



PHARMACOLOGY



☒ **Sheet**

☐ **Slides**

Number: 18

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Subject: Antibiotics (6)

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****This sheet was written according to the record that belongs to section 3.**

❖ Topics of this lecture:

Part (1), related to cell wall inhibitors:

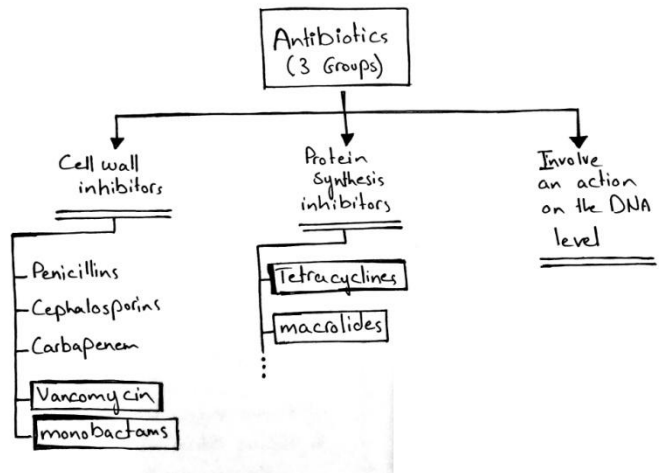
*The last part concerning vancomycin (the 4th member of cell wall inhibitors)

* Monobactams (the 5th group)

Part (2), the beginning of protein synthesis inhibitors:

* Tetracyclines

* Macrolides



Part (1), related to cell wall inhibitors:

❖ Vancomycin

*In the last lecture, the doctor talked about vancomycin, and ended up with the sentence "Ototoxicity and nephrotoxicity can occur due to the use of vancomycin". Is this true?

In fact, the incidence of this happening is very rare, but this information is always mentioned in books because back in the 1960s (till 1980s), vancomycin was used along with Aminoglycosides (particularly, Gentamycin)—as a combination (vancomycin to cover Gram +ve, and Gentamycin to cover Gram -ve)-. To be precise, these side effects are more linked to aminoglycosides, not vancomycin.

*After intensive studies concerning this subject, the following rule was introduced:

For treatment of MRSA and resistant Enterococci,

- In normal doses (10-15 mg /kg per day), vancomycin —alone— is not ototoxic nor nephrotoxic. (The incidences are very rare).
- If we increase the dose to 25-30 mg/kg per day (we have to do that in certain situations due to development of resistance), ototoxicity and

nephrotoxicity may occur with higher percentage, however, these are not very common side effects of vancomycin. (*ototoxicity is even less common than nephrotoxicity*)

→ In other words, ototoxicity and nephrotoxicity are very rare with monotherapy (vancomycin alone), more common when vancomycin is administered with other nephro- or ototoxins(*for example: gentamycin*).

*Currently, vancomycin is not given combined with gentamycin for many reasons.

*Risk factors (of ototoxicity and nephrotoxicity due to the use of vancomycin) include:

- 1) Renal impairment (if the patient that has renal impairment was given a dose of vancomycin without adjustment).
- 2) Prolonged therapy.
- 3) High serum concentrations.
- 4) Other toxic medications may exacerbate the effect of vancomycin.

❖ Monobactams

- The fifth group of cell wall inhibitors.
- The only member in this group that is actually used is **Aztreonam**.
- To make things easier, think of monobactams as if they are the opposite of vancomycin.

*Spectrum of Aztreonam:

Narrow spectrum, against Gram negative, including psuodomonas. It covers all aerobic gram negative bacteria, it doesn't have a great activity against anaerobes.

Remember:

Vancomycin → narrow spectrum, gram **positive**

*Clinical use of Aztreonam:

If the patient is allergic to penicillins and cephalosporines, and has an infection caused by a gram negative bacteria, the drug of choice will be Aztreonam (this is the only case in which we use Aztreonam).

Vancomycin → If the patient is allergic to penicillins and cephalosporines, and has an infection caused by **normal type staph. Aureus**.

*Side effects:

Disturbances of GI flora, and diarrhea may occur.

Part (2), the beginning of protein synthesis inhibitors:

❖ Notes concerning this group

- They are active against wide variety of microorganisms (broad spectrum)
- Most are bacteriostatic, but **Aminoglycosides are bactericidal**.
- Because of over-use, resistance is common.

These drugs have been really over-used because most protein synthesis inhibitors are oral drugs, so they are community drugs (used daily by people). *They are not hospital drugs, because in hospitals we want bactericidal antibiotics.*

→ this fact increased the chances of resistance. For example, most of the activity of Tetracyclines - a group of protein synthesis inhibitors - was lost due to the continuous use.

Remember:

Most cell wall inhibitors are injectable, examples:
Carbapenems, Monobactam, vancomycin, most (not all) penicillins, and most (not all) Cephalosporins.

- Bacterial ribosomes differ in molecular detail from eukaryotic ones enabling antibiotics to exhibit **selective toxicity**. Antibiotics, in general, target structures in bacteria different from those found in humans. Protein synthesis in prokaryotes is very different from that in eukaryotes, thus, giving these drugs **wide therapeutic index**.
- The main ribosomal processes (main targets) that these drugs interfere with are:
 - 1) Binding of aminoacyl-tRNA
 - 2) Normal codon:anticodon recognition
 - 3) Transpeptidation
- Tetracyclines work by inhibiting the tRNA carrying the amino acid to the codon.
Aminoglycosides (they are bactericidal) exhibit their action by many mechanisms, one of which is causing mismatch between the codon and anticodon which will lead to the insertion of an incorrect amino acid. And the peptide that will result is going to be different from the normal one.
- Groups of protein synthesis inhibitors include:
Tetracyclines, Macrolides, Aminoglycosides, clindomycin (or clindamycin) .

❖ Tetracyclines

- Tetracyclines are very old drugs, they have been over- and mis-used but they include one new member, that is Tigecycline.
- Members of this group include; Tetracycline, Methacycline, Moxycycline, **Doxycycline**, Minocycline, and **Tigecycline**.

It's enough for you to memorise only two members:

Doxycycline (an example of an old tetracycline).

Tigecycline (an example of a new tetracycline).

***Spectrum of tetracyclines- Generally, before the development of resistance:**

Their spectrum of activity is very wide and includes Gram-positive and Gram-negative bacteria, some spirochetes, and some protozoa (for example, amoebae).

***Spectrum of old tetracyclines (Doxycycline) in reality:**

- The spectrum covers *Bacillus anthracis* only from Gram-positive bacteria.
- The spectrum covers few gram negative bacteria
- The activity against most bacteria was lost (the spectrum does not cover staph, strep, H.influenza, klebsiella, E.coli, salmonella, shigella, and many others)
- What is left and that is included in the spectrum of the old type: **Chlamydia, Mycoplasma, Burrelia, Brucella, Rickettsia** (these five are the ones important to memorise). And **cholera**.

Generally speaking, the previously mentioned bacteria are not real bacteria; chlamydia and mycoplasma are atypical bacteria, burrelia (spirochete) is also different.

Note: in Jordan, we don't have Burrelia, that causes Lyme disease, nor rickettsia. Both are more common in US. So we'll focus on the other three:

- An old tetracycline is active against **Chlamydia, Mycoplasma, and Brucella**.

***Clinical uses of tetracyclines:**

- 1) Mycoplasma and chlamydial infections.
- 2) Treatment of brucellosis.
- 3) Doxycyclin is used for treatment of acne (حب الشباب).
- 4) They are great alternatives to penicillin G for treatment of syphilis because they have activity against Treponema.
- 5) They have a use related to Helicobacter pylori.
(the doctor said that we'll take this point concerning treatment of peptic ulcer later in the GI system).

***Back to the spectrum with more details, linking the spectrum to the clinical uses:**

- (1). **Chlamydia trachomatis** causes chlamydial urethritis (in both, males and females, but the type is different in females). This disease is common in western countries and is transmitted sexually. It's difficult to detect and treat such infection cause by chlamydia (many people may get infected by chlamydia without them knowing that).

The drug of choice in this chlamydial infection is Doxycycline (100 mg twice a day for 7 days). Note: in this subject, the doses are important.

How to treat any chlamydial infection??

100 mg twice a day for 7 days by Doxycycline.

(all chlamydial infections are susceptible to old -and new- tetracyclines)

- (2). **Mycoplasma pneumoniae**

The common causes of atypical pneumonia are: chlamydia, mycoplasma, and legionella

Tetracyclines do not cover legionella. Knowing this information, can tetracyclines be used as an empirical treatment for atypical pneumonia?

No, because we would be covering only 2 of 3 causes.

- As a **definitive** therapy, doxycycline can be used for treatment of atypical pneumonia. (after the culture results are back telling you that the cause of atypical pneumonia in your patient is mycoplasma for example).

Mycoplasma pneumoniae is a common cause of pneumonia in young adults and in people who live in close confines, such as in military camps. (it's known as the military camp bacteria because when it first appeared, it was common in military camps).

When a child (<5 years) comes with community acquired pneumonia, the first thing doctors do to know whether he has typical or atypical type is asking his mother if he goes to kindergarten, school,...

- If the answer is yes → we have to include mycoplasma as part of the problem.
- If the answer is no (the child mostly stays at home) → the child is more likely to have **typical** pneumonia (possible causes; strep, staph, H.influenza). we treat by cefuroxime or augmentin (back to lecture 3 of antibiotics).

Note: lyme disease and cholera can be treated by tetracyclins but are not very common in jordan, that's why the doctor did not talk about them in details.

(3). Brucella (can be found in jordan)

The drug of choice for treatment of brucellosis (الحمى المالطية) is always:

100 mg twice a day for 30 days (long-term and harsh treatment) of **Doxycycline** combined with 1g injection of Drug X for 7 days (we'll talk about drug X when we reach it, *it's an aminoglycoside*).

- Why must the treatment of brucellosis persist for such long period?
Because brucella is an intracellular bacteria (it's going to live within the cell, it's closer to being a parasite rather than bacteria, because it occupies the cell). That's why the treatment is different.
- The treatment is by giving a combination of high doses of antibiotics (the high dose will not be of doxycycline, the other drug (X) that we'll talk about later is the one given in high doses)
- Doxycycline is a key drug in treatment of brucellosis to make sure that reoccurrence will not happen in the patient.

(4). Acne

Treatment of acne can be by prescribing 100 mg of doxycycline twice a day, because doxycycline has a good activity against the bacteria causing acne.

(5). Syphilis

Again, doxycycline is an alternative to penicillin G in this case. (if the patient is allergic to penicillin).

Note: before we talk about macrolides after few points from now, it's important to know that the two group (tetracyclines and macrolides) share many similarities and have spectrums close to each other, for example, mycoplasma, chlamydial infections and syphilis can also be treated by certain macrolides. *But tetracyclines are cheaper.*

***What about resistance against tetracyclines?**

- **Old** tetracyclines : bacteria developed resistance against them.
- This resistance is due to a plasmid-mediated energy-dependant efflux pump (typical of the multiple drug resistance type). The up-use and mis-use in the 60s and 70s caused the bacteria to become able to pump out the tetracycline.
 - Tetracyclines became ineffective against most gram-positive and most gram-negative (except **the important 5—*mycoplasma, chlamydia, rickettsia, Burrelia, Brucella-* and **treponema**** we mentioned before, these are still sensitive towards tetracyclins).
- All tetracyclines are substrates for the pump we talked about above except Tigecycline (the new member).
Tigecycline was designed in a certain way so as not to be a substrate for the pump.
→ thus, in this drug, we gained the wide spectrum activity back (includes Gram-positive and Gram-negative bacteria, some spirochetes, some anaerobes, and some protozoa (for example, amoebae)).
- Tigecycline is a great drug, but always keep in mind that it's bacteriostatic (not used in life-threatening situations).
Note; in cases where brucellosis is life-threatening, we use a bactericidal drug.
- Although we said that tigecycline is a great drug (with wide spectrum of activity), it's not used due to FDA warning, why?
Treatment by tigecycline increases the mortality rate (the cause isn't known), that's why it's not a popular drug.
If 100 patients with community acquired pneumonia were treated by tigecycline, and another 100 were treated by another antibiotic, the mortality rate within the group treated by tigecycline is higher.
Doctors think 100 times before prescribing a drug like tigecycline.

Note: a bacteriostatic drug causes bacteria to become static. Then, the immune system is what gets rid of the infection "it's all about the immune system".

→ Never think about using a bacteriostatic antibiotic in immunocompromised patients (for example, cancer patients and patients taking immuno-suppressants) because using bacteriostatic drugs requires the help of a strong immune system.

***Other pieces of information we need to know about tetracyclines:**

- All Tetracyclins chelate (bind to) divalent (+2) and trivalent (+3) metal ions (examples: Ca^{+2} , Al^{+3} , Mg^{+2} , Fe^{+2} ...) forming insoluble complexes. Absorption is decreased in the presence of milk, antacids, and iron preparations (don't take any of these with tetracyclines to avoid food-drug interactions, *if you have to, keep a 2-hour period of separation*)
- The most common side effects –which you should tell the patient about- are GI disturbances in **normal** situations due to modification of gut flora. In addition, Doxycycline and Tetracyclines in general- cause direct irritation (4-5% of patients suffer from severe heart burn and irritation).
If a patient took doxycycline and he suffered from heart burn, we must immediately stop the drug.
→ Due to the previous side effects, we don't prefer using doxycycline in reality, another reason is the presence of alternatives to doxycycline in most cases, but we study these drugs because alternatives are not always available (*for example; no alternatives in treatment of acne*).
Another thing we should know is that tetracyclines are the cheapest drugs ever (UN cares about them due to their use in refugee camps).
- Tetracyclines are deposited in growing bones and teeth causing staining and sometimes dental hypoplasia and bone deformities.
→ Tetracyclins shouldn't be given to (they are contraindicated in) **children, pregnant women and nursing mothers** (because they can be transferred through milk to the newborn causing problems).
Tetracyclines may also cause liver problems (hepatotoxicity) in pregnant women (not the fetus. In the fetus, they may cause problems related to bones and teeth like bone deformities).
They have dual contraindication in pregnancy.

- A rare side effect of tetracyclins is phototoxicity. For example; severe sunburn occurs when the patient receiving a tetracycline is exposed to sun or UV light (common in individuals who tan a lot).

The next point is important to dentistry students not medical students, Dr. Malik said that it's an extra information (not to be memorised):

- Tetracyclines –in particular, low doses of doxycycline, **in adults**- can be used for the treatment of ANUG (Acute Necrotizing Ulcerative Gingivitis), which appears with stress. College students can get it during finals.

Note that although we said that the side effects of doxycycline include being harmful to teeth and causing deformities, it's used for treatment of gingivitis (because it has a very good penetration under teeth).

❖ Macrolides

** protein synthesis inhibitors, bacteriostatic.*

*Members include; **Erythromycin**, **Clarithromycin**, **Azithromycin**, and **Telithromycin**.

* **Erythromycin**, **Clarithromycin**, **Azithromycin** are not considered the same drug, they are 3 different drugs.

***Erythromycin** has a different spectrum compared to **Clarithromycin** and **Azithromycin** (clarithromycin and azithromycin share similar spectrums)

*Telithromycin is a new member, it's a good drug but it's related to certain problems.

- One of the people who were against the use of this drug said: "how does one justify balancing the risk of fatal liver failure against one day less of ear pain?"
→this means that if I want to treat otitis media (ear pain) with telithromycin, this may increase the risk of the patient getting fatal liver failure.
- Dr. Malik asked us all to read about this drug and provided us with a link that might be useful.
(http://www.nytimes.com/2006/07/19/health/19fda.html?_r=0).
The Dr. also said that he'll talk about this drug in the next lecture.

*we said that erythromycin, clarithromycin and azithromycin are different drugs. We'll begin talking about azithromycin and clarithromycin together, then erythromycin.

***Spectrum of Azithromycin (and to a lesser extent, Clarithromycin):**

- A little bit close to the spectrum of tetracyclines and includes:
 - 1) **Chlamydial infections**
 - 2) **Mycoplasma pneumonia**
 - 3) **Syphilis**
(the previous three are included in the spectrum of tetracyclines)
 - 4) **Legionella**
- Chlamydia, mycoplasma, and legionella are causes of atypical pneumonia.
→ Causes of Atypical pneumonia are covered by macrolides (all macrolides but the best one in this case is Azithromycin (Azithromax), *max because it covers every thing*).
- In addition to chlamydia, mycoplasma, legionella, Azithromycin - and to a lesser extent, Clarithromycin- have a great activity against:
Strep.pyogens, strep.pneumonia, moraxella.catarrhalis, H.influenzae
(these four are the causes of upper respiratory tract infections).

***Clinical uses of Azithromycin (and to a lesser extent, Clarithromycin):**

Both are bacteriostatic drugs that can be used to treat:

- (1). Atypical pneumonia (lower respiratory tract infection)
Because they have activity against **chlamydia**, **mycoplasma** and **legionella**.
- (2). Upper respiratory tract infections
Because they have activity against **Strep.pyogens**, **strep.pneumonia**, **moraxella catarrhalis**, **H.influenzae**
→ Azithromycin is a great alternative to augmentin and to zinat.

→Till now, we've learned that *Amoxicillin with clavulenic acid*, *cefuroxime* (a second generation cephalosporine), and *Azithromycin* can be used in the treatment of upper respiratory tract infections. (their trade names respectively; Augmentin, Zinat, Azithromax)

Why is the use of Azithromax in treatment of upper respiratory tract infections so common?

Because in many cases, we don't prefer sending the child to get a skin test to see if he has allergy to penicillins, so from the beginning we give Azithromax (oral, liquid).

Note that we use Azithromax for treatment of upper respiratory infections in **normal** situations (not life-threatening situations) that's why we can give bacteriostatic drug.

(3). (this point was mentioned in section 1)

(back to slide #3):

- Chlamydia, mycoplasma, legionella, strep.pneumonia, H.influenza, are 5 of the 6 possible causes of community acquired pneumonia (ignore klebsiella for now)

These 5 are all covered by azithromycin (azithromax).

- In reality, Azithromax is the drug of choice in treatment of community acquired pneumonia (empirically before we figure out if it's typical or atypical) because azithromax covers the possible causes (typical and atypical microorganisms).

- Why did we accept Azithromax as an empirical treatment in this case although it doesn't cover klebsiella which is one of the possible causes of community acquired pneumonia?

Because if pneumonia (lower respiratory tract infection) is caused by Klebsiella, it will be obvious because the infection will be very severe and the condition of the patient will be very bad.

Another reason is because community acquired pneumonia due to klebsiella is very rare (1% of cases).

That's why we can exclude klebsiella as a cause of normal (not severe) community acquired pneumonia in which Azithromax covers the other 5 causes.

- All over the world, if a patient comes with community acquired pneumonia and his condition is stable (**doesn't need hospitalization**) the drug of choice is : Azithromycin (Azithromax). But if the patient does need hospitalization which means a life threatening situation, we don't give bacteriostatic antibiotics, that's why we won't give Azithromax.

***Spectrum of Erythromycin:**

- Generally has activity against Gram-positive bacteria(*strep, staph*)
- Doesn't have an activity against Gram-negative bacteria (like H.influenza).

That's why Erythromycin is excluded from the treatment of Upper respiratory tract infections EXCEPT **strep throat**.

- In the case of strep throat (caused by *strep.pyogens*), Erythromycin can be considered as an alternative to penicillin G.

➔ If a patient has strep throat and is allergic to penicillins, the drug of choice is Erythromycin.

(one of the questions in USMLE)

Note (was mentioned in section 1): we can give cephalexin – a first generation cephalosporine-, but if the patient is also allergic to cephalosporins (or if we don't want to carry out the test to see if he is allergic to cephalosporines or not), we can from the beginning give Erythromycin.

***Dr.Malik ended the lecture with the following question:**

If a pregnant lady has a chlamydial infection, should we treat her by tetracyclines or macrolides?

The answer:

Macrolides

The dose: ??

(the Dr. asked us to look up the answer (the dose=??) and said he'll explain this point in the next lecture).

I apologize for any mistake I may have made.

Wish you all best of luck : D