PHARMACOLOGY

◉ Sheets ○ Slides

Number: 14

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Subject: Cell Wall Inhibitors

Doctor: Malik Alzohlofs

◘ Dear Colleague:
- Through this sheet we shall cover the second lecture for Dr.Malik for Antibiotics.
- The slides will be very convenient for studying this lecture if you have st udied this part (the lecture's subject) in Microbiology well!
- For more detailed Info. You can refer to ' Basic & Clinical Pharmacology by Katzung, 12 edition: from pages 790-796 '.
- You should know that some of the things written in this sheet are NOT f or memorizing, but more like to get the concept out of it.

◘ Before we start the lecture's subject; let's re-call few things we might n eed ahead of us. (You can skip this part if you want)

* Two main types of Bacteria depending on how they interact with the gr am stain ;

1- Gr+ve Bacteria : those include the following 7 members :
• *Streptococcus*
• *Staphylococcus*
• *Enterococcus*
• Bacillus (spore-forming rods)
• Clostridium (spore-forming rods)
• Corynebacterium (non-spore-forming rods)
• Listeria (non-spore-forming rods)

2- Gr-ve Bacteria : basically it includes the rest of Bactria , like :
• *Neisseria*
• *Moraxella*
• *E.coli*
• *Salmonella*
• *Shigella*

P.s : Re-call that *Mycoplasma* don't have a cell wall ; so they are neither G r+ve nor Gr-ve .

* Re-call the three types of antibacterial chemotherapy (sheet 13 /Pharm a) :
• Narrow-spectrum • Broad-spectrum • Extended-spectrum

* There are four major needs a drug is prescribed according to it : (the use of antimicrobial chemotherapy falls into one of these general categories)

• Prophylaxis therapy • Empirical therapy • Definite therapy • Post-treatment suppression therapy (sheet 13 /Pharma)

◘ Now we start :D ~

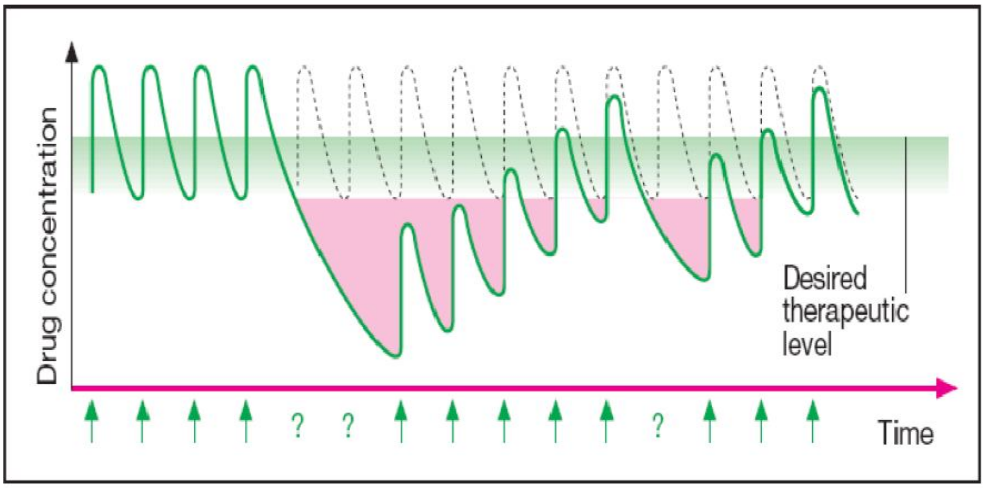
* After we have blown-up the **Green-Mucus Myth** , we are at point where we ought to understood that **Antibiotics** don't act on **viral infections** .

- So the next time your patient shows up at your clinic you have to tell him that! (Check the figure on Slide11) He would then understand that it takes time to get over such viral infection and **NO** need for an antibiotic! (Of-course in some cases we give treatments for viral infections; mostly known as ' Antiviral agents ')

* Why is an Antibiotic Misuse give arise to problems?

1- Antibiotics become less effective and may not work the next time you use them.

2- Improper use of antibiotics leads to more antibiotic resistant bacteria. (Remember when we talked about pharmacokinetics ; the Dr warned us from patients who don't stick to the dose given to them for treatment ; some tend to stop taking the antibiotic as soon as the feel better about themselves ; causing that drop in the **Desired Therapeutic Level** ; the thing th



at will give space for resistant bacteria to arise !)

3- Antibiotic resistant bacteria can be spread throughout the community and from person to person.
(So remember when the Dr has said that someone's misuse of an antibio tic is not only a problem for that individual ; cause when that bacteria bec omes resistant ; simply it won't stay in that host ; it will start to spread ca using more infected individuals due to that new resistant Bacteria !)

* We have already discussed three types of therapy before (Prophylaxis, Empirical, Definite), which leaves us with the last one:

- **Post-treatment suppression therapy**: When drug is prescribed after th e treatment of a certain condition in the patient to prevent the arising of another pathogen. These patients have a high *load* of bacteria
(Remember when the doctor said that women after delivery might have UTI and it could affect her 4 times in a year, she has a high load of bacteri a, she is given a certain treatment to cure her. After she is cured; she is gi ven a low dose of antibiotic to **suppress** the arising of other bacteria again ! /decrease bacterial load)
What about producing resistance? The benefit is more than the risk, you have to solve the problem.

Post treatment suppression therapy is taken for a long period, while pro phylactic therapy is taken for short time like before surgery.

* **Bacterial resistance mechanisms** (Already covered in Microbiology)

- The spontaneous rate of mutation in bacteria is very low; about 1 in 10 million cells per division will be a mutant!

- Four main mechanisms of resistance include:

a. Production of an enzyme that in-activates the drug.
(B-**lactamase**; we ought to know that there are types of it. The most com mon one was known to be against Penicillin; so was named **Penicillinase**. There is more complex type that is appearing nowadays and pushing agai nst the Antibiotics known as **Extended-spectrum-B-lactamase.** Now; with c ontinuous usage of **Cephalosporins**; Bacteria is developed enough to prod uce more new enzymes. Note that these new enzymes are even no more linked only to Gr+ bacteria; as Gr- has now the ability to produce B-lacta

mase like *Klebsiella* & *H-Influenza*! Pay attention that those Gr- bacteria ar e not producing **Penicillinase**; rather than producing that new enzyme kno wn as **ESBL** ' **E**xtended-**S**pectrum-**B**-**L**actamase ', it is extended to include t he **Cephalosporins** as well as Penicillin which is of course covered too. Not e that the phrase Extended is used here to describe the spectrum of the e nzyme against the Antibiotics!

Again, B-lactamase; an enzyme that Gr+ bacteria were known to have it; t hat had the ability to work against Penicillin. But with more usage of Anti biotics especially Cephalosporins, even Gr- are now capable of producing such an enzyme that was modified to the new enzyme known as **ESBL**.

b. Mutation in the target macromolecule for the Antibiotic (Receptor). (What happened is that a mutation caused a structural change in that rec eptor making it inappropriate for an Antibiotic to attach. We took **MRSA** ' ***M**ethicillin **R**esistant **S**taphylococcus **A**ureus* ' as an example in Microbiolo gy when it changed its binding site for Penicillin & Cephalosporins; so the y are of no use against it! Leaving only Vancomycin as an active antibiotic against it.)

c. Induction of mechanisms to reduce accumulation of the drug. (Pumping the antibiotic out of the cell, like against ***Tetracycline***. To imagin e this function; re-call MDR-1 receptor found in the intestine from pharm acokinetics lectures). > No buildup of antibiotic in bacterial cell

d. multiple drug resistance involving all these mechanisms, which is the worst!

* Antibacterial Chemotherapy:

Let us mention the main molecular targets for antibiotics:

A. External integrity of bacterial cell

- Cell wall synthesis; 5 types: • Penecillins • Cephalosporins • Monobactam • Vancomysin • Carbapenems

B. Protein synthesis: • Tetracycilnes • Aminoglycosides • Macrolides • Clindamycin

C. Perturbation of nucleic acid synthesis

- Inhibition of the synthesis and function of folic acid:

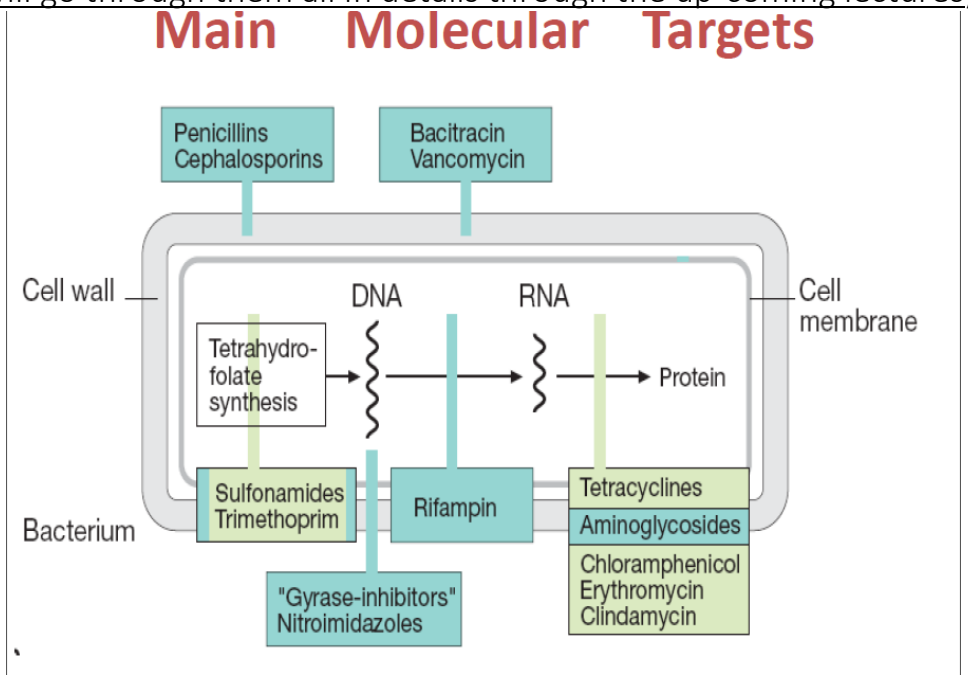
• Sulfonamides • Trimethoprim

- Inhibition of DNA gyrase (works just like DNA topoisomerase II in humans; which is related to the un-coiling of the DNA during replic ation):

• Fluoroquinolones • Nalidixic acid

- Inhibition of RNA polymerase: • Rifampicin

(We will go through them all in details through the up-coming lectures)



* You should know that Antibiotics are either **Bactericidal** (killing the bacteria) or **Bacteriostatic (inhibiting** the bacteria's replica tion).

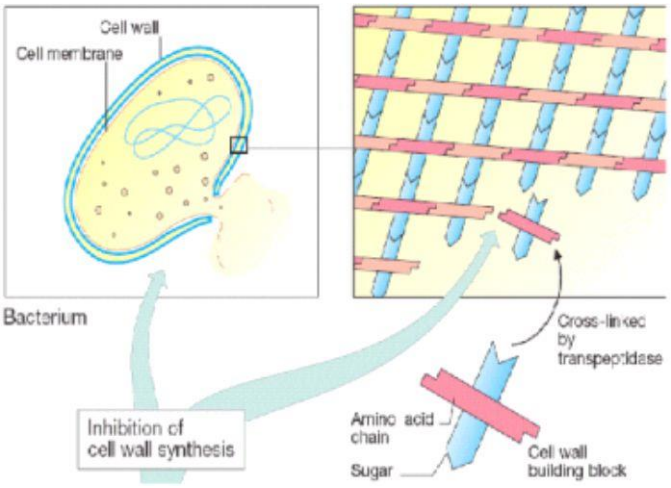
- The ones in greenish color are **Bacteriostatic**. (Protein-synthesis inhi bitors except Aminoglycosides, are bactericidal)
- The ones in bluish color are **Bactericidal**. (Affecting the cell wall + Rif ampin + Gyrase-inhibitors)

* Slide num. 19 is just to understand why do we study the antibiotics ; it's because there are hundreds of them; so in order to understand how to deal with them & how to choose from them for our treatmen t.

Cell wall inhibitors:

* Five groups: • Penecillins • Cephalosporins • Monobactam
• Vancomysin • Carbapenems

- Penicillin is the oldest then Cephalosporin then Vancomysin then Monobactam then Carba penems!
- Known to have a very good bactericidal activity.
- Most antibiotics are from cell wall inhibitors family cause we usually need the bactericidal activity in our treatment (a reason why cell wall inhibitors are more commonly used than protein synthesis inhibitors ' bacteriostatic ')



* Penicillin :

- This graph sums it up for penicillin's mechanism of action on Bacteria .
- Penicillin works on inhibiting the cross-linking at the final stage of cell wall synthesis; so the cell wall remains un-linked; and the osmolality dysfunction occurs leading to the rapture of the cell and its death.
- The main site for its work is **transpeptidase.**

- Let us talk pharma now:
We shall discuss 4 classes in the penicillin divided by the Dr; which are:

1. Penicillin G & V
2. Methicillin & flucloxacillin & Oxacillin
3. Amoxicillin & Ampicillin
4. Ticarcillin & Piperacillin

• **Penicillin G;** discovered by Alexander Fleming, The oldest and the first drug!

- Its spectrum: it covers 90% of Gr+ (except for *Staph. aureus*) + *Nei sseria* from the Gr- ***Neisseria meningitis*** & ***Neisseria gonorrhea***.
- Clinical use *FOCUS*:

What diseases are caused by Gr+?
Generally a LOT! Like; pneumonia, sinusitis, otitis media.

- Keep this in mind; as a physician you ought to prescribe the narrowest antibiotic (Why ?) because we don't want to disturb the normal flora in our bodies!

- Where to use Penicillin G?

Empirically; Treatment for beta–hemolytic streptococcal pharyngitis.
Definitely; Treatment for infections that include pneumonia, otitis media, meningitis & s eptic arthritis.
It is used mostly in the definite therapy (Why?); because it is not a wide spectrum antibiotic, it's narrow!

- Check this: in the last lecture we said that pneumonia (lower respiratory ' community acquired ') is caused by 6 different microorganisms!

Q: Is it wise to prescribe Penicillin G for a patient who has pneumonia *empirically*?

A: Of-course NO . (Why?) You ought to know that Penicillin doesn't cover all these micro organisms in the box (It doesn't work empirically on them all at once)!! Only when the lab culturing tells you that it is caused by ***S.Pneumonia;*** you can then prescribe Penicillin G *definitely* for your patient.

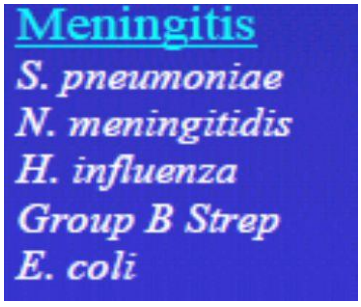
Q: Can I prescribe Penicillin G for a patient who showed at my clinic with meningitis *empirically*?

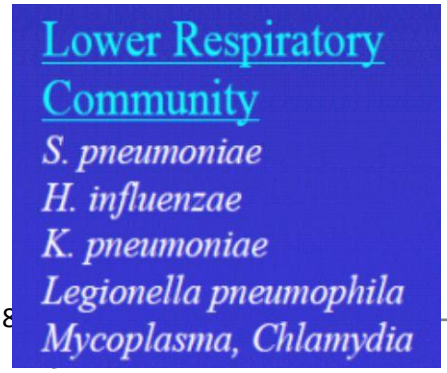
A: NO. (Why?) Just like the first case!

Q: What would you do if a patient came to you with **streptococcal pharyngitis** (also known as 'Strep. throat')?

A: You prescribe Penicillin G for him, with no need for culturing even; *empirically*!

- Streptococcal infection is linked with **rheumatic fever** (happens when the body produ





ces antibodies against the cell wall of the strep. when the body is infected ; the bad news is that those antibodies may recognize some cells in the connective tissue as foreigners and attack them ; 'autoimmune attack' & it could be lethal on the heart's valves level !)

Q: How can we deal with this?

A: If a patient is diagnosed with a streptococcal infection; and then develops rheumatic fever (commonly in the age of 4-14 years-old); this patient must **NOT** have another streptococcal infection. (Why?) Cause the next time; the antibodies released against the *streptococci* that got into the body will attack the patient's body cells too. (Treatment?) Prophylaxis! ; I must 'prophylact' my patient with an antibiotic (what is the narrowest antibiotic here for streptococcal Infection?) which will be Penicillin G. He'll need an injection every day

Q: How to overcome the long time course for the injections of penicillin that my patient needs (this process needs to be continuous from the day he/she is diagnosed of rheumatic fever till 21 years-old) to take ?

A: Simply by increasing the **Half-Life** of Penicillin G. (How?) By mixing it with other material making colloids. So we use **Benzathine penicillin** given i ntramuscularly IM & given once every 3-4 weeks. (Sustained release)

- The Dr mentioned in section 1 that people in India are *genetically* more susceptible for rheumatic fever infection than here in Jordan!

In India, strepto pharyngitis treatment is Penicillin injection, In Jor dan, it is Penicillin V - which is taken orally -

- Only one cause for **syphilis** , **tetanus** , **diphtheria** are known (each i s different) ; and you should know that Penicillin G is the antibiotic we use to cure the patient of these three medical conditions ; given as an injection ! (Though; it is worthy to mention that in your career you might not encounter these three; as the first is kind of rare here in Jordan, and the other two got vaccines against them)

- Note: don't forget to go through the slides too, while studying the sheet! : D

• Penicillin V; known to be more acid stable, orally active yet less potent than penicillin G. Also, it is used in the oral infection where it is effective against some anaerobic organisms.

- Spectrum: *Streptococcal pyogen* & *Streptococcal pneumonia* + An aerobes + *Neisseria Meningitis* & *Neisseria gonorrhea*.

- How can we benefit from it?
You can use it against streptococcal pharyngitis (strep. throat) which is as common between kids as discussed earlier as pills, instead of using Penicillin Gas injections. About the dosing, if an adult; then 4 times a day with 500mg each! Kid of–course differ in the dosage!

Q: Based on a true event ; Jordan has ran out of its supply from Benzathine penicillin injection (the one that lasts for about 3-4 weeks in the body) , what can we do ?

A : Either the patient goes to the hospital everyday to get a normal penicillin G injection , or he can take penicillin V as a prophylactic therapy for 2 instead of 4 times a day orally which is more convenient of-course !

- Around the world but not in Jordan , Dentists usually prescribe Penicillin V for oral infections . (why?) As most of these infections come from anaerobes . Learn that odontogenic infections are the same as oral infections . (In Jordan , they prescribe Clindamycin)

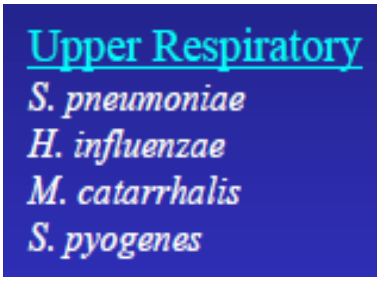
• Cloxa-Flucloxa-Oxacillin ' B-lactamase-resistent Penicillins '

- They were introduced after Penicillin G & V .

- Not present in Jordan & we rarely would en-counter them and yet even to use them clinically for a simple reason ; which is that we have produced the Clavulanic acid ; a compound which has the ability to inhibit B-lactamase .

- We mentioned them to say that one drug of this family which is Methicillin ; which was withdrawn back from use ; because of introducing one of the worst Gr+ bacterium known as MRSA! It is good to be aware that there has been cases related to infection with a type of bacteria known as VRSA ' *Vancomysin-Resistant-Staphylococcus-aureus* ' .

-Spectrum : *Strep*. & *Staph*. + *Neisseria Meningitis* –like Penicillin G.Amoxicillin & Ampicillin ' Broad Spectrum Penicillins '



-Ampicillin is usually taken as injections while Amoxicillin is taken orally & it's a pro-drug to Ampicillin , so you coul d say they are considered as one drug .

- Spectrum : Gr+ & Gr- .

Q: Why is *Enterococci* is more applied to the spectrum of Amoxicillin & Ampicillin than of Penicillin G ?

A: Bactria change over time and become more resistant to an antibiotic ; so nowadays , after about more than 30% of *Enterococci* which have become resistant for Penicillin G ; it is convenient to cut it out from its spectrum & to find another appropriate antibiotics to use against them .

Q: How can we enhance the spectrum of Amoxicillin & Ampicillin to include more types of bacteria ?

A: Joining them with B-Lactamase inhibitor ; mainly Clavulanic acid ! Making them more efficient against all H.Influenza & E.coli as an example. (What is it called?) Then the complex-drug will be known as Augmentin . *Refer to slide num. 32&33 to see how the spectrum got more wide by joining Clavulanic acid with them .

Q: What is a clinical use for that ?

A:* Joining the groups that the new spectrum has covered will help in *Empirical* therapy for the Upper Reparatory infections from this box . This Makes Augmentin the drug of choice & the narrowest for the upper respiratory infections (like; otitis media , sinusitis , tonsillitis & bronchitis).

* It can also cover the urinary Tract infections . So ; we can treat them *empirically* too !
The Dr. said that Augmentin here is a good/nice choice to be used ; but it's not the drug of choice for urinary tract infections for other several factors .

The End !
Sorry for any mistakes ..
GOOD LUCK ~•

◘ Study Smartly ; more than Hard ;D