Last lecture doctor talked about vancomycin and its side effect, today's lecture will be about:

1-Monobactam ((a cell wall inhibitor)).
2-Protein synthesis inhibitor antibiotics.

- Monobactam: it is a cell wall inhibitor and active only against gram –ve aerobic bacteria (including pseudomonas), Proteus, Serratia and Enterobacteria as E. coli.

_ Vancomycin is used to cover the gram +ve in hospitals since it is active against MRSA, resistant type enterococci and Clostridium difficile.

_ Aztreonam is the main Monobactam, it has a narrow spectrum and it's resistant to most B-lactamases .Where do we use it? We use it with pneumonia (hospital acquired), meningitis, sepsis caused by gram –ve pathogens … and where we really use it? With patients that have allergy towards the penicillin and cephalosporins.

_Monobactam has no side effect.

* By that we finished all cell wall inhibitors: ((penicillin, cephalosporin, carbepenem, vancomycin and Monobactam))

- Protein synthesis inhibitors

1- Tetracyclin

2- Macroloids

3- Aminoglycosides

4-Clindamycin

There is also another group: Linezolid

_ most protein synthesis inhibitors are bacteriostatic, except Aminoglycosides which are bactericidal. When you deal with life threatening conditions, you go toward Tazocin, Carbapenem or Cefepime and to cover the gram +ve we use vancomycin.

-NOTE:

1- Usually protein synthesis inhibitor work on the ribosomal level → means on translation, and they will not inhibit the transcription >> except for Rifampicin it binds and inhibits RNA polymerase.

The protein synthesis inhibitors inhibit the synthesis by

a- blocking binding site of tRNA on ribosome.

b- Mismatching.

c- Frame shift.

d- Or inhibiting ribosome activity.

1- Tetracycline: it is a very old and good example on these antibiotics that we lost within clinic.
((Tetracycline, Methacycline, Moxycycline, doxycycline Minocycline and Tigecycline)) any drug ends up with (CYCLINE) is from the tetracycline group.
-what we have now in markets are doxycycline and Minocycline.
-WE HAVE BIG ISSUE WITH TIGECCYCLINE (it is a new drug, we will talk about it later)
- Tetracycline binds to m-RNA and ribosomal 30s subunit where it prevent binding of aminoacyl-t RNA
- They are mostly bacteriostatic.
- They have a very wide spectrum of activity (for gram +ve, -ve, some spirochaetes and protozoa) but we have now a problem because we lost gram +ve and mostly lost gram –ve, due to abuse.
And there is problem with tetracycline... they are substrate for the proton pump exchanger that excrete antibiotic, this is mainly found in bacteria resistant to tetracycline.
Extra note: The mechanism of resistance in tetracycline is by efflux pumps that actively eject tetracycline from the cell, preventing the buildup of an inhibitory concentration of drug.

- **Most microorganisms now are resistant to tetracycline ,but still it is active against [Chlamydia (which causes atypical pneumonia and urethritis) , Mycoplasma →** atypical pneumonia)**, (H-pylori →**causes ulcer) , (**Cholera →** gram –ve rods **), Rickettsia, Syphilis]**
{ In slide 60 there is a pic shows diseases treated by tetra.}

*** NOTES:**
1- In treating Brucella we combine 2 drugs
((Aminoglycosides {mostly Streptomycin } + Tetracycline {Doxycycline}))
2- In treating ulcer caused by Helicobacter p / H pyloir , we give combination of drugs either
→ ((Amoxicillin + clarithromycine))
or
→ ((Tetracycline + Metronidazole))

Simply speaking : Tetracycline has a good activity against H-pyloir but it is not giving alone , because single drug response is only 40% while when you combine 2 drugs the response will be 95%

3- Acne : mostly we use doxycycline (in low dose due to its side effects).. Why do we use antibiotics with acne?? To reduce the metabolism of lipids within skin that produces fatty acids that cause skin irritation.

* SIDE effects of tetracycline:
- GI disturbances ((irritation))...solution is to take the drug with food, although food affect the absorption.
- Deposition in growing bones and teeth, causing staining and sometimes hypoplasia and bone deformities... and due to that effect it is contraindicated to children under 8 years old.
-Phototoxicity
- food –drug interaction... all food that have Ca (ex: milk) or antacid because they will interact with tetracycline and inactivate it. So it shouldn't be taken with milk or antacid.
- Tetracycline must not be given to pregnant women because it have tendency toward liver toxicity and it is increases in pregnant women.

2- Macrolids: (Clarithromycin, Azithromycin, Erythromycin, Telithromycin) they are community drugs.

we use them in :
a- in upper respiratory tract infection as alternative amoxicillin or cuforxime , to patients that have allergy or children afraid to have allergy to treat (otitis media , pharingytis , tonsillitis, sinusitis)
2- lower respiratory tract (Legionella , mycoplasma , Chlamydia, syphilis, diphtheria [drug of choice for it])

Macrolids are better than tetracycline in what??
a- on activity against gram +ve bacteria < it is active against staph. And strep.
B-Azithromycin is active against H-influenzae, the drug of

pneumonia (hospital acquired) cause it covers all atypical pneumonia [H-infleunzae, legionella, mycroplasma, pneumococcus, Chlamydia], while tetracycline is not active against Legionella.

***Notes:**
-Azithromycin is similar to Cefuroxime and Amoxicillin.
-Its antibacterial spectrum is very similar to penicillin.
- Azithromycin is the drug of choice for children and pregnant women...

* Azithromycine can be prescribed only for 3 days (6 tablets 500 mg) or (3 tablets 1 g) , while usually antibiotics are given for 7 or 10 or 14 days ..Why could this happen with Macrolids mostly Azithromycin??
Because there is a buildup of drug within most tissues ((except CSF, so we don't use it with meningitis)) the tissue work as reservoir → releases drug and keeps the concentration above MIC.
WITH TISSUE CONCENTRATION EXCEEDDING SERUM CONCENTRATION. What does this means? means that the half life that is measured in blood not real because all the Azithromycin is found in tissues and slowly released ... I need to build a loading dose .

- Also we give Azithromycin as one shot (2 gram) in treating urethritis, because the 2 gram will penetrate in your body and will be slowly released.

* Side effects:

1- GI disturbances, common with erythromycin but not common with Clarithromycin or Azithromycin.
2- Drug-drug interaction (SYP3A4 It is an enzyme in our liver that metabolize the drugs >> Induction or inhibition will affect the level of the drug within blood.
If you make induction, you will reduce the level of other drugs that metabolized by that enzyme...
If you inhibit it, you will increase the level of other drug that you patient use...
- We are interested in drugs that have a narrow therapeutic index

**ex. grapefruit juice effect SYP3A4 , it induce it , so people that drink it with drugs >> the level of these drugs will be reduced in the blood due to induction of the enzyme . x. grapefruit juice effect SYP3A4 , it induce it , so people that drink it with

Macrolids inhibit SYP3A4 specially the erythromycin and to lesser extend Clarithromycin and to very lesser extend Azithromycin ,, the inhibition of SYP3A4 enzyme will increase the level of some drugs ((Warfarin , Digoxin , Cyclosporins and Corticosteroids)) a toxic drugs , and all have a narrow therapeutic index >> IF A PATIENT WAS GIVEN ONE OF THESE DRUGS ((Warfarin , Digoxin , Cyclosporins and Corticosteroids)) WITH erythromycin , the patient must to be monitored .

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