Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 28

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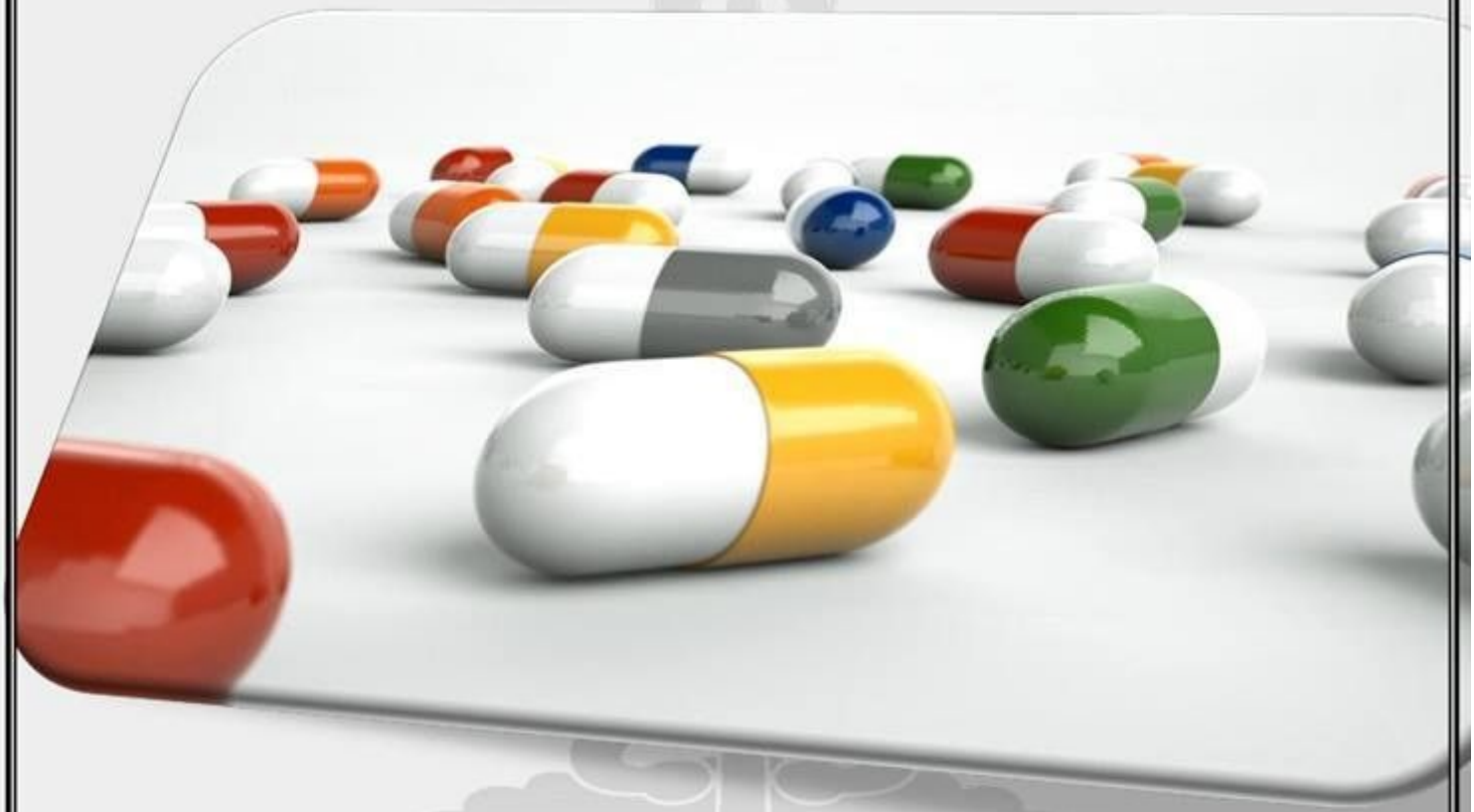
SHEET ■

SLIDES □



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ANTIBIOTICS (CONT.)

Kindly note that this sheet is written according to section 1 recording

* Cephalosporins:

* 1st generation: (recap)

- They're staph and strep antibiotics, so we use it them to treat infections within the skin (epidermatitis, dermatitis, **cellulitis** which is a disease caused by staph and strep that affects cells of the skin causing infection around the skin {around the epidermal area}.

- All previous cases are similar to each other and the drug of choice is an **oral** drug called **Cephalexin**.

- **Cefazolin** is used for **prophylaxis** in hospitals.

* 2nd generation: (recap)

- We talked about **Cefoxitin** and **Cefotetan** which are active against **B.fragilis** that's why we used them in the treatment of peritonitis or diverticulitis (which are inflammations of the intestinal membranes الأغشية المعوية that contain *anaerobes*; such as fragilis).

- They (Cefoxitin & Cefotetan) are also used in colorectal surgery for the sake of **prophylaxis**, if we are afraid of the *anaerobic* intestinal flora.

- Here the **heterogeneity** appears

We use **Cefuroxime** (Zinnat) [which is Augmentin's best friend] in cases of upper respiratory tract infections. Its usage differs from country to country; according to the spectrum found in each country.

- Cefuroxime is used in the same cases of Augmentin, and we said that it can be used in the empirical therapy for the treatment of community-acquired-pneumonia if the child was under 4years of age, because mycoplasma, legionella and chlamydia won't be the causes of pneumonia in that case.

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* 3rd generation Cephalosporins:

- These groups are used a lot and thus are considered very important in hospitals.

- Again, moving through generations, the effect against G-ve will increase. The problem with **heterogeneity** is that some of them have a good activity against *pseudomonas* and some of them (a large group of them) lose part of their activity against G+ve.

- The good news is that two of this group; Ceftriaxone (it has an effect against G-ve however it didn't lose its activity against G+ve→ it's still active against staph, strep, all G-ve "including Neisseria meningitis or gonorrhoea".

- So Ceftriaxone doesn't have pseudomonal activity; only **Ceftazidime** has **pseudomonal activity**. Ceftazidime has a very nice effect against G-ve but unfortunately some of its activity against G+ve was lost.

- Two important guys in the story: 1) Ceftriaxone

2) Ceftazidime

- Ceftazidime has a very nice activity against pseudomonas and ALL G-ve

- Ceftriaxone also has a nice activity against G-ve and G+ve but it NO activity against pseudomonas.

- The previous two are **injectable**

- Oral types:

- **Cefnidir** it has a nice activity against G+ve and G-ve , NO activity against pseudomonas. So it's similar to the activity of Ceftriaxone, however it's a bit weaker against G+ve compared to the 3rd generation, but it's still active against streptococcus pneumonia and staph in a good way (but not the best way).

- So this is a good oral activity.

- **Ceftriaxone** is very famous and wildly used.

- It differs from other drugs in having a nice penetration of the blood brain barrier. So it's the drug of choice (never think about another drug rather than Ceftriaxone) for **meningitis**.

- All types of meningitis are treated by Ceftriaxone, because it can cross the blood brain barrier, and it was chosen because of its nice activity against staph, strep and Neisseria meningitis; which are the basic causes of meningitis:

- First comes Neisseria meningitis, then streptococcal pneumonia (main two causes) also H.influenzae causes meningitis. So we need to cover these three organisms to have a good activity against meningitis.

- This is not the only reason for choosing Ceftriaxone, we also need to penetrate the blood brain barrier, and the best penetration (among all drugs we've taken already) is for both; Ceftriaxone and Cefotaxime.

- From where did Ceftriaxone become very popular?

- It's used A LOT in hospitals to the extent that it's called "Hospitals' candy ملبس المستشفيات " and its trade name is **Rocephin**.
- The medical services and Al-Bashir hospital ruined it because they used it a lot, since it's prescribed by nurses rather than doctors. Nurses there are good (even better than doctors) but their problem is that they weren't trained well, so they prescribe Rocephin without even thinking.

- So Ceftriaxone and Cefotaxime have a very nice penetration to the blood brain barrier, so they build high up the MIC in the cerebrospinal fluid "CSF". That's why you should never think about any drug other than Ceftriaxone for the treatment of **meningitis**.

- What does **Cefotaxime** have to do with this?

- It's used for <u>initial treatment</u> of meningitis in non-immunocompromised patients. Even in immunocompromised patients; we use it as <u>empirical therapy</u>.

- So these two drugs are used to **treat meningitis**, which should be treated rapidly, because it's the WORST case of infection. Treatment of meningitis should be started whenever there is a sign of it.
- The doctor knows two people who had got meningitis lately even though they were vaccinated, so he suspects that there's something wrong going on due to antibiotic abuse.
- Meningitis should be treated rapidly, and the drugs of choice is due to their antibacterial activity (against streptococcus pneumoniae = gonococci "Neisseria gonorrhoeae", Neisseria meningitis, H.influenzae→ the three main causes of meningitis should be covered).

- How are they covered?

- By using the 3rd generation cephalosporins "Ceftriaxone", which has a good penetration into CFS and record of clinical success. This is the bottom line of it.

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- From where did the action against Neisseria gonorrhoeae come?

  - It's included in the spectrum of the third generation cephalosporins.

  The 3rd generation cephalosporins have a very nice activity against Neisseria generally (they're the drug of choice).

- We mentioned Neisseria meningitis previously in Penicillin G, we said that Penicillin G is active against strep and Neisseria meningitis.
- Why not using Penicillin G in that case?
  - Because Penicillin G does not really cover all the causes of meningitis. It does NOT cover H.influenzae (although it covers strep), that's why it's NOT a good choice for the empirical therapy of meningitis.

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* Cefotaxime:

- It's used a lot.
- It's very important, since there is an overlap between Ceftriaxone and hyperbilirubinemia found in babies.
- Most infants upon delivery look yellowish, which is an indicator for having hyperbilirubinemia (where bilirubin is carried on albumin).

- So Ceftriaxone displaces (drug-drug interaction = drug-bilirubin interaction) bilirubin from albumin causing elevation of the free bilirubin concentration in the blood. That's why whenever the patient has hyperbilirubinemia or jaundice "in elderly patients having jaundice, if they got meningitis or anything that requires usage of Rocephin "Ceftriaxone" we should not prescribe it to them, it's **contraindicated**.
- This idea is still new, it was found in 2012.

- That's why babies under 28 days (4 weeks after delivery) or babies who were born on the 7th month of pregnancy سباعي are susceptible for having hyperbilirubinemia until they become older than 28 days, in the second case (born on the 7th month = 35 weeks) you'll have to wait for 2 months (until they complete the 9 months= 42 weeks) + 28 days → during that time Ceftriaxone should NOT be prescribed.
- Why?
  - Because the baby is more susceptible for developing jaundice or hyperbilirubinemia, and Ceftriaxone displaces bilirubin from albumin causing increase in bilirubin concentration, which can result in serious problems for the baby affecting his liver and brain (causing kernicterus).

- **Ceftriaxone** has a bad activity when it's given in the hospital through a drip (to inject the drug in the patient's hand), when there is **calcium** in the solution of the drug or if the patient is taking any calcium solution; Ceftriaxone reacts with calcium

resulting in precipitation of Ceftriaxone in many locations; such as kidneys, liver causing severe problems.

- The younger the child, the more severe the problems are.
- That's why whenever the patient is taking calcium as a supplement (especially babies), Ceftriaxone should NOT be given with it.
- However in **adults**; to prevent this, Ceftriaxone and calcium should be given through different lines (each line going to one hand) at different lines.
  This is very clinical (clinical pharmacology); you are only required to understand the situation
- Patient with **hyperbilirubinemia** (especially babies under 28days are susceptible for having hyperbilirubinemia) should NOT take **Ceftriaxone**.
- Also patients who are taking **calcium** should NOT be given Ceftriaxone. It's not totally contraindicated in that case.
- That's why we use Cefotaxime instead of it, whenever you need to treat meningitis by the 3rd generation cephalosporins and your patient is taking calcium or you're dealing with a baby under 28 days; you have to *switch from Ceftriaxone to Cefotaxime.*
- They both have good penetration into the blood brain barrier, and both work against Neisseria meningitis, streptococcus pneumoniae and H.influenzae.

- Why not giving Cefotaxime at first?
  - Because the activity of Ceftriaxone is better and stronger (higher potency). All drugs we mentioned until now are given IV, the only oral drugs we talked about are; Cephalexin (1st generation), Cefuroxime "Zinnat" (2nd generation) and Cefnidir (3rd generation).

- Cefotaxime and Ceftriaxone are most active cephalosporins against penicillin-resistant strains of pneumococci and are recommended for empirical therapy of serious infections that may be caused by those strains.

- We are facing a problem now which is that not only the mid-resistant strains are treated by increasing the dose of ampicillin or amoxicillin (instead of giving 40 we're giving 80-90) there are also other strains developing in the community which are completely resistant (ampicillin-resistant or amoxicillin-resistant streptococcus pneumoniae) the only active drug against it is (until now) is Ceftriaxone.

- Ceftriaxone is active against the penicillin-resistant strains.

- How penicillin-resistant strains occurred?
  - Penicillin-resistant streptococcus pneumoniae is becoming more popular because we are using antibiotics for upper respiratory tract infections when we don't need it. So the drug of choice now for the majority of cases is Ceftriaxone.

- When do we know that streptococcus is the strain responsible for the disease?
  - From what is common in the community or hospital; if the hospital is full of strep-resistant, as in that case:

- **JAMA 1998:**
  - Prior to 1980, 99% of all S. pneumoniae cases were susceptible to penicillin.
  - In the past decade, 40% of isolates have intermediate to high penicillin resistance.

  - We need to learn that because with time, streptococcal pneumoniae is growing its resistance. So whenever you suspect that your patient is affected by resistant streptococcal pneumoniae you give him 3rd generation cephalosporins **empirically**.

- 3rd generation cephalosporins are also used in **gonorrhea** (very popular). Neisseria Gonorrhea (not meningitis) which causes urinary tract infections "in the urethra and other places". The drug of choice is **Ceftriaxone** (never think of any drug rather than Ceftriaxone).

- Why?
  - Returning to the spectrum → it includes Neisseria gonorrheae (including beta-lactamase producing). And this beta-lactamase has a wide-extended spectrum so when it's from G-ve it'll be very active, *but Ceftriaxone is still active against Neisseria gonorrhea that produces extended-spectrum beta-lactamase*, that's why it's the drug of choice.
- Do G-ve bacteria produce beta-lactamase? Yes
- The bottom line: Ceftriaxone (Rocephin) is the drug of choice in meningitis (whenever we suspect that resistant-streptococcus pneumoniae or Neisseria gonorrhea).

- In the US, you don't prescribe any drug for **Neisseria gonorrhea** other than Ceftriaxone.
- It's an **injectable** drug.
- **Ceftriaxone** is the drug of choice for severe forms of **Lyme disease**. We're not required to know what Lyme disease is until we take it in pathology, but basically Lyme disease is caused by Borrelia (a specific genus of bacteria) that attacks us through bites of worms إم أربعة وأربعين).
- Luckily this type of bacteria is not found here in Jordan, it's found in Africa and America.
- The treatment of Lyme disease is Ceftriaxone.

- The 3rd generation cephalosporins with or without aminoglycosides, have been considered to be drugs of choice for serious infections caused by several **G-ve** : Klebsiella, Enterobacter, Proteus, Serratia and H.influenzae.
- They may be particularly useful in treating hospital-acquired infections, although increasing levels of extended-spectrum beta-lactamases are reducing the clinical utility of this class of antibiotics.
- Who produces extended-spectrum beta-lactamase?
  - Neisseria gonorrhea (but luckily Ceftriaxone is still active against it), but others such as, Klebsiella, E.coli, produce extended-spectrum beta-lactamases that cleaves the beta-lactam ring that's found in Cephalosporins.
- So we're still facing a problem here, if we went to the hospital and make a test, we'll find out that a huge number of microorganisms are resistant to the 3rd generation cephalosporins , except for streptococcus pneumoniae Neisseria gonorrhea, H.influenzae.
- So in empirical therapy, we can use them against the non-resistant types.
- This is where the clinical uses came from.

* Other use:

- Many patients become immunocompromised (cancer or AIDS patients), when we treat cancer patients with chemotherapy, their bone marrow will be supressed. Upon giving them drugs they become **febrile** (tremoring; close to epilepsy) this is a result of the patient becoming **neutropenic** (low neutrophils) so the immune system is reduced, so the patient is susceptible more for developing infections.
- These patients are affected mostly by G-ve in most cases.
- In neutropenic, febrile immunocompromised patients, 3rd generation cephalosporins are often used in combination with an aminoglycoside. (forget about the combination, we'll mention it later on)
- Other potential indications include empirical therapy of sepsis of unknown cause in both the immunocompetent and the immunocompromised patient.

- The bottom line:

- We're talking about sepsis, which happens in most cases in hospitals, and hospitals are full of G-ve bacteria. Especially hospitals that approved that the causes of sepsis are still susceptible for the 3rd generation cephalosporins. Unfortunately this is not the case here in Jordan, we lost Rocephin (Ceftriaxone), we're using it only in cases of meningitis caused by gonorrhea or strep. We're recording high (20-30%) of the isolates are resistant toward the 3rd generation cephalosporins.
- So we're losing this clinical use, according to the hospitals in Jordan, which are all in a bad situation regarding this issue.

* uses of 3rd generation cephalosporins:

- Meningitis, gonorrhea, streptococcus pneumoniae (the penicillin-resistant type).

- When we suspect being affected by **pseudomonas**, we don't use Ceftriaxone but we give instead **Ceftazidime**.
- Why?
  - Because Ceftazidime covers all G-ve plus pseudomonas.
- If we're not suspecting having pseudomonas aeruginosa, we give Ceftriaxone.

* Cefnidir:

- It's an **oral** drug.
- When do we use the oral type of the 3rd generation cephalosporins (extended spectrum)?
- When the broad spectrum does NOT work, when?
  - When the patient has otitis media for example, and we give him 80-90 Augmentin (broad-spectrum) and it doesn't work. So the broad spectrum is not working with him (the patient isn't being treated). This indicates that the patient is infected with *resistant-streptococcus pneumoniae*. So we either give him injectable Ceftriaxone (but in cases of otitis media, giving an injectable drug is logical since it's a simple infection), or Cefnidir (which is more suitable for that case).

- Other examples:
- A patient with pneumonia, or upper respiratory tract infection by streptococcus pneumoniae (upstream not downstream), or a patient with H.influenzae who is not responding for Augmentin.
- So when do we need to **grade up**?
  - When the patient does not respond upon giving him broad-spectrum, this indicates that he's infected with the resistant type.
- How do we know that our patient is infected with the resistant type?
  i. By trying different antibiotics
  ii. By sending culture to the lab, then the lab result will tell you for example (you're patient has a resistant type for Augmentin, don't give him Augmentin)
- In most cases of Augmentin resistant, the patient will also be resistant for Zinnat (Cefuroxime), so we need to scale-up a bit and use oral 3rd generation cephalosporins.

- If the patient is resistant to Augmentin we don't even try to give him Zinnat, because resistance to Zinnat is becoming more common (above 20% of strep are resistant). So we scale-up instantly to the 3rd generation.

- You have to understand the regional factor:

- We discussed in pharmacogenetics the ethic factor. However, in antibiotics we talk about the regional factor, which means that what applies in England does not apply in the US.
- In the US, the streptococcus pneumoniae is much more resistant that streptococcus pneumoniae found in England.

- This leads us to:
  When treating meningitis in the US, we don't use Ceftriaxone alone; we should combine it with a more complex drug.

- If we knew that we're dealing with resistant streptococcus, how do we choose whether to use Ceftriaxone or Cefnidir?

- If we're dealing with a life threatening situation the drug of choice is Ceftriaxone, otherwise we use Cefnidir (the oral type).

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* 4th generation cephalosporins:

- Cefepime combines everything; including Ceftazidime, Ceftriaxone and Cephalexin (already Ceftriaxone has Cephalexin).

- So Cefepime's trade name is Maxipime.

- What does Maxipime mean?

- It means that this drug has the maximum spectrum; all G+ve, all G-ve, all anaerobes and all pseudomonas.

- Cefepime has everything, so some might say: why not forgetting about all previous drugs, and take that one for granted?

- This drug is very precious to us, we have to save it and keep it for the future, because we don't want to lose it.

- When to use it?

- When your patient is in the hospital and you don't know anything about that hospital nor about the patient or if the patient suffers from **mixed infection** (the cause might be G-ve or G+ve or anaerobes or even pseudomonas).

- Is Cefepime better than piperacillin with tazobactam (Tazocin)?

- Yes it is better, but not so much better.

- Is Cefepime better than the 3rd generation cephalosporins?

- Yes. Why? Because its spectrum is very beautiful.

- Extended spectrum of activity
  - gram-positives: similar to ceftriaxone
  - gram-negatives: similar to ceftazidime, including *Pseudomonas aeruginosa*; also covers beta-lactamase producing *Enterobacter* sp.

- What are beta-lactamase producing Enterobacter?

  - Enterobacter cloacae, Enterobacter aerogenes (we haven't mentioned them before) they are one of the worse microorganisms that could be found since they're G-ve and produce a very bad extended-spectrum beta-lactamase.

- What do we mean by extended-spectrum beta-lactamase?
  - This means that it cleaves penicillin, ceftriaxone, Rocephin, Zinnat (basically everything)
- What is the only drug that's still active against these types?
  - Cefepime!

- Therefore, whenever you're thinking that Enterobacter cloacae or Enterobacter aerogenes (these two are the most important types and are associated upper respiratory tract infections or pneumonia, so they can be found in hospitals living inside the ventilator "it's full of microorganisms").

- Believe it or not; If we do a nose swab for each other right now, we'll find that a lot of us have MRSA in their nose! We're living with microorganisms.

- So dealing with Enterobacter is a huge issue, the active drugs against them are the 4th generation cephalosporins.

- What is good about the 4th generation cephalosporins?

  - They combine between Ceftazidime, Ceftriaxone and they work nicely against Enterobacter.

- Did the 3rd generation work on Enterobacter?
  - Yes it was, but the Enterobacter developed itself by producing an extended-spectrum beta-lactamase, so some of its species became insusceptible for Ceftriaxone nor Cefnidir nor Ceftazidime (3rd generation).

- So the only drug that is still active on Enterobacter (hasn't developed any resistance toward it) is Cefepime "Maxipime", which is the only currently available drug of the 4th generation.

- Stability against β-lactamases; poor inducer of extended-spectrum β -lactamases
- Only cefepime is currently available

Fourth-generation cephalosporins

- ***cefepime,*** **have an extended spectrum of activity compared with the third generation.**
- **The fourth-generation cephalosporins are indicated for the empirical treatment of nosocomial infections**

particularly useful when gram-positive microorganisms, Enterobacteriaceae, and *Pseudomonas* all are potential etiologies.

- Enterobacteriaceae includes: (G-ve causes)

  - Klebsiella, Serratia, E.coli, Proteus, Enterobacter.

- Whenever you think that the mixed infection is going to be either G+ve or G-ve or pseudomonas (you don't know anything about the patient).

- The patient came with an abscess, it might be green abscess "indicator for pseudomonas" combined with millions of other causes, so we need to cover all of them.

* Clinical uses:

- Cefepime has superior activity against nosocomial isolates of Enterobacter, Citrobacter and Serratia (Enterobacteriaceae), Compared with Ceftazidime and piperacillin.

- So we have 3 very extended-spectrum; 3rd and 4th generation cephalosporins and piperacillin are called extended. All the rest drugs we took previously are broad.

- Does Cefepime cross the blood brain barrier?

  - Yes it crosses it, and results in building up its concentration.

- Is it used in cases of meningitis?

  - We don't use it immediately because we don't want to lose it.

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* Carbapenems:

<<We are still talking about cell-wall inhibitors>>

- Doripenem, ertapenem, imipenem, and meropenem are licensed for use in the USA. The most important two (found here in Jordan) are:

  1- imipenem (tienam تاينام ما بنام) it's widely used
  2- meropenem

- All of them are **injectable**, no oral types.

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* Imipenem:

- It's Cefepime's best friend, and unfortunately we lost it. It was found before Cefepime and became very popular in the medical community.

- It's not part of the cephalosporins, it's part of the Carbapenems.

- It's the same as Cefepime, there are no differences between them; Imipenem has a wide spectrum with good activity against many gram-negative rods, including P aeruginosa, gram-positive organisms, and anaerobes.

- There's a small problem in imipenem;

- The potentiation activity is clear here:

  - Imipenem is inactivated by dehydropeptidases, in order to make it active we need to inhibit dehydropeptidase in renal tubules. So it should be administrated along with an inhibitor of renal dehydropeptidase called Cilastatin, for clinical use.
  - Therefore imipenem should not be prescribed alone, because it goes to the kidney where it's hydrolysed rapidly so we lose it fast.
  - That's why when prescribing imipenem, an inhibitor for dehydropeptidase should also be prescribed with it.
  - This process is neither additive nor synergic, it's considered ***potentiation*** (making the drug stronger "1+0>2").

Carbapenem

- **A carbapenem is indicated for infections caused by susceptible organisms that are resistant to other available drugs, eg, *P aeruginosa*, and for treatment of mixed aerobic and anaerobic infections.**

- **it is also the treatment of choice for infections caused by extended-spectrum beta-lactamases–producing gram-negatives.**

- Who produces extended-spectrum?

  ➢ E.coli, Klebsiella and some species of Enterobacteriaceae.

Example:

A carbapenem is the beta-lactam antibiotic of choice for treatment of enterobacter infections because it is resistant to destruction by the lactamase produced by these organisms;

- We said the same sentence in Cefepime; that's why they're best friends.

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* Side-effects:

- Its side-effects are similar to those seen with other b-lactam antibiotics→ it causes diarrhea but there's NO allergy against it.

- ***Nausea and vomiting*** been the most frequently encountered, it happens in 20% of the population (very common).

- Carbapenem causes nausea and vomiting, it's the first drug (from all previously mentioned drugs) that has side-effects other than diarrhea or allergy.

- It's an **injectable** drug (since all Carbapenems are injectable) administrated in the hospital (all wide-spectrum antibiotics are given in the hospital).

- At high doses **neurotoxicity** can occur, but it's very **rare**. It can develop to the level of seizure.

- So this is the first drug that has its own side-effects, the rest cause diarrhea that has to do with micro flora, and allergy to heart fluid immune system.

- Where do we use menopenem?

  - Imipenem is here, but we're facing a problem called Klebsiella pneumoniae which has developed itself upon the excessive use of imipenem (which was found before Cefepime) by nurses of weak doctors.
  - This resulted in the adaptation that was firstly noticed in Klebsiella pneumoniae, by producing a very bad type of beta-lactamase that cleaves imipenem. 20% of Klebsiella in Jordan produces that very extended-spectrum beta-lactamase.

- If you have a patient in the hospital with pneumonia and you suspect that it is caused by Klebsiella, what should you do?
  - You don't prescribe imipenem, you give him meropenem instead.