# Pharmacology

**Number: 17**

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**Subject: Cephalosporins 2**

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Topics of the lecture:

- Cephalosporins
- Carbapenem
- vancomycin

# ❖ Cephalosporins:

Last lecture we finished the cephalosporins which have 5 generations (the fifth generation is not included).

To recap the story back:

## ❖ The first generation:

- Cephalosporins are the drug of choice in skin infection (caused by staph and strep.)
- Two drugs: -cephalexin: oral form.

  - Cefazolin: injectable.

## ❖ The second generation:

- Cefuroxime: like Augmentin, the drug of choice in the upper R.T infection.
- Cefotetan and cefoxitin: Bacteroides fragilis, prophylactic towards anaerobes.

## ❖ The third generation:

- generally active against G-ve except pseudomonas(common characteristic between all of the third generation drugs)
- the important two groups:
  - **Cefoperazone and ceftazidime** are the only two drugs from the third generation are active against pseudomonas aeruginosa. However they don't have an extended spectrum because they lost some of the activity against G+ve bacteria.
  - **Cefotaxime and ceftriaxone** cover G+ve and G-ve without pseudomonas. They are the drug of choice in: Gonorrhea, penicillin resistant S.Pneumonia, meningitis.

- Ceftriaxone binds to bilirubin, so when we have hyperbilirubinemia we don't use it (especially in meningitis) .Instead we use cefotaxime. Also cefatriaxone is not used when there is a problem with calcium, may interact with it.
- cefaberazadone and cefatriaxone are excreted through the bile so if the patient suffers from Gonorrhea , infection caused by penicillin resistant pneumonia, meningitis and:
- Has a kidney problem (kidney failure) we use cefotaxime and cefatriaxone, because we don't have to adjust the dose.
- Liver problem we don't use them, go to an alternative drug.

### ❖ The fourth generation:

- cefepime or called cefamax
- Its spectrum is like ceftazidime (in G-ve, so it include pseudomonas aeruginosa) and like ceftriaxone (in G+ve) so they combine everything together even to Enterobacter, that's why it's called cefamax.
- They are comparable towards piperacillin (with tazobactam), so they are used instead of pipercillin if the patient has a penicillin allergy.
- BUT KEEP IN MIND: All Cephalosporins are not effective against enterococci.

## ❖ Side effects of cephalosporins:

They cause the common side effects + other effects:

1-**disrubance in the GI tract** (may cause diarrhea) and as you extend the spectrum you will increase this side effect (this rule is applied to all antibiotics not Cephalosporins only). A wider spectrum more likely to cause diarrhea. And this is related to the use of the probiotics which we use them to reduce this side effect.

2- **Disulfiram like effects:**

- *As we know we have different groups of cephalosporin. One of these group is called N-methyl thiotetrazole-containg Cephalosporins (Cefamandole, **Cefotetan**, Cefditoren, **and Cefoperazone**). We will talk about 2 of them: Cefotetan (second generation, injectable, against Bacteroides fragilis), Cefoperazone (third generation, anti-pseudomonal drug).these two drugs cause a specific side effect "disulfiram-like effect". To understand this we need to know about disulfiram.

- **Disulfiram:**

- This drug is used more commonly in the west as it is related to alcohol addiction.
- Its mechanism: disulfiram inhibits aldehyde dehydrogenase (an enzyme in alcohol metabolism pathway).so it causes accumulation of aceteyl-aldehyde in the body (build up).
- Acetyl aldehyde gain entry to the CNS and causes agitation, tremor, restlessness, vomiting, nausea. So each time the patient drinks alcohol he will suffer from all of this, eventually will stop drinking.
- NOTE: we give the patient low doses of it, to prevent sever effects of it, which means we need these effects (vomiting, tremor….) but in a specific range which is not toxic. A high dose of it may cause toxicity in brain. We give these drugs is a rehabilitation centers so these patients are under control all the time.
- Back to cephalosporins, these 4 drugs when administrated with alcohol drug-food interaction will occur. That's lead to the same effects caused by disulfiram. So simply these side effects are called "disulfiram-like effects"
- Note: alcohol addiction is dangerous. IT causes: liver cirrhosis, liver cancer, stomach cancer, head and neck squamous carcinomas….. So we aim to treat the patient from addiction.
- Note: alcohol is addicted socially (psychologically) like smoking. His brain adapted to ingest alcohol whatever the situation is.

3- **Bleeding:** these two drugs may also cause hyprothrombinemia) which may lead to bleeding.

4-**Hypersensetivity:**

"A patient who is sensitive towards penicillin, he is sensitive towards cephalosporins as well."

"A patient that develop an anaphylactic response when administrated penicillin should avoid Cephalosporins."

These two sentences are written in the book. BUT be careful they are not true. **They are wrong!!!**

- Actually, 10% of the 10% of people with penicillin allergy are cephalosporins sensitive, which means only 1% of people are allergic towards Cephalosporins (if any). It is very rare hypersensitivity. But the penicillin hypersensitivity is not rare, as doctors, we will see it.

- REMEMBER: we still in cell wall inhibitors.

## ❖ Carbapenems:

- widest spectrum cell wall inhibitors, even wider than the extended spectrum drugs (piperciilin and cefapime)
- they have a great activity against everything: active against G+VE, G-ve including pseudomonas aeruginosa AND ANAEROES
- Their advantage over cefepime and piperacillin (with tazobactam) is that they have a great spectrum against ANAEROBES AND **(GREATER ACTIVITY AGAINST ENEROBACTER) *****!!!**
- **(GREATER ACTIVITY AGAINST ENEROBACTER)*****!!!** : This sentence is written in books BUT it's questionable.
- So what we need to know about them that they are active against everything **except MRSA.**
- NOTE: REMEMER until now we didn't mention any drug active against MRSA.
- Doripenem, ertapenem, **imipenem** and **meropenem** these are carbapenems.
- **Imipenem** and **meropenem** are what we will talk about.
- Imipenem is the used in Jordan and its trade name is **TIENAM.**
- Unfortunately this drug has been misused by some doctors and nurses because we don't have a resistant against it and it covers everything (the doctor calls it **TIENAM** الذي لا ينام). Logically, a resistant will be developed with time due to this misuse.
- NOTE: until now, Klebsiella pneumonia is the only bacteria that have develop a resistant against imipenem (**TIENAM**).
- Again, Meropenem and imipenem have a spectrum that covers everything (G+ve, G-ve/aerobic and anaerobic) **except MRSA. Imipenem** has a wide spectrum with a good activity against many G+ve/G-ve including P aeruginosa and anaerobes.

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- **They are the drug of choice in:**

1-infactions caused by extended beta lactamases producing bacteria (EPSL), 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 organism.

They are used in **mixed infections**. And mixed infection is an infection diagnosed with a many pus formation and a large amount of fluid. And usually it is caused by more than

one bacteria (usually G+VE **+**G-ve**+** anaerobes).So to cover **empirically** all these causes we use carbapenems (imipenem or meropenem).
2- If we start treatment with cephalosporins and the patient is not responding to the treatment, this usually means that the causative agent is **resistant to cephalosporins**. In this case we use carbapenem (it's the last defense line we have).
NOTE: this part the doctor said that it is not totally required.

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- Don't EVER state treatment with carbapenems unless you have a mixed infection.
- Again, they have activity against : P.aeruginosa,enterobacter,G+ve(sterp+staph),anaerobes,fragilis(all bacteroids fragilis),H-influenza….. EVERY THING EXCEPT MRSA.
- the difference between imipenem and meropenem:
- Imipenem: is metabolized rabidly in the kidney so it has a short half-life. It is metabolized by dehydropeptidases in kidney tubules, that's why it is administrated with **cilastatin** an inhibitor of renal dehydropeptidases. Cilastatin inhibit the quick metabolism of imipenem. So in the injection we use a mixture of imipenem and cilastatin. This is simply an example of potentiation. While meropenem is not a substrate for dehydropeptidases so it is not given with cilastatin.
- **Note**: imipenem and Meropenem are injectable only. No oral forms of them.

## ❖ Side effects:

**1**-the most frequently causing nausea and vomiting of all antibiotics: the patient ether tolerates this side effect or we give him a long with the antibiotic anti-vomiting and anti-nausea drugs.
**2**-at high doses neurotoxicity may occur: in imipenem(less extant to meropenem) neurotoxicity may occur which means seizures may happen specially when a patient with history of seizures or epilepsy and has been diagnosed with a mix infection. So we want to prescribe carbapenem for him we do not go for imipenem. **Go for meropenem** to avoid this side effect.

- Also they cause the common side effects also (GI disturbance, diarrhea……)

❖ **To sum up** :

- Carbapenems are the widest spectrum of the cell wall inhibitors.
- The most frequently causing nausea and vomiting of all antibiotics.
- Imipenem may cause neurotoxicity.
- They are the drug of choice: mixed infection, infection resistant to third generation Cephalosporins.
- They are injectable drugs only.

# ❖Vancomycin:

We started with narrow spectrum drugs (penicillin) and we will end cell wall inhibitors also with narrow.

- Vancomycin is bactericidal, acts by inhibiting the cell wall synthesis.
- Binds to its binding site with very strong affinity and has a high efficacy and high potency. (That is the difference between it and other cell wall inhibitors).
- MRSA produce resistant y mutation in the binding site of the Penecillins. But because of the high affinity vancomycin still active against MRSA and binds to its binding site (even when mutated)
- NOTE: vancomycin is very similar to a drug called teicoplanine.
- Spectrum: G+ve particularly staphylococci (including MRSA).
- Vncomycin is injectable only (with one exception mentioned later)
- **So in any infection, if MRSA can be a cause we add vancomycin to the treatment.**
- It is a baseline for nosocomial infection (hospital acquired infection): sepsis, bacteremia, pelvic sepsis, uteritis…..whatever the infection is. The cause may be P.Aeruginosa, Enterobacter, and Klebsiella **OR MRSA: use VNCOMYCIN with other antibiotics to cover all causes including MRSA.**
- We know that clostridium difficile is the cause of psuedomembranous colitis. And the drug of choice in this case is **metronidazole (Flagyl**). But if the patient show no response (CL.difficile is resistant) we move to VANCOMYCIN.
- CL.difficile is not sensitive to most antibiotics except metronidazole and vancomycin.
- Vancomycin here is taken **orally**. Although it is not absorbed (totally unabsorbed) by the GI. But we need vancomycin to stay in the GI tract.

- To treat MRSA (nosocomial infection) or resistant enterococci don't use oral vancomycin. We use injectable form (IV).but when treating psuedomembranous colitis we use the oral form (to stay in the GI).
- Again, oral vancomycin has only one use: treating psuedomembranous colitis.
- Vancomycin is important drug in ICU and الخداج because there is a lot of MRSA and it is a common causative agent of infections there.

- **Resistant enterococci:**

- Endocarditis is treated by ampicillin (injectable form with tazobactam) "Augmentin" (and Augmentin is used to prophylact the patient from infectious endocarditis.)
- But if the patient doesn't respond to this treatment. This means there is resistant enterococci. In this case use vancomycin.
- **NOTE:** the main cause of endocarditis is staph then enterococci
- The main indication for parenteral vancomycin is sepsis or endocarditis caused by methicillin-restsisant staphylococci or enterococci.

- **Vancomycin and its relation to Hypersensitivity :**

  - The patient with penicillin and cephalosporins hypersensitivity and has a staph infection then **the drug of choice here is vancomycin.**
  - Vancomycin in combination with gentamycin is used for treatment of enterococcal endocarditis in a patient with serious penicillin allergy.
  - **REMEMBER: cephalosporins are not active against enterococci.**
  - So when talking about enterococci we care **about penicillin allergy only**.
  - If a patient has staph infection and he is sensitive towards penicillin → use cephalosporin or vancomycin.
  - BUT:

  If a patient has enterococcal infection and penicillin sensitive → use **vancomycin ONLY!**

- **To sum up:**

  -vancomycin cover G+ve **(including MRSA)**
  -vancomycin is the alternative when we have staph (susctale or resistant) infection with cephalosporin and penicillin allergy
  - Vancomycin is the alternative when we have enterococcal infection and penicillin allergy.
  -CL.difficile: when no respond to metronidazole⟶ use vancomycin **(ORALLY).**

- **Resistance towards vancomycin**:

  *the resistant may be developed due to changing the permeability to the drug ⟶ decreasing vancomycin's binding to its receptor.
  *In Jordan, we don't have resistant except in one bacterium VRSA (vancomycin resistant staph aureus.

- **Side effects:**

- Vancomycin must be administrated in a dilute solution (100-200 ml) slowly over at **least** within 60 min (may be taken over 2- 3 hours)
- This is due to the high incidence of pain and thrombophlebitis (التهاب الوريد) and to avoid an infusion reaction known as "red man syndrome" or "red neck syndrome".
- So if vancomycin is taken intravenously in a quick manner it will make the neck red ….
- NEVER give vancomycin in a bolus.
- Always remember red neck syndrome is linked to vancomycin.

*Sorry for any mistakes ….*

*Wish you high doses of luck*.