanic acid, there is some drop, but clavulanic acid is not an antibiotic, may it degrades specific things, specific mechanism, but it it's not anti-bacterial effect.
- When we give amoxicillin, we have haigh anti-bacterial effect
- When we give both: amoxicillin and clavulanic acid, there is a big drop, this what we call synergism or potentiation (1+0>2).
- This combination doesn't increase the killing rate only, it also increase the spectrum, because the drug now is not just gram (+) only, it's against gram (+) which secretes lactamase.

Beta lactamase inhibition combinations:

- Augmentin® (amoxicillin/clavulanate), Orall
- Unasyn® (ampicillin/sulbactam) , IV
- Timentin® (ticaricillin/clavulanate), IV

- Augmentin is a generic name for amoxicillin and clavulanate (it was brand name, but became generic).
- Augmentin is very broad spectrum, doesn't need for tonsillitis, we need it in upper respiratory tract, sometimes with spultum and renal infection and dental infection, because it has higher distribution than amoxycillin alone.

- Unasyn is ampicillin and sulbactam and it's given IV.
- There is no amoxicillin IV, it is always orally even if it was combined.
- That means in hospital I have to start with ampicillin, and in home I have to change it to amoxicillin, this is called shifting.

يعني عندي مريض اعطيته بالمستشفى ampicillin على شكل unasyn وبده يطلع, لازم أحوله على augmentin لأنه ما فيه unasyn تبعت ال combination نفس ال

- Timentin is a ticaricillin and clavulanate, and it is anti-pseudomonal

- Route of administration:
- There is 3 orally, which are:

1) Penicillin V : the old one and now it's not recommended, why?

because it's taken every 6 hours (4 daily) and patient can't adhere with timing and frequency so it's noisy

2) Amoxicillin : the half life is 8 hours, so it can be given 3 times daily can't be extended to 12 تبعه $t_{1\backslash 2}$ ال لانه صيام لو حتى باليوم مرتين نعطيه انه ضد احنا failure of treatment وبالتالي رح يعطيني

3) Augmentin : has longer half life, so I can use it in fasting, has 2 concentrations (low and high) so I can take it twice or 3 times depending on the dose, so higher concentration can be extended.

- Depot form: means they have extended duration of action, they are give once weakly ore once every month and this is very good for patient inconvenience to medication.

Resistant to penicillin

1. Beta lactamase activity (G+ve and G-ve)
2. Decreased permeability of drugs (efflux mechanism in ***Kelbsiella pneumonia***)
3. Altered PBP (ex. **MRSA)**

- Distribution is very important because if the drug can't go to the tooth and gum, I can't use it for dental abscess.
- We know that penicillin is very difficult to enter dental abscess.
- Amoxicillin is better in distribution.
- EX: prostate infection isn't recommended, because the drug must be distributed to the site of infection to treat it, especially the antibiotic because other drugs for example if it was for pain in leg, it's not necessary to go to the leg, it is targeted to GABA in the brain to act in the brain center, but the infection must have local effect, if the antibiotic for the urinary infection, then it must go to the urine to act.
- So when we say it's insufficient prostate, it means it can't be used for prostate infection.

- Bone and CSF, this is only in inflammation
- In normal condition there will be no distribution because it's ionized, but during inflammation it can
- EX: during meningitis it can distribute, however in normal patient can't distribute or it could very minor

- When the drug can cross placenta:

crossing placenta doesn't mean that it's teratogenicity

- Not all drugs enter placenta should do mutation or make teratogenicity effect, it could be safe.
- Amoxicillin is considered as class B , class B means it can be given in first trimester (the first 3 months or above).
- All drugs (except 2 drugs) are mainly secreted by renal, this is good and bad.

good: for urinary bladder infection

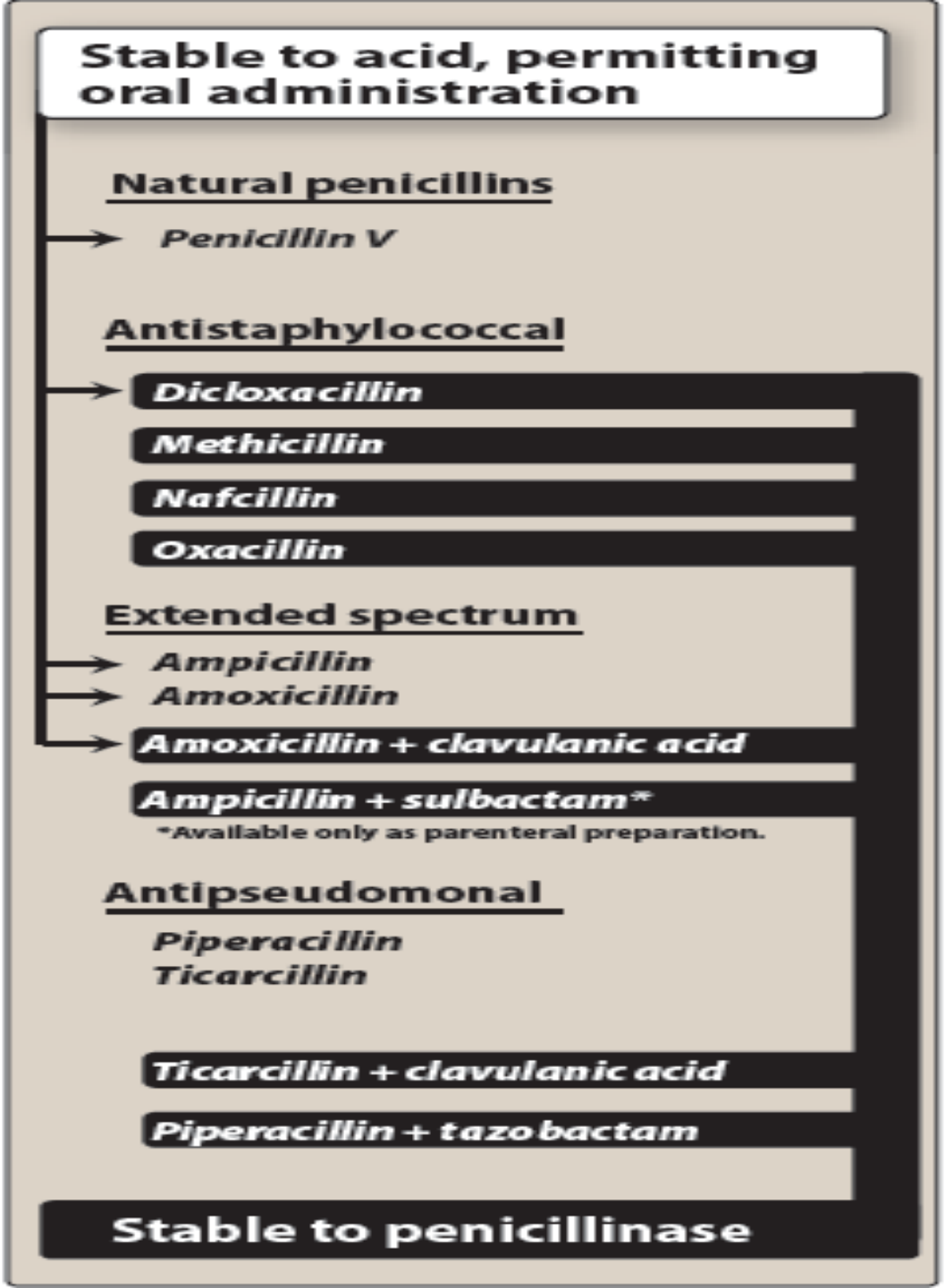
bad : during renal insufficiency (for example has low clearance rate), so you have to change to cephalosporine or other drugs.

- Probenecid: they are mainly eliminated by active transport system in the distal convoluted tubule and loop of henle.
- when it presence with other acidic drug both of them are competing for the same transporter carrier, the result that probencid will be eliminated, this considered Advantage because it helps in extending the duration of action.

- EX: probencid with penicillin, probencid with methoxate.

- you must know that penicillin isn't a narrow therapeutic drug, so increasing it in the plasma isn't very significant, so it helps making more duration of action, but if it is warfarin it will cause bleeding. (this is just an example, warfarin is not eliminated in urine).

- For EX: digoxin which is excreted by renal can cause arrhythmia.


Stable to acid, permitting oral administration
Natural penicillins
Penicillin V
Antistaphylococcal
Dicloxacillin
Methicillin
Nafcillin
Oxacillin
Extended spectrum
Ampicillin
Amoxicillin
Amoxicillin + clavulanic acid
Ampicillin + sulbactam*
*Available only as parenteral preparation.
Antipseudomonal
Piperacillin
Ticarcillin
Ticarcillin + clavulanic acid
Piperacillin + tazobactam
Stable to penicillinase

يلي عليهم أسهم يعني orally وهم 5 أنواع, نحفظ ال orally والباقي IV/IM

- Those drugs in black color are extended against ß-lactamase
- Other drugs, any one of the I give with it: Calvulanic acid, sulbactam, tazobactam will be ß-lactamase resistance so I will broad the spectrum

- side effect of penicillin are similar to side effects for all the cell wall inhibitors:

1) Hypersensitivity:

اذا المريض ما بعرف history تبعه بدي اساله اذا عنده حساسيه الى اي medication او profile مسكن يكون

- most of people who take amoxicillin or penicillin are the same thing, they are cross allergic

فيه ناس ممكن أحط fewdrop intradermal, بشوف دائرة بكون الها قطر معين

مثلا اذا كان القطر 15mm بكون متحسس, بعطيني زي دائرة حمراء على الجلد

هاي مهمة كثير لأنه الحساسية تبدأ ب rash, بعديها angiodema, بعديها anaphlactic shock

- Anginedema: means peri oral (lips) enlargement.

زي ما بعملوا filler وبكن هذا ال filler بكون معبى كثير فال lips رح تنفخ وال perioral بتصير مخدرة وال lung بتتخدر
وتحسس عالي في منطقة الperiorar وهاي اسمها angioedema واللي ممكن تتطور وتعمل anaphylactic واللي هي
shortness of breath
وممكن تؤدي للموت

- who is allergic to penicillin, is alergic to all drugs that contain ß-lactam, for EX:

1) allergic to penicillin has 10% cross allergic with cephalosporine, so the best that I avoid all of them. The solution is that I use another group of cell wall inhibitor which is quinolones.

- Nephritis methicillin the most one.
- Diarrhea because it has extended Spectrum which kills the normal flora and cause superinfection with clostridium difficiles we call this case pseudomembranous colitis.
- pseudomembranous colitis with clostridium difficiles which has limited the drugs which are against, just three drugs targeted to this case.
- neurotoxicity: it is very rare because it is intrathecally.

- How are bacteria develop resistance against my drug?

1) changing the binding site.
2) changing the number of penicillin binding protein.
3) changing structure morphology.
4) Kelbsiella, by pumping out efflux.
5) ß- lactamase activity, we solved this problem but I could be against bacteria without this activity, by mutation.

B. Cephalosporins (generalized)

- Beta-lactam antibiotics
- Closely related to penicillin
- Mostly semisynthetic (7-aminocephalosporanic acid)
- Have the same mechanism of action to as penicillin
- More resistant than penicillin to beta-lactamases
- Classified according to their spectrum and beta-lactamases susceptibility

Cephalosporins Classification

- **1st Generation**
  - Cephalexin (oral) Cefazolin (parenteral)
  - They are resistant to the staphylococcal penicillinase
- **2nd Generation**
  - Cefuroxime Na (cross BBB, parenteral) , Cefuroxime axetil (oral, bid), Cefoxitin, cefaclor , cefotetan,
- **3rd Generation**
  - Cefotaxime (CSF), Ceftriaxone (CSF and bone), Ceftazidime (P. aeruginosa), Cefixime (orall OD)
- **4th Generation**
  - Cefepime (parenteral, Active P. aeruginosa)

Advanced generation

- **Ceftaroline** is a broadspectrum, advanced-generation cephalosporin
- administered IV as a prodrug.
- active against MRSA and is indicated for the treatment of complicated skin and skin tructure infections and community-acquired pneumonia.
- it also has similar gramnegative activity to the third-generation cephalosporin ceftriaxone.
- The twice-daily dosing regimen

- Cephalosporins:
- They also have ß- lactam ring but has slightly differences structure.
- Has seven aminocephalosporanic acid this is the main structure for it, this is semi synthetic.
- We don't have natural cephalosporin we just have natural penicillin.
- that means we took the basic structure of penicillin and we added some structures then it is converted to cephalosporin.

- they have one advantage which is they are not sensitive to those which secrete ß-lactamase, they are more active against those have ß-lactamase.

- there isn't any necessary to put ß-lactamase inhibitor with them because they have this character.

- 1^0 generation:

1) cephalexin

2) cefazelin

3) cefadroxil

- the older generation was most against gram (+) oriented to (+) more and less (-) then more (-) and (+) then more (-) then (+) then more (+), because of methicillin resistance to staphylococcus aureus.
- methicillin resistance staphylococcus aureas it is most happen on the 5th generation.

- 1^{st} generation has lower $T_{1/2}$ → 3-2 times
- 2^{nd} generation has lower $T_{1/2}$ → 2 times
- 3^{rd} generation has lower $T_{1/2}$ → once
- 4^{th} generation → once
- 5^{th} generation → 2 times

Half-life extended the duration of action

The Cephalosporins (generalized)

1st Generation	Gram (+), some gram (-) PEcK (Proteus, E. coli, and Klebsiella Pneumoniae)
2nd Generation	HEN-PEcK Decreasing Gram (+) and Increasing Gram (-) HEN (H. influenzae, Enterobacter aerogenes, and some Neisseria species) cefotetan, cefoxitin against anaerobes (Bacteroides fragilis)
3rd Generation	HEN-PEcK + Pseudomonas aeruginosa
4th Generation	Pseudomonas aeruginosa. (More) G-ve above Some G +ve

- There is 2 types of cefuroxine:

1) Sodium (it's given parental)
2) Axetil (in pharmacies has another name which is zenate, and it's given orally).

- 2nd generation:
- they are liver metabolism.

- 3rd generation: also has pseudomonas aeruginosa (cefataxime, ceftazidime, ceftriaxone).
- Ceftriaxone is:

1) given in emergency
2) Gram(-)
3) widely distribution, can enter CNS and cerebrospinal fluid and Bone so It is very important to drug in hospital.

- Cefataxime: it is mainly for meningitis has highly concentration.
- Ceftazidime: it is for pseudomonas auroginosa, Gram(-) and orally

And it is the only drug orally from the 3rd generation.

- 4th generation is parenteral

EX: caffeine which is most gram (-) plus more pseudomonas aeruginosa.

- 1st generation:
- which is gram (+) and some Gram (-)
- we call them PECK this is a generic name for Proteus, E coli, klebsiella

- 2nd generation:
- becomes HEN-PECK: means H.influenzae, enterobacter aerogenes and some neisseria (neisseria is the only gram (-) diplococcus)
- Cefotetan and cefoxitin are also for anaerobic and this is a good thing.

- drugs which are working in anaerobic are limited, and the most important one is anaerobic bacteria which is bacteroides fragilis and clostridium defficie.
- if I had Dental infection and I gave amoxicillin or Augmentin it is impossible to work, I have to mix it with anaerobic drug because the gum is anaerobic location more than it is aerobic, so I should give with it metroxidazole, tinidazole, or any other anaerobic drug.
- So these drugs (cefotetan and cefoxitin) are idol.

- 3rd generation: HEN-PECK and pseudomonas

- 4th generation: the same of the above but more against pseudomonas aeruginosa.
- it means in penicillin we were talking about antipseudomonal those where selective to pseudomonas.
- here is the same thing if I wanted a drug which is selective For pseudomonas, I choose one of those 4th generation.

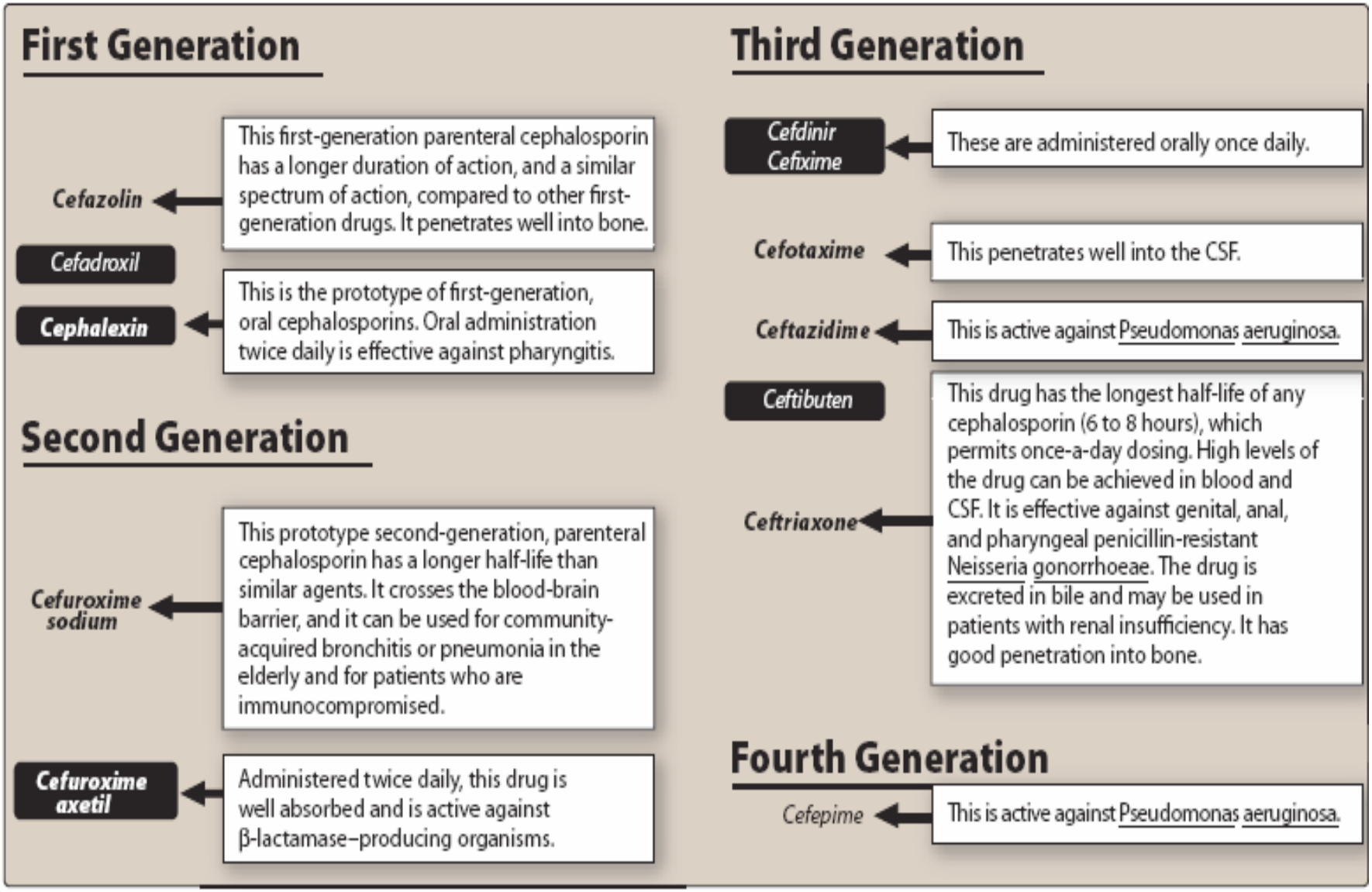
- 5th generation:
- HEN-PECK pseudomonas but also:

against streptococcus pneumonia which causes community-acquired pneumonia and methicillin-resistant staphylococcus aureus.

- I have to know each drug for each generation that belongs to it, because every generation has a specific spectrum and has specific uses and specific half life and frequency.

- Caftaroline: some call it Advanced generation are we call it 5th generation.
- Cefepime is taken once daily (4th generation), while 5th generation is twice daily.
- nearest drug for the penicillin is the first generation cafazolin.

لو واحد عنده **acute pharyngitis** او **sore throat** ممكن اعطيه بديل **amoxicillin** او **augmantin** وبكون مرتين في اليوم, احنا كثير نستخدم **amoxicillin** وبالتالي صار عليه مقاومه من الجسم يعني استخدامنا كثير, فأي التهاب تنفسي مش حاد **(upper respiratory tract infection, sore throat pharyngitis)** هاي الحالة بنسميها التهاب اللوز, وهذا الدواء يعتبر بديل لل **amoxicillin** لانه ال **amoxicillin** صار عليه مقاومة


First Generation
Cefazolin
This first-generation parenteral cephalosporin has a longer duration of action, and a similar spectrum of action, compared to other first-generation drugs. It penetrates well into bone.
Cefadroxil
Cephalexin
This is the prototype of first-generation, oral cephalosporins. Oral administration twice daily is effective against pharyngitis.
Second Generation
Cefuroxime sodium
This prototype second-generation, parenteral cephalosporin has a longer half-life than similar agents. It crosses the blood-brain barrier, and it can be used for community-acquired bronchitis or pneumonia in the elderly and for patients who are immunocompromised.
Cefuroxime axetil
Administered twice daily, this drug is well absorbed and is active against β-lactamase–producing organisms.
Third Generation
Cefdinir
Cefixime
These are administered orally once daily.
Cefotaxime
This penetrates well into the CSF.
Ceftazidime
This is active against Pseudomonas aeruginosa.
Ceftibuten
Ceftriaxone
This drug has the longest half-life of any cephalosporin (6 to 8 hours), which permits once-a-day dosing. High levels of the drug can be achieved in blood and CSF. It is effective against genital, anal, and pharyngeal penicillin-resistant Neisseria gonorrhoeae. The drug is excreted in bile and may be used in patients with renal insufficiency. It has good penetration into bone.
Fourth Generation
Cefepime
This is active against Pseudomonas aeruginosa.

Cephalosporins

- Well tolerated but more toxic than penicillin .
- **Adverse effects**
  - Pain After I.M Injection
  - Diarrhea
  - Hypersensitivity Reaction (10% Cross – Sensitivity)
  - Nephrotoxicity

اما second generation لا يعتبر بديل penicillin ممكن استخدم للحالات المعقده شوي زي urinary tract infection

- Note: cephalosporin is very important drug for urinary tract infection because it is very concentrated in Urine.
- Cefuroxime is very important for E.coli resistance
- 3rd Generation has a specific uses meningitis bone infection (osteomyelitis)
- bone is very difficult to treat because there is no blood supply to the Bone.

مره كانت حالة بالمستشفى انه الطفل عنده دمل برجله واحنا بنعرف انه الطفل ما في كثير من العضلات والدهون على العظم تبع الفخذ هاي الدملة مع المده انتفخت وصلت للعظم لانه ما في عندي كتله في العظم فكان العلاج

21 IV infusion

- osteomyelitis is fatal and cause septicemia(blood toxicity).

- Neisseria ganorrhoeae:

1) Penicillin
2) Ceftriaxone

- we use it for sex transmitted disease which are resistant to penicillin.

- Neisseria ganorrhoeae:
- The First Choice is penicillin
- The second choice is Ceftriaxone

- cephalosporin has the same mechanism of action and the same side effect of penicillin because they are at the same group.
- the remaining drugs are used just in hospital and it is very limited because of two things: hepatotoxicity and costly.
- these drugs should have indication (justification) means why you choose this drug:
- 1) because it is the only drug
- 2)because all other drug is resistance
- 3)because this disease is life threatening

Carbapenems

- **Imipenem, Meropenem, Ertapenem**
- For life threatening infections only
- Broad-spectrum coverage:
  - beta-lactamase-producing gram-positive
  - Gram negative: most gram-negative organisms including Pseudomonas sp.
  - Anaerobes
- Imipenem/cilastatin and meropenem are administered IV once daily.
- Ertapenem can be administered via IV or IM injection once daily.
- **Imipenem** is compounded with ***cilastatin*** to protect it from metabolism by renal dehydropeptidase to inactive metabolite which is potentially nephrotoxic.

Carbapenems

- **Adverse effects:**
- **Imipenem/cilastatin can cause nausea, vomiting,** and diarrhea.
- High levels of imipenem may provoke seizures,

- imipenem always come with other drug, for example: it is coupled with Cilastatin (it is zero, doesn't have any antibacterial activity).
- imipenem is very important because it is for all bacteria producing ß-lactamase gram (+), gram (-), and anaerobic. we use it in life-threatening and it causes nephrotoxicity.

- they found that it is hydrolyzed by dehydropeptidase which is available in the kidney (nephrons) so it will be converted to very nephrotoxic material.
- dehydropeptidase: enzyme in our body degrades imipenem and give me toxic inactive ingredient

- we combine it with Cilastain they're 1 + 0 is also one but it is for protection (decrease the side effect).
- given by IV for once-daily.

Monobactams

Aztreonam IV, IM

- Spectrum: ONLY → **Gram negative aerobic bacteria**; **including P. aeruginosa**. "narrow spectrum"
- beta-lactamase resistant
- Pharmacokinetics:
  - Well distributed into tissues, esp. inflamed tissues
  - Excretion: renal clearance

Adverse reactions:

- Skin rash

- Monobactam:
- Aztreonam is given IV or IM
- It's a narrow spectrum just for P.laeruginosa

من ال life threatening صار عندي خمسه او سته بشتغلوا على pseudomonas بحكيله مثلا افحص هاي البكتيريا مع ال third generation

تبع ال cephalosporins او مع ticarcillin, يعني بكتب ٥ او ٦ انواع من الادوية

ولما تيجي ال results بتصير تختار ال more safe

- ztreonam has few toxcicity and costly
- just for pseudomonas, if there is no pseudomonas there is no need to use it.
- it's indication that you have to do culture and sensitivity test, for example I have pseudomonas and it didn't respond to ticarcillin and piperacillin.

Vancomycin

- Glycopeptides
- **MOA:** inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization
- Resistant Gram positive infection
- Life threatening MRSA and MRSE (*methicillin-resistant Staphylococcus epidermidis*)
- Intravenous
- Narrow therapeutic index
- Orally for local effect (not absorbed – clostridium difficile)
- Slow IV infusion (60–90 minutes)

- Vancomycin is very important drug for methicillin resistance staphylococcus aureas and some anaerobic
- and it is good for methicillin-resistant Staphylococcus epidermidis
- it's given IV
- cause nephrotoxicity and autotoxicity.
- that means if I gave Vancomycin I have to do therapeutic drug monitoring.

maximum con. وبعد ساعتين بشوف **bolus** مش **infusion** يعني بعطيه الجرعه وباخذ التركيز بعد اول جرعه هاي بعطوها
ولازم هذا ال **max** ما يتجاوز ال **micro 20**

اذا زاد عن ال **max** بنقلل الجرعة او بعمل **extended the duration** يعني مثلا كانت بعد ساعين بعطيها بعد ٣ ساعات
وهاي الها حسابات خاصة

- we talked about a Clostridium difficie which cause pseudomembranous colitis
- it is anaerobic infection
- can be secondary for broading spectrum antibiotic (extended) because it kills normal flora and cause superinfection.
- this case is hard to treat except for some drugs Vancomycin is one of them.

- there is two drugs you must not give them orally because there will be no absorption, which are: neomycin (aminoglycoside) and Vancomycin.
- but we give them orally just for local effect to enter the GIT.
- for example before the abdominal surgery we give that patient mg^{+2} salt and neomycin for emptying the stomach. this neomycin isn't absorbed into the blood, it is go to GIT to make local effect to prevent postoperative infection.

- the same Vancomycin isn't absorbed but we give it orally for clostridium difficie for GIT infection (local effect) so it isn't taken orally for systemic infection like infection in the bone.

- it binds with phospholipid also, and the penicillin binding protein for Vancomycin is different (not as this which penicillin bind with).
- because there are types: 2X or 2A
- so they have mechanism of action which is different little, so that's why they are more active to MRSA

Daptomycin and Telavancin

- ynthetic derivative of vancomycin
- Bactericidal
- Concentration-dependent antimicrobial
- For: Resistant Gram positive infection including MRSA (same like vancomycin)
- Use for : Complicated skin infection and endocarditis
- s/e: renal impairment, arrhythmia

- daptomycin and Telavancin are alternative to Vancomycin.

- we use them in endocarditis caused by MRSA in this case these two drugs is better than Vancomycin because they are safer.

Polymyxins

- Polypeptide
- **MOA**: bind to phspholipidson the cell wall of Gram negative bacteria
- Active agains P. aurigonosa , E.Coli, K. pneumonia
- **Polymyxin B**: parenteral and ophthhalmic, topical
- **Polymyxin E** (Coilistin) , IV or inhaled
- s/e: nephrotoxicity and neurotoxicity

- Polymyxins:
- this is not like a other cell wall inhibitor that means it's mechanism of action is different.
- it doesn't work at penicillin binding protein
- cell wall has binary layer of phospholipid
- it binds with phospholipid on which responsible for making the cell wall (not responsible for the cross-linkage)
- this make it more active on a gram-negative (-)
- polymyxin is an emergency drug and not recommended to use
- it is given IV
- it has a problems because it causes nephrotoxicity and neurotoxicity so why it is a present? because it's used as ophthalmic (eye drop).

لازم استخدم مرهم معين في بعض الحالات الجلديه و هذا المرهم عباره عن **antibiotic** بالتالي معظم الادويه ياللي بتكون كريم او **ointment** بيكون ال **polymyxin** معها بالتالي **nephrotoxicity** له مش موجوده وهو **topical** مهم في **combination**
خصوصا **burn infection** (التهاب الحروق الجلديه)

- it has 2 combination
- 1) polymyxin B
- 2) polymyxin E, it is important for cystic fibrosis in Laung ,and it is safer and inhaler.
- we use a topical and ophthalmic for local effect but when it is parenteral it is very toxic.

THANK YOU