Notes about the final exam :

The doctor begin the lecture talking about our choices with regard to the final material, and the conclusion was :

- Mid-term material isn't included in the final exam

- Dr. Hamzeh will have about 15 marks

- Dr. Malik will have 45 marks in the final exam that will be in the 16 of January .

In this lecture we will talk about some stories :

1- **Enterobacteriaceae story .**
2- **Enterococci story .**
3- **Cephalosporins story (completing the story).**
4- **Carbapenems story .**
5- **Vancomycin story .**

Please look at this sheet as stories it will really help you studying it ^_^

Abbreviations :

pn. :pneumonia

amox. : amoxicllcin

strep. : strepcocci

staph. : staphylococci

#Revision :

- All what we were talking about (he means the type of therapy) in the previous two lectures was empirical ...
- Definitive therapy we are done with it, because the lab is going to send you the type of microorganism and the sensitivity, then you prescribe the drug accordingly, but at least you should know that this type of drugs are active for this type of disease . Example if I want to treat community acquired pneumonia and I want to treat it empirically, I need to look at the spectrum but in definite therapy the spectrum is clear (the definition is clear) and you know that the patient need this concentration of the drug.
- Another question the doctor was asked, that he has some contradiction….

He answered : "yes and that is because of the problem of enterobacteriaceae, (but if you keep up with him you will know that he is not)" .

The problem of enterobacteriaceae –we are having nowadays – that it is producing new type of extended spectrum B-lactamases (ESBL), which become more common these days .

Question: Do we give amoxicillin for E.coli ?

Yes, but in definite not empirical therapy , because a lot of E.coli produce B-lactamase that destruct the amoxicillin, even when using amoxicillin with clavulanic acid, there is still E.coli that produce types of B-lactamase, which make the microorganism not susceptible to this combination .

1) Enterobacteriaceae story :

Enterobacteriaceae : include (E.coli / salmonella / shegella / klebsilla / protues / enterobactor /seriata).

- The problem is that they are producing new type of B-lactamases, so the activity of the antibiotics - that is associated with the gram(-) bacteria, (which are 2nd and 3rd generation of cephalosporins and the extended and broad spectrum penicillins, these four act on the enterobacteriaceae) - is affected .
- Now the 2nd generation and the amoxicillin are not really active, because high percentage of enterobacteriaceae are producing extended-spectrum-beta-lactamases (ESBL) or other types of B-lactamases for the 2nd generation.
- the 3rd generation is questionable; depends on the hospital / community / abuse of the antibiotics
- some of the enterobacteriaceae are resistant to: ceftriaxone / ceftazidime / cefaxtine , but most of enterobacteriaceae are still susceptible to the 3rd generation.

- If you know that your hospital has high percentage of resistant type of enterobacteriaceae that produce ESBL , here we need to use cefapime, because it is resistant to ESBL, or imipenem -the trade name is tienam - (we are not allowed to use ceftriaxone or ceftazidime).

- The Dr. believe that when we graduate that all enterobacteriaceae will be resistant to ampicillin (amoxicillin) and the 3rd generation, the development of the bacterial resistance is really in its course nowadays .

At the end of the story of enterobacteriaceae we say that :

1- we use 3rd generation chepalosporins, except if enterobacteriaceae in our hospital produce ESBL .

2- if it produce EBSL we use cefapime, imipenem and pipercillin (not alone, we use it with tazobactam).

3- broad spectrum is still used in the ICU in life threating infection which are : cefapime, imipene and tazocin (pipercillin and tazobactam) .

2) Enterococci story :

-All cephalosporins aren't active against enterococci except for the 5th generation, which is not mentioned in the slides because it isn't approved yet by the FDA, and in Jordan we don't have yet, the 5th generation is active against enterococci and MRSA .

-The enterocooci include : E. faecium and E. faecalis they cause endocarditis.

Question: Do we use cephalosporins prophylactically for endocarditis ?

The answer is no,because the common cause of endocarditis is enterocooci - in addition to strep.pn. and MRSA -and the cephalosporins are not active against enertococci (either in prophylactic or in treatment).

The drug of choice here is the amoxicillin.

info: Dental surgeries may cause endocarditis due to enterococci and we use amoxicliin prophylactically, (2 grams before 2-4 hours of the surgery) .

#note that penecillns are active against enterocooci chephalosporins are not .

Now some Notes :

cephalosporins aren't active against MRSA, staph. Epidermis

penecillins also aren't active against MRSA .

penicillin resistant strep. Pn. : these are some type of strep.pn. that are resistant to penicillin.

The story of resistance is :

- Some of them are resistant to penicillin G so we treat them with amoxicillin, but this was long ago, now most of them is resistant to amox. so the drug of choice here is ceftriaxone (which is the most active cephalosporin against penicillin resistant pneumococci and is recommended empirically is serious infection) .
- Example : if a child has otits media and we give him amox., if he doesn't respond we give him one of the 3rd generation cephalosporin, since he is a child we give him oral cefixime (the only type of the 3rd generation that is given orally).

Sadly penicillin G isn't used in Jordan anymore because the doctors aren't appreciating it's spectrum .
and Penicillin V is being driven to the same path .

3) Cephalosporins story (recapping the story):

1st generation : 1- cefazolin used prophylactically .
2- cephalexcin used in cellulaitis and pharangitis (it cover staph and strep).

2nd generation : 1- cefotetan used in fragilus.
2-cefaruxime used in community acquired pneumonia (active against H.influenza and K.pnuemonia) .

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Question : *K.pnuemonia is considered as typical or atypical ?*

It is both, how ? because long ago atypical was referring to the microorganism (non-complete bacteria) which are (legionella /chalmidya / mycoplasma) , later the atypical was refering to non-common pneumonia .

Simply, it is typical because it is a complete bacteria, and we said that any complete bacteria that cause pneumonia it will be typical and the atypical is caused by not complete bacteria such as the mycoplasma. But the naming had changed, and in some books we will find that it is considered as typical and others considered it atypical .

3rd generation : 1- They are used against meningitis, penicillin resistant strep. Pn. , n. gorronhea and gram(-) enterobacteriaceae, unless I'm afraid that they (enterobacteriaceae) produce ESBL, if they produce it we use cefipime and imepinim .
2- Some of them is used against pseudomonas such as ceftazidime and

cefaperazone .

Adverse or side effects of cephalosporins :

1- **hypersensitivity**, which is similar to penicillin , there is a crossing between patients that are penicillin allergic and patients that has cephalosporin allergy, and it reach about 20% - that what is written in books, but in clinic they are only 5% - the problem that there is no test to know that your patient is cephalosporin allergic, so to cut the story short, **Do not prescribe cephalosporin for penicillin-allergic patients**, and the alternative will be azthromax(alternative drug of penicillins) .

A disulfriram-like effect and the hypoprothrombinemia are associated with 4 types of cephalosporins.
There are two of our concern, **cefoperazone** (which is used against pseudomonas just like ceftazidime) and **cefotetan** (used against Fragillis), the problem is that they have this molecule **N-methyl-thiotetrazole** that bind with enzymes in our body such as : aldehyde dehydrogenase and vitamin K epoxide reductase .

2- **binding with vitamin K** :
vitamin K epoxide reductase is responsible for activation of coagulation factors, these cephalosporin (because of their anti-vitamin K activity) will make the patient more susceptible to have bleeding (it willl inhibit the activation of coagulantion factors)

3- **binding with aldehyde dehydrogenase** :
Small story here :p
people who drink alcohol, they became addicted; social addiction (In west countries) and that because every now and then they drink, and we have it here but not the social addiction type. To treat this patients with alcohol addiction we use disulfiram, that inhibit the degradation of acohol, How ?
Alcohol when entering the body it will be transformed to aldehyde then continue its degradation, there is an enzyme called aldehyde dehydrogenase that will let the aldehyde continue in its metabolism pathway , inhibiting this enzyme will cause the accumulation of acetylaldehyde in the body and this has a vomitic and nauseic (from nausea) effect on the patient, he will feel unpleasant, uncomfortable .
so if the patient is drinking while having cefotetan, cefoperazone, he will have this bad feeling .
4- ceftriaxone with calcium will precipitate in the lung and kidney especially in infant 28 days .
5- ceftriaxone with billirubin in jaundice cases .

 # Important note:

Cefoperazone and ceftriaxone are excreted in bile not urine .

Usually you will be dealing with people who have renal problems (renal failure, renal function reduction , renal impairment), so if you want to give any drug, that is excreted in urine, to a patient with these problems you have to reduce the dose except if the drug is excreted in the bile .

So if your patient has renal problems, and you don't want to go through the hassle of adjusting the drug dose, by calculating ceriatine clearance in the kidney (function test of the kidney) you can administrate cefoperazone and ceftriaxone (without adjustments).

- they are the only two drugs that we have taken till now that are excreted in bile (cefoperazone and ceftriaxone).

Question: *Can we give patients with renal problems urine-excreted drugs ?*

- If renal failure sometimes yes, if renal impairment always yes but with adjusting the dose (here reducing the dose).

Question: *Why we have to adjust the dose in those patients ?*

- Because the clearance of the drug will be reduced and its concentration in the body may reach the toxicity line.

 # Example: sometimes we reduce the dose of the pipercillin according to the ceriatine clearance which is normally 30mg/ml, if the patient has less than this then we reduce the dose to one third or two thirds according to the impairment in his kidney .

4) Carbapenems story :

The most impotant one for us is the **tienam** which is the trade name of **imepinim**, which is the :

1- the broadest cell wall inhibitor

2- the broadest B-lactamase, it cover gram(+) and (-) aerobes and anaerobes , E.coli " bla bla bla " everything aerobs and anaerobs, fragills, enterococci (it cover faecalis but not faecium).

#note up to now the best drug for enterococci are the penicillins, cephalosporin has no activity and the imepinim is questionable (not all of them) .

Question: *where to use imepinim?*

* With susceptible organisms that are resistant to other available drugs.

#example: if my hospital is full with enterobacteriaceae that produce ESBL here it is resistant to 3rd generation of cephalosporins, such as P.aeruginosa, so I use imepinim .

* We use it and with aerobic and anaerobic mixed infection such as the lung abscess (the simplest example), sepsis and it can occur in the GI tract .

* The treatment of choice for infections caused be ESBL-gram-negative bacteria (E.coli, salmonella, shegilla, klebsilla, seriata, enterobacter), they will not respond to cephalosporins

except 4th generation .
*infection caused by enterobacter aerogenes, very common in hospitals .(always enterobacteriaceae is common in hospitals).

important notes :

The carbapenems are resistant to desrtruction with B-lactamse producing bacteria .

There is other carbapenems such as ertapenem that can be seen in some hospitals, and in the future we may see doripenem and meropenem, they are not in Jordan now .
Imepinim has a wide spectrum but has a little problem; it is rapidly metabolized by dehydropeptidase, in order to build high concentration of the drug I need to inhibit this enzyme by cilastatins, so instead of building about 25% of the concentration I can build about 75% .

Cilastatins should not be mistaken by statins, which are antihyperalipidemic drugs .

Side effects :

1- Imipenem especially -and the other drugs - causes **nausea** and **vomiting** with high percentages (20% percent of patient will produce these side effects).
2- At high doses it will cause **neurotoxicity,** this is important (in 0.5%- 1% it will cause **seizure).**

Question: *ok why I should use high doses of imepinim ?*

* Because there is a new group of B-lactamases called K.pnuemonia carpabinmase (imipenenase), they have the activity to destruct or deactivate imepinim, so sometimes we need to give high dose of imepinim if we have intermediate resistance, but if we have full resistance imipenem won't work .
Nowadays this is one of the big problem in hospitals, KPC (K.pneumonia carpabinemase) they don't respond to any other drug, these days we don't have drugs for imipenem resistance microorganisms, except for some drugs that really don't work on all patient –they depend on the spectrum- , what actually we are losing is the empirical therapy, **why**?
If the hospital is full of KPC or any microorganisim that produce this enzyme all the empirical therapy will have no value, because we can't cover KPC in the therapy, which is resistant to pipercillin, cefapime and imipenem, the only active drug is gentamycin where half of these microorganism may respond and the other half will respond to "colistine".
#note: The cause of this resistance is the abuse of the imipenem.

Vancomycin story :

It is a gram(+) antibiotic that covers all the staph., all the strep., and the most important is MRSA.
Also it has activity against all entercocci and colstridium difficile .
So, If the patient has resistant enterococci or I'm afraid of that (here we are talking about empirical not prophylactic, and empirical is always associated with fear because I'm not covering the real causative agent then I need to give vancomycin), Or if he have endocaritis and mostly it is enterocoocal endocarditis, we used to give him ampicillin and gentamycin, in these days the enterocooci developed resistance to penicillins including (ampicillin) so we give vancomycin, but if I'm not certain about the resistant enterocooci or the community /hospital enterococci didn't developed the resistance so I give ampicillin and gentamycin.

- If I'm afraid of MRSA, or my hospital is full of MRSA, and the patient has meningitis or sepsis or pn. Then I should cover MRSA, and I give vancomycin combined with other drugs .
#example : if my patient has meningitis I give cefatriaxone to cover, gram(-), gram(+) mostly I will cover (H.influenza, strep.pn., N.meningidetits), so the cefatriaxone will cover them and it can build a good concentration inside the brain, but that is not enough because the permaturity section in the hospital is full of MRSA so I need to cover MRSA with vancomycin.
#note: Whenever I suspect to have MRSA in my hospital I need to cover it , and this will be by vancomycin .

- Colstridium difficile cause psuedomembranous colitis , which is treated with metronidazole as the first line therapy (the trade name is flagyl that is taken in homes and has no good effect), if it doesn't work we will use vancomycin as a second line therapy.

- The route of adminstaration of vancomycini either injectable (is the main route because it isn't absorbed from the GI tract) or oral. So if we have meningitis, sepsis, pn. , we use injectable vancomycin, and is used **orally only with colstridium difficile**, why and how ?
Colstridium difficile reside in the intestine, so because of the poor absorption from the GI tract it will reach the intestine and exert it action against the colstridium difficile .
- Vancomycin is used orally only against colstridium difficile.
- Parenteral vancomycin main indication is : sepsis by MRSA and enterococcal endocarditis .

Some cases to use vancomycin :

1- enterococcal endocarditis in patients with pencillin allergy, I can't give cephalosporin –as we said up in the sheet- what are my choices ?

I can give imepinim, but it doesn't cover the entercocci, so the drug of choice to cover the enterococci in these cases is vancomycin with gentamicin .

 # rememeber : if the enterococci is resistant toward penicillins what we will use ? vancomycin also .

2- To treat the GI infection because it isn't absorbed from the gut (we metioned how) .

3- It will be one of the choices in patient with penicillin or/and cephalosporins allergy, who have severe staph. Or step. Infection usually staph.

side affects :

We have a big problem with administrating the vancomycin, it produce allergy at the site of the IV injection, it will produce; fever, rashes and local phlebitis .

The solution for the administration problem is to give the vancomycin in a diluted solution for 60 min .

I'm not allowed to give a bolus of vancomycin, I need to put it in a diluted solution and give for more than one hour because direct injection will cause – in high percentage of patients – fever, rash, thrombophlebitis ((تخثر في منطقة الحقن) ,

It may produce also a case of red neck syndrome or red man syndrome (is caused by vancomycin if not given in a long period of time) .

If any of these complications happened during giving vancomycin I should **stop the administration**

#note: vancomycin is **a bad drug** because the side effect and the administration is very difficult .

- There is a point in the slides but the doctor didn't mentioned it :

"Ototoxicity and nephrotoxicity can occur and hypersensitivity reactions are occasionally encountered."

عندما نعيش لذواتنا فحسب ، تبدو لنا الحياة قصيرة ضئيلة ، تبدأ من حيث بدأنا نعيش ، وتنتهي بانتهاء عمرنا المحدود, أما عندما نعيش لغيرنا ، أي عندما نعيش لفكرة ، فإن الحياة تبدو طويلة عميقة ، تبدأ من حيث بدأت الإنسانية ، وتمتد بعد مفارقتنا لوجه هذه الأرض. سيد قطب

فلتعش لفكرة