Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 29

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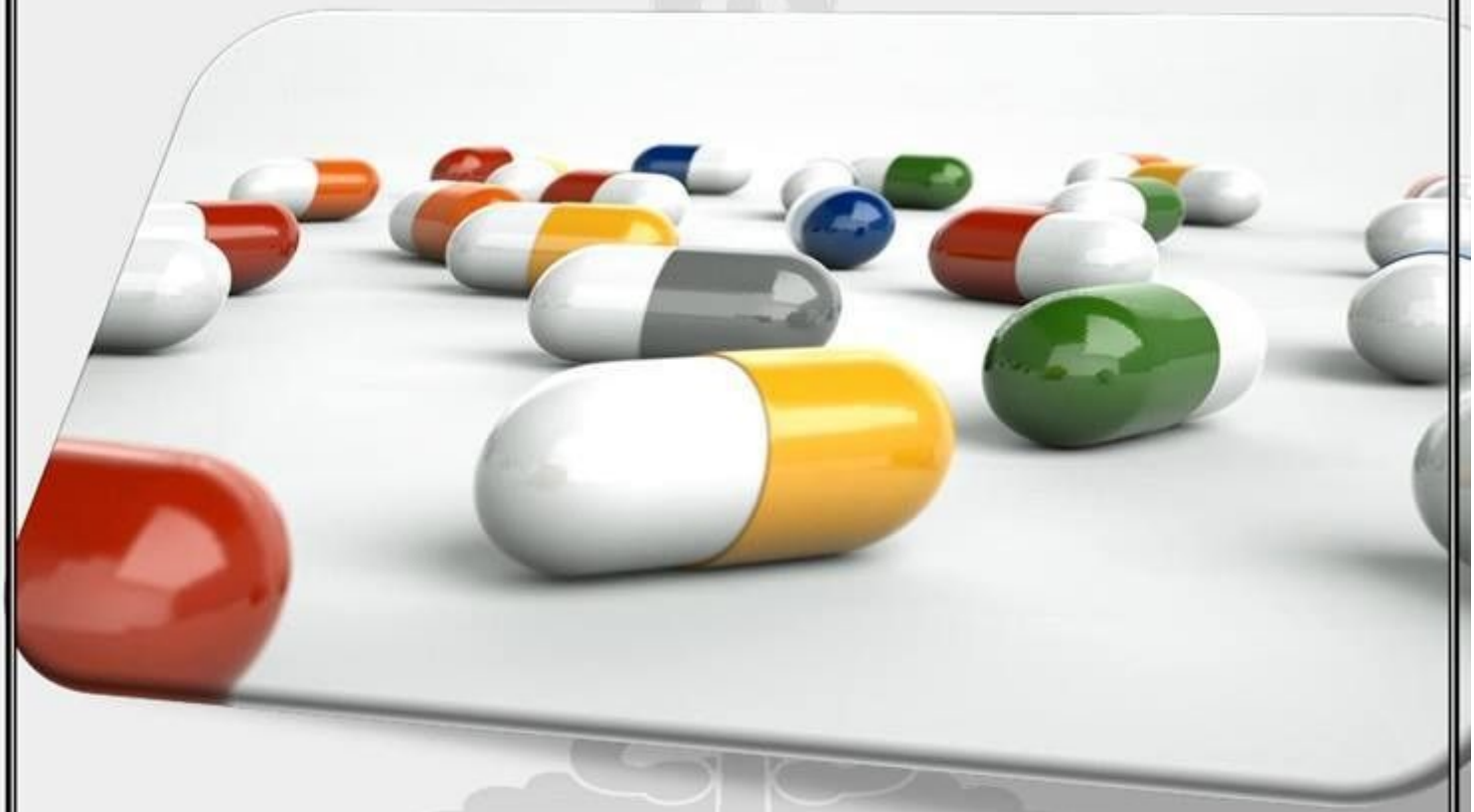
SHEET ■

SLIDES □



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ANTIBIOTICS (4)

We have already discussed Penicillins, Cephalosporins generations, their features and the clinical uses. In the last lecture, we studied some few basic points about the new class of antibiotics - a cell wall inhibitor-; Carbapenem. The lecture today will be a continuation of what we started before besides studying other antibiotic classes.

I-Carbapenems:

Carbapenems have a wide spectrum - similar to that of Cefipime -against many gram-negative rods including *P aeruginosa,* gram-positive organisms, and anaerobes.

Examples of this class are:
Doripenem, ertapenem, **imipenem, and meropenem** are licensed for use in the USA.

Imipenem:
known as Tienam (elle 3umro ma nam :P)

has a wide spectrum with good activity against many gram-negative rods, including *P aeruginosa,* gram-positive organisms, and anaerobes. It's inactivated by dehydropeptidases in renal tubules, so it's administered together with an inhibitor of renal dehydropeptidase, cilastatin, for clinical use.

The misuse of this antibiotic resulted in some resistant bacterial species producing (Beta lactamases) like: klebsiella pneumoniae, these produce carbapenemases (very effective beta lactamases which deactivate imipenem). However, there is a carbapenem drug with great activity against many types of bacteria which is Meropenem but unfortunately this antibiotic spectrum does not include MRSA species.

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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.

Example:

Carbapenem is the beta-lactam antibiotic of choice for treatment of **RESISTANT** enterobacter infections because it is resistant to destruction by the lactamase produced by these organisms, as well as community acquired infections not caused by MRSA. Mainly imipenem and moropenem are used for treating such infections as well as cefepime (cephalosporin).

When do we use these antibiotics more precisely?

When you suspect that your patients got mixed infections treat them with Tienam (Imipinem) and keep Cefepime for the later use to treat the more resistant bacterial spp.

#Imipenem is the most carbapenem that causes vomiting and nausea besides diarrhea but it does not cause any hypersensitive reaction like cephalosporins and penicillins.

These antibiotics are injectable not oral

Now we will talk about another cell wall inhibitor:

II-Vancomycin

Vancomycin:

1- Most active drug against MRSA species.
2- Narrow spectrum antibiotic
3- Acts against gram +ve only (Staph mainly and enterococci)

Can we really use Vancomycin anytime? WHY?

The answer is NO, thumma NO, it must be used only when really needed, because nowadays we have VRSA spp; (Vancomycin-resistant Staphylococcus aureus), they may cause a serious resistance to the antibiotic that culminates in loss of the antibiotic therapeutic value. VRSA cases are rare in Jordan and more common in the US.

What is meant by "only when really needed"?
When patients aquire MRSA from hospitals (nosocomial infection). Remember: for the treatment of meningitis, Vancomycin is combined with ceftriaxone because ceftriaxone covers all the causes except MRSA which are covered by vancomycin.

Remarks about Vancomycin:

Community acquired meningitis is not caused by MRSA
Vancomycin is prescribed empirically -combined with other drugs- when we suspect the patient has MRSA from: nosocomial infections or mixed infections, mixed infections may include wound mixed infections, mixed pneumonia, meningitis, septecimia, etc.
MRSA are either community or hospital acquired spp, what we are talking about here is the hospital-acquired type.

The role of Vancomycin in the treatment of Endocarditis:

1- For dental problems, amoxicillin is given orally to treat patients and prevent endocarditis
2- For more serious cases where patients have active endocarditis, Ampicillin is prescribed
3- For resistant enterococci and allergic patients Vancomycin is given.

Remember: all cephalosporins are not active against enterococci.

The role of Vancomycin in the treatment of pseudomembranous colitis:

Generally speaking, Vancomycin is injectable and it's slowly absorbed from the GIT, this actually explains why we don't use the oral dose of vancomycin to treat blood infections but rather the injectable ones. However, this antibiotic is given orally for the treatment of pseudomembranous colitis caused by Clostridium Difficile, the oral use here is of a great benefit. The antibiotic is poorly absorbed so it will stay longer in the GIT and therefore attack the bacteria (Clostredium Difficle) which affects the intestine. **Metronidazole is the drug of choice in cases of infection with Clostredium Difficle, if the patient doesn't respond to that drug, we switch to oral vancomycin**. Keep in mind that these bacteria shouldn't be resistant here to vancomycin.

Now what are the main indications for the parenteral Vancomycin?

1) Sepsis and endocarditis caused by methicillin resistant staph.

2) Severe Staph infections in allergic patients (allergic to penicillins and cephalosporins).

Note: Penicellins and Cephalosporins have bactericidal effect on Staph, for allergic patients we give another antibiotic with a bactericidal effect which is Vancomycin. (we can't give bactereostatic drugs to patients with severe infection)

General notes about Vancomycin from the slides:

- Vancomycin in combination with gentamicin (mentioned later) is used for the treatment of **resistant** enterococcal endocarditis in a patient with serious penicillin allergy.
- It is not absorbed from the gut and is only given orally for treatment of GI infections. It is generally administered intravenously.

• Resistance can be caused by changing the permeability to the drug and by decreasing the binding of Vancomycin to receptors. This is responsible for VRSA and VRE (vancomycin resistant enterococci). So now, vancomycin usage restriction is really important, because the more we misuse this antibiotic the more the resistance exacerbates.

How is Vancomycin given intravenously?

•Vancomycin must be administered in a dilute solution slowly, over at least 60 minutes.
(This is due to the high incidence of pain and thrombophlebitis; (vein inflammation or localized inflammation in the injected area) and to avoid an infusion reaction known *as the red man syndrome or red neck syndrome.*
• Unwanted effects are a series problem and include *fever, rashes and local phlebitis.*

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

Further Elaboration!

Vancomycin can't be given in a single bolus nor quickly but rather slowly with a longer time of administration; once this antibiotic is **administrated fast** it will cause the previous mentioned problems. Vancomycin is associated with "administration allergy" unlike the allergy caused by penicillins and cepahlosporins, it just occurs in the site of administration.

Note: Vancomycin may cause anaphylactic shock when administrated fast.

Once you be a doctor (اتراه يأزف قبل موتي ذلك اليوم السعيد:D)
Don't rely on nurses and Pharm-D, always tell them the way the antibiotic is given.

What about ototoxicity and nephrotoxicity?

Whether vancomycin causes nephrotoxicity or not is still a debatable point among doctors. Nevertheless, some studies proved that vancomycin is rarely associated with ototoxicity and nephrotoxicity, except when given with another nephrotoxic drug like gentamicin.

Dr.Malik thinks that Vancomycin does not cause nephrotoxicity unless administered to children below five years old.

Back to pharmacodynamics and side effects occurrence: Nephrotoxicity is a rare occurrence and for a side effect to arise or to be considered seriously, we rely on the drug's trough and peak levels. Side effects occur when the trough value is above a certain level, and in vancomycin case nephrotoxicity arises. Does that mean doctors should ask for the trough and peak every time they administer the drug?! Well, no… This depends on which clinical trials the doctor follows, whether the old or the new, and both doctors are right. (*Frankly the above two paragraphs explain nothing clearly but one thing; they made the sheet longer haha "ma tfarju hai eljumlil lal* ***Dr****).*

Mainly we are done with Vancomycin and the last thing to be mentioned is a little recap:
** vancomycin is used against enterococci, colistridium difficile and MRSA
** when administrated fast it would be associated with Red neck/man syndrome and rare nephrotoxicity and ototoxicity.
** used against gram +ve only and combined with drugs to treat the mixed infections EMPIRICALLY.

III-Monobactam

- A narrow spectrum antibiotic
- A cell wall inhibitor
- Unlike vancomycin, this one is a gram –ve drug.

- An example is **Azt**reo**nam** (Monobactam **zetto** o **nam** memorize it that way :P)
- Doesn't work on gram +ve or anaerobes

- Used to treat patients allergic to penicillins and cephalosporins, those with serious infections such as pneumonia, meningitis, and sepsis caused by susceptible gram-negative pathogens.
- Since it has a narrow spectrum it is preferred more than imipenem and meropenem because they have wider spectrum.
- A good substituent for the gram-ve activity of ceftazidime (but ceftazidime has a little gram +ve activity).
- The side effects are similar to those of other b-lactam antibiotics.
- Not a commonly used drug.

We are done with cell wall inhibitors and now we will discuss protein synthesis inhibitors.

Protein synthesis inhibitors

1- They have bacteriostatic effect **except** for Aminoglycosides
2- Used in the treatment of community acquired problems rather than the major problems like sepsis because of their bacteriostatic effect.
3- Great activity with a broad spectrum
4- Because of overuse, resistance is common
5- Bacterial ribosomes (30S & 50S) differ in molecular detail from eukaryotic ones enabling antibiotics to exhibit selective toxicity so antibiotics affect the microorganism rather than the host cell.

The main ribosomal processes they interfere with are:
(1) Binding of aminoacyl-tRNA
(2) Normal codon:anticodon recognition
(3) transpeptidation

1st group: Tetracyclins:

They are old drugs and we lost their effects to the resistance, but by the new drug –Tigecyclin- many changes happened (mentioned in the next lecture).

Examples of these drugs:

Tetracycline, Methacycline, Moxycycline, doxycycline minocycline and **Tigecycline.**

- They bind to both mRNA and the ribosomal 30S subunit where they prevent the binding of aminoacyl-tRNA.
- They are bacteriostatic not bacteriocidal.
- Their spectrum of activity is very wide and includes Gram-positive and Gram-negative bacteria, some spirochaetes and some protozoa (eg amoebae).

Really Important:

Forget about treating gram positive and gram negative by Tetracyclins because they have already developed resistance. Nevertheless, tetracyclins are still working against some intracellular infective spp that haven't developed any resistance against them, such as: mycoplasma, Chlamydia, brucella, treatment of Cholera, Lyme disease and rickettsia.

Chlamydia Tra5omaris (trachomatis)

The main cause of STD in the US

Doxycycline is used to treat Chlamydial infection. (the drug is given for 7days)

But if we want to treat the disease with azithromycin, one shot is all that is needed. We'll know why in future lectures

#Mycoplasma Pneumonia:

The main cause of community acquired Pneumonia. Remember that Mussleh مصلح causes community acquired pneumonia :D mussleh is abbreviation of Mu: mycoplasma, S: staph, S: strep, Le: leiogonella, H: H.influneza. (add Chlamydia as well)

You can never treat all the previous bacteria by tetracyclins as they have lost their activity toward gram +ve & -ve but still they are great for the treatment of the listed bacteria in the box above. (meaning if we're sure mycoplasma is the causative agent of the disease, we can use tetracyclins as a definitive treatment).

Staph, strep and h.influenza normally cause pneumonia while Chlamydia, legionella and mycoplasma abnormally cause pneumonia.

The details in slide 63 about the diseases are not required just understand the previous details o (kathar alla kherkum :D).

Again: tetracyclins are used for chlamydia, brucella, mycoplasma.
A tetracycline—usually in combination with an aminoglycoside—is indicated for brucellosis
Acne **resulted from bacterial infection** is treated by Doxacyclin.
Gastric and duodenal ulcer caused by helicobacter Pylori are treated firstly by 3 drugs combination, once they fail we move to a combination that includes tetracyclines.
Used for Syphilis, but this is not common

Remarks about tetracyclins:

Resistance is common and is mainly due to a plasmid-mediated energy-dependent efflux pump, (typical of the multiple

drug resistance type). Meaning there is a pump similar to p-glycoprotein in concept, responsible for that pump is a plasmid, the pump is very common in gram –ve and +ve bacteria, so tetracyclines don't work against these bacteria. Mutations in the tetracycline target site are also found. **Species treated by tetracyclins haven't developed these pumps yet.

•The Tetracyclines are usually administered orally but can be given parenterally. Absorption from the gut is irregular and better in the absence of food.

•Since Tetracyclines chelate di- and trivalent metal ions, forming insoluble complexes, absorption is decreased in the presence of milk, certain antacids and iron preparations. So never take tetracyclins with milk and antiacids like renin and others which are basically Aluminum hydroxides and Mg-hydroxides.

That's it for today: we are done with cell wall inhibitiors and we've learnt few points about tetracyclins.

Note: I have written everything in the slides here so if you don't have time to read them then no need.

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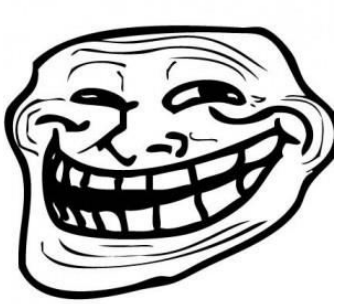

اللهم لا عيش لنا الا عيش الاخرة ....

واعطوها فاكيشين في اسطنبول.....