University of Jordan
Faculty of Medicine

Medical Committee
The University of Jordan

Introduction to

PHAMACOLOGY

SHEET ○ SLIDES

LECTURE # : 

TITLE: **Antibiotics - 2**

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PRICE: .....

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Antibiotics (2):

- Before you start: this lecture has a lot of names and things get entangled together, but I have nothing to do but to write everything the Doctor mentioned. I hope it will be clear.

- Last lecture, we said that the antibiotics have a common **community problem**; which is the misuse (especially abuse) that leads to development of resistance against the drugs. This problem is mainly caused as a result of non-continuing the dose or non-taking the total course regularly (skipping some doses). So, a general advice that you have to give to your patients is to stick with the schedule of the drug until they complete the prescribed antibiotic.

- Different antibiotics have different dosing rates (note: the Doctor won't be asking about dosing rates (intervals or amounts) in the exam, so you don't have to memorize any of them during the up-coming lectures because - in the future - you are going to have all the needed references with you (Internet, iPADs…), and thus, easily getting the information about the dose you need).

- Antibiotics usually attack the bacteria in a way that destroys specific structures within it and at the same time, doesn't affect the human cells, thus, having a high **therapeutic index**. So, we can say that antibiotics don't have real side effects. An exception of that is the **diarrhea**, all antibiotics cause diarrhea because of disruption of the normal flora (mainly GI flora) and this will be manifested by the presence of diarrhea or **Epigastric distress** (GI problems).

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Revision of most important therapies types:

1- **Prophylaxis**: protecting the patient from infections.
2- **Empirical**: treatment of the patient depending on your own expectations. For example, you are suspecting if the patient has a **penicillin-resistant-staphylococcus aureus**-infection and you have two drugs as options. Here, you give the drug according to the signs and the symptoms that you find on the patient. Another way is using hospital **charts*** that describe the main **nosocomial** (hospital acquired) infections' causes in the hospital, so if you know that this hospital has a high possibility for (**Pseudomonas**, **Acinetobacter**… etc), you treat the patient by expecting those possibilities. In brief, this expecting therapy is the most important and most difficult part of your life. **Meningitis**, **pneumonia**, **sepsis**, and **bacteremia** are the most common life threatening problems with which we are going to deal. So, the life of your patient becomes dependent on your expectation.
3- **Definitive**: the culture results come back to you from the lab and once the microorganism becomes **defined** and after being told that this type of causing agents is sensitive to certain types of antibiotics, you give the patient the antibiotic as a definitive therapy. So, all of that result in naming it: "definitive".

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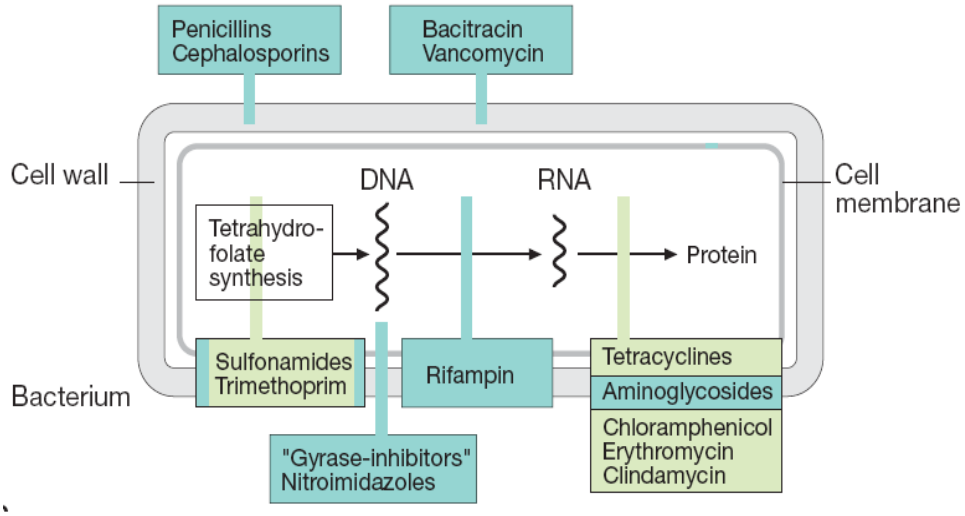
*: retrospective chart review (RCR) for estimating nosocomial infection rates (NIRs) in individual hospitals.

- There are hundreds of types of antibiotics; the one I should give to my patient depends on the type of the microorganism (check slide 16 just to have a review).



- Simply, (Penicillins, Cephalosporins, Bacitracin, Vancomycin) work on the cell wall (inhibition of the cell wall).

- (Tetracyclines, Aminoglycosides, Chloramphenicol, Erythromycin, Clindamycin) work by inhibiting protein synthesis.

- (Penicillins, Cephalosporins, Bacitracin, Vancomycin, Aminoglycosides, Rifampin, Mitrondiazole) are bactericidal.

- (Tetracyclines, Chloramphenicol, Erythromycin, Clindamycin, Sulfonamides, Trimethoprim) are bacteriostatic.

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Inhibition of the cell wall:

- Inhibiting the cell wall by drugs means that you are disturbing the **Osmolarity** of the cell until the cell explodes, and that is why all of the drugs working this way are bactericidal.

*Not important, you will take it in the respiratory system:

Rifampicin (Rifampins) also produces bactericidal effect because of inhibiting **gyrase** (**topoisomerase** and gyrase cut, pull, and rejoin the DNA so as to reduce the over winding (coiling) that is caused after the DNA is unwound via Helicase), thus, inhibiting the rejoining of the DNA which was normally done via gyrase, then, the DNA won't be rejoined but will be broken down (breaking the DNA causes -cidal effects because no cell can live with a break in the DNA).

- Why are other drugs that work by inhibiting protein synthesis bacteriostatic?

*Because the cell can stay alive without protein synthesis, but only, it won't be able to replicate.

- Why do Aminoglycosides produce bactericidal effect while they work by inhibiting proteins synthesis?

*Actually and although they have been discovered for a long time, Aminoglycosides' mechanisms of action are still poorly understood (in fact, they're not protein synthesis inhibitors but we will stick with what is written for now).

- What would happen if we increase the concentration of a bacteriostatic drug?

*It will be produce bactericidal effects.

- Mainly, concentrations of the drugs in the patient's blood are what determine the produced effect. So, if the concentration of a bacteriostatic drug is increased and exceeds the steady-state concentration, it'll become bactericidal (and might touch the toxicity line).

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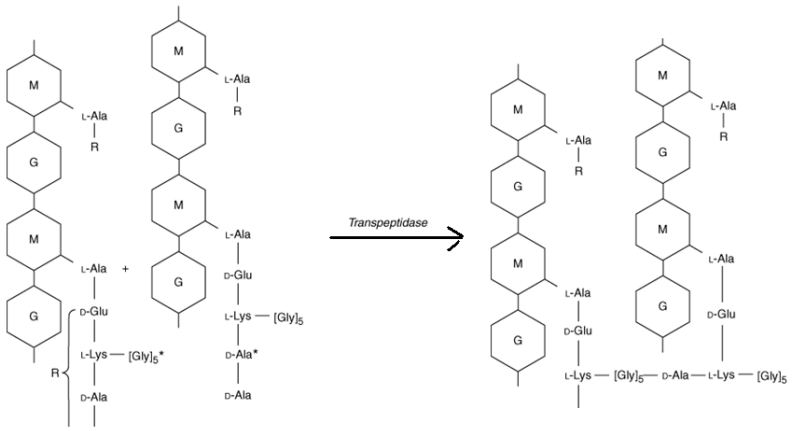
Cell wall inhibitors are:

Penicillins, Cephalosporins, Monobactams, Carbepenems, and Vancomycin.

- All cell wall inhibitors inhibit an enzyme called **Transpeptidase**. Normally, Tranpeptidase binds to the last D-Alanine in order to make cross-linking and join the blocks together towards cell wall synthesis. These drugs bind to the active site of Transpeptidase and inhibit it. The cell wall won't be completed and some pores will appear, subsequently, cause explosion to the cell (-cidal effect).

*Don't worry about these mechanisms because the Doctor said that his questions would be mostly about clinical cases not about mechanisms.



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The main forms of Penicillins resistance:

1- β-lactamases (penicillinases): the production is particularly important in staphylococci, but they are not made by streptococci.

* 90% of staphylococcus species produce β-lactamases.

- One of the ways to overcome the problem is the development of β-lactamase **antagonists** such as **clavulanic acid** which is a suicide inhibitor of the enzyme, and by this, we combine clavulanic acid with certain types of penicillins to treat the infections caused by staph species.

2- Reduction in the permeability of the outer membrane in gram-negative bacteria: most of gram -negative bacteria are resistant to unmodified penicillins. There are some modified types of penicillins (E.g.: Amoxicillin & Ampicillin) that can penetrate gram-negative's cell wall/outer membrane, and thus, are effective against gram-negative via this mechanism.

3- Mutations to the penicillin-binding proteins: As in **MRSA (Methicillin-resistant-staphylococcus-aureus)**: in this form, mutations happen to penicillin-binding-proteins, so whatever types of (penicillins, Monobactams, cephalosporins… etc) you use for treatment, they won't be effective. The drug of choice in this case is **Vancomycin** because its binding proteins are different from binding proteins (that are defected by mutations) for other cell wall inhibitors.

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We will start with penicillins:

Penicillins

- First & oldest class of penicillins: penicillin G and penicillin V (1940s, 1950s, 1960s):

- They are used mainly against gram-positive (mainly against streptococcus pneumonia and streptococcus groups A (pyogenes), B, C, D and some staph species).

1- **Penicillin G**

- Penicillin G is used specifically to treat **gram-positive** infections (S.pneumonia, pyogenes infections). It has a limited activity against gram-negative, active only against Neisseria species (Gonococcal infections (N.Gonorrhoeae), N.menigitidis) and some other species (E.g.: Treponema palladium). So, other types of gram-negative (Salmonella, H.Influenzae, Klebsiella, E-coli) cannot be treated with this penicillin.

- As an exception regarding gram-positive, penicillinase-producing S. aureus (E.g.: MRSA) isn't affected by Penicillin G.

- Notice that penicillin G is only administrated intravenously or intramuscularly NOT orally, because it's sensitive to the stomach's acidity.

- Penicillin G is susceptible to β-lactamases that attack β-lactams, and thus, inhibiting all of the penicillin G.

- Clinically, what are the main uses of penicillin G?

*Actually, Penicillin G has lost most of its clinical uses against staph species (because there are better drugs to be combined with clavulanic acid which are amoxicillin and ampicillin), but we use it in the definitive therapy against infections caused by strep species such as (**pneumonia** (community-acquired), **otitis media** (التهاب الأذن الوسطى), **meningitis**, and **septic arthritis** (التهاب المفاصل), **Cellulitis)**. The reason why we use it is that we tend to use the effective antibiotic with the narrowest possible spectrum.

- Am I allowed to use penicillin G as an empirical therapy against streptococcus pneumonia?

*No, because: 1. Pneumonia can be caused by bacteria other than strep (like **H.Influenzae**) 2. In general, bacteria have developed a wide range of resistance against penicillin G, thus, there is high possibility for the treatment to be ineffective. (same story with meningitides species, we cannot use penicillin G empirically with them)

- Name a case in which we can use penicillin G as an empirical therapy.

*In cases of **pharyngitis**, because they're mostly (up to 95% of the cases) caused by streptococcus pyogenes which haven't developed any resistance against penicillin G. Actually, in cases of pharyngitis, we use penicillin G exclusively in both definitive & empirical therapies.

- Notice that using penicillin G in some cases doesn't mean that it is the drug of choice there, as in pneumonia, otitis media and meningitis because they can be caused by other types of bacteria resistant to penicillin G.

- Note: regarding cellulitis (skin infection): although it's caused by streptococcus pyogenes, there are better antibiotics other than penicillin G that can be used, simply because they have more penetrating ability through the skin.

- Other clinical uses (definitive & empirical): **Streptococcal pharingytis, N.Gonorrhea**, **Clostridium tetani, Corynebacterium diphtheriae, Treponema pallidum** ((السفلس) يسبب مرض الزهري).

Uses of penicillin G in prophylaxis therapy:

- We said that with most cases of strep- species infections, penicillin G is a good choice. But what if I want to cover someone (for example until he becomes 21 years old) from developing serious infections by strep-?

* We combine penicillin G with **benzathine** to have (**benzathine penicillin**) which is given intramuscularly and this will provide us with a prolonged action (as if we want to protect the patient during his childhood from developing serious streptococcal infections which might develop to Rheumatic fever or problems in the heart or the kidney). **Examples**:

1- You can give the injections (1.2 million units) once every 3-4 weeks against β-hemolytic streptococcal pharyngitis (also to prevent streptococcal infections (prophylaxis) that might develop to Rheumatic Fever).

2- In syphilis, we give (2.4 million units) once every 1-3 weeks (from a week up to a month); as in cases of prophylaxis, when we want to cover the patient over a year or more, we give it once monthly. But in treatment, we give it weekly.

*If you compare the two examples, we use a larger dose in shorter intervals in the second one because in syphilis, we need to build up more concentration of the antibiotic because it has a higher MIC (minimal inhibitory concentration).

2- **Penicillin V**

- Is another type of penicillins which can be given orally. It's active against strep, gonococcal.

- In cases of streptococcal pharyngitis (not serious types but mild ones such as **tonsillitis**, **bacterial sore throat)**, there is no need to give the patient an injection. Alternatively, we give him 500 mg of penicillin V four times a day for 8-10 days (don't memorize the numbers).

- Penicillin V is used a lot in **Dentistry** and the brand name of it is **Dalacin C** (although I found Dalacin C to be a brand name of clindamycin (macrolide)). :/

- The importance of penicillin V in dentistry (most prescribed drug) is coming from its activity against anaerobic microorganisms, and under the teeth, the microorganisms are mostly anaerobic. Additionally, it has a narrow spectrum. Examples of odontogenic (سنّيّة المنشأ) infections are:

1- Post extraction infection (بعد الخلع).

2- Pericoronitis: is an inflammation of the soft tissues surrounding the crown of a partially erupted tooth (not important).

3- Salivary gland infection.

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- Second class of penicillins: β-lactamase-resistant Penicillins:

- They include: **(cloxacillin, floxacillin, oxacillin (cloxafloxaoxa) + Methicillin): D**

- Methicillin isn't available anymore because it causes nephrotoxicity, but it's still of high importance due to the type of bacteria named accordingly (MRSA).

- After the first class and before the discovery of clavulanic acid, the development of this class has taken place.

- Do we still use these drugs clinically nowadays?

*No, because they have the same spectrum of activity as penicillin G and are less potent. They were used in 60s and 70s before the discovery of clavulanic acid. **Oxacillin**, for example, is rarely found in Jordan and the others are not found.

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Third class of penicillins: Extended spectrum penicillins (amoxicillin and ampicillin):

- (Remember the second mechanism of resistance regarding gram-negative): here, we have changed the structure of previous classes of penicillins in order to make them able to penetrate gram-negative's outer membrane.

- Ampicillin and amoxicillin are among the most useful antibiotics for treating children suffering from infections caused by sensitive gram-negative aerobic bacteria, enterococci (E. faecalis + E. faecium), β-lactamase-negative H. influenza, and E-coli (so as we can see, β-lactamases can be produced by gram-negative bacteria).

- Amoxicillin is much well absorbed than ampicillin and is a prodrug for ampicillin (Amoxicillin needs activation in order to be an active ampicillin). Other than that, there is no difference between them.

- The Doctor advised us to read about β-lactamase-producing-gram-negatives (E.g.: Klebsiella, E-coli) because they are of an importance in the future.

- Amoxicillin activity = penicillin G activity + pre-mentioned gram-negatives (enterobacteriaceae family (E. faecalis + E. faecium, salmonella, shigella), H. influenza, and E-coli).

- Important note: the only antibiotic that can be taken with food is amoxicillin due to its very good absorption.

- Amoxicillin is very popular. Actually, most people take them.

- Clinical uses of amoxicillin: it's widely used orally in the treatment of upper respiratory tract infections and upper RTI (sinusitis, tonsillitis, pharingytis & otitis). **Why**?

*Because most causes of RTIs are streptococcus (pyogenes + pneumonia) and H.Influenzae (gram-positive + gram-negative), which are all covered by the spectrum of amoxicillin.

Sorry For Any Mistake

"Carelessness or overconfidence is foreshadowing someone's downfall"