



☒ Sheet

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number : 14

doctor : Malek

done by : Abdullah kadi

correction : Fahed Al karmi

Protein Synthesis Inhibitors: A group of drugs that are divided into: Tetracyclines, Aminoglycosides, Macrolides and Clindamycins. Tetracyclines was a great drugs group in the 1950s and 60s but the bacteria has developed resistance against them. So for once, we **will not** see a bacteria that is really sensitive towards all kinds of drugs; Tetracyclines, Minocyclines, Doxacyclines. They're not really working against Gram positive and Gram Negative Bacteria, and that's because the bacteria -most of them- has developed a protein which we call a **Pump protein**, which pumps the drug out of the cell. So generally speaking, most of the Gram Positive and Gram Negative Bacteria are **not susceptible** towards Tetracyclines. That being said, what's the real value of Tetracyclines in life? The answer is that there are types of Bacteria called '**Atypical Bacteria**' and these types of Bacteria are tiny and they, generally speaking, **don't have a normal cell wall**. So when you stain them they remain colorless.

There are three kinds of Atypical Bacteria :

1- Mycoplasma

2- Chlamydia (The most common cause of sexually and non sexually transmitted Urethritis)

3- Legionella (We classify this one as Gram Negative although it's an Atypical Bacteria which doesn't have a normal cell wall to stain. But when we use a gram stain it remains colorless, so we stain it with other types of stains).

So what's the importance of these Atypical types of Bacteria? They **do not develop the protein pump** that pumps out the Tetracyclines out of cell. So they're **sensitive against Tetracyclines** unlike other types of Bacteria. So if the patient has a Chlamydial infection or an infection by Mycoplasma Bacteria, Tetracyclines are a great choice, but they're **not** as great for Legionella bacteria. Rickettsia, in Rocky Mountains, and Lyme disease, in Nigeria, are also examples of Atypical Bacteria that are susceptible towards Tetracyclines.

How do we treat Chlamydia? Penicillins, Cephalosporins, Monobactams, Carbapenems and Vancomycins **are not active** against Chlamydia. **Doxacyclin** (250mg, twice a day for 5-7 days) is given to the patient to treat **Chlamydial Urethritis** or **Macrolides**, but we'll talk about this one later.

Another type of bacteria that is sensitive against Doxacyclin is **Mycoplasma Pneumoniae** which causes Pneumonia. However, there are 5 other causes of **Pneumonia**, which are:

2- Streptococcus Pneumoniae

5- Legionella Pneumophila

3- H. Influenzae

6- Chlamydia

4- Klebsiella Pneumoniae

So this drug **will not** cover all these 6 types bacteria, therefore, it shouldn't be used in **Empirical Treatments**. Meaning that I should not give this drug to any patient with Pneumonia **unless** I'm sure that

this patient has *Mycoplasma Pneumoniae* from the lab culture. Only then it will be a **Definitive Treatment**.

Mycoplasma is a **very common** cause of Pneumonia in young adults and in people who live in closed and confined areas; like Military Camps or Class rooms.

****P.S.:** We even call *Mycoplasma* '**Military Mycoplasma**' because it was originally found in Military camps and confined places as such.

Conclusion: we only use **Doxacyclines (or Tetracyclines)** as a **definitive treatment** when we're %100 sure that this Pneumonia is caused by *Mycoplasma Pneumoniae* bacteria (or Chlamydia).

USMLE Question:-A 4 year-old child who doesn't go to closed/confined places like School or Kindergarten has Pneumonia. What would the drug of choice in this case be? (Empirically)

Answer: Augmentin in the US, Zinnat in the UK.

However, if this kid goes to school this drug **would not** be of benefit to him/her; because Pneumonia Bacteria is everywhere in School/Kindergarten/University.

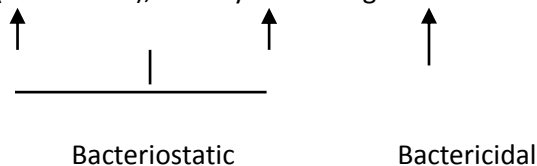
➤ **Back to Tetracycline**

Cholera is caused by *Vibrio Cholerae* and it is treated with **Doxycycline**. However, there is no single case of Cholera in Jordan so this information is unnecessary but just in case Cholera reaches Jordan you would know how to treat it. Same thing with *Rickettsia* and **Lyme disease** (a.k.a Nigerian Fever) but we don't have those as well, what we do have in Jordan is Chlamydia and *Mycoplasma*.

With **Acne** which is caused by *Propionibacterium acnes*, few years ago **Doxycycline** was used. But this is an outdated treatment for Acne, now we use **Retinoid (vitamin A)** to treat Acne. With **Syphilis** we previously said that we use **PenicillinG**. **Doxycycline** is considered another choice to treat Syphilis, but until today we treat it with Penicillin G or **Benzathine** intramuscularly.

- Now, we took in Microbiology that **we can't combine Bacteriostatic with Bactericidal antibiotics**. Why is that? Because Bactericidal antibiotics is more active on a **dividing cell**, and Bacteriostatic **stops cell division**. So basically one of them (Bacteriostatic) will stop the other.

But although this is true on paper, **in real life we actually combine Bacteriostatic with Bactericidal antibiotics in some cases**. Like for example to treat **Duodenal Ulcers** we take a 'triple therapy': Clarithromycin (Macrolides), Tetracycline + Augmentin.



Also, the treatment of **Brucellosis** by combining Aminoglycosides (Bactericidal) + Tetracycline/Doxycycline (Bacteriostatic)

Bactericidal + Bacteriostatic? Is that even possible?!

That is because this is only in theory, but as I said in real life you actually **can** combine Bactericidal + Bacteriostatic. But theoretically, we think that Bactericidal drugs will not give their full activity if combined with Bacteriostatic drugs. But it's been done a million times before, so don't worry ;)

➤ Peptic Ulcers

For now, you only need to know that we treat **Helicobacter Pylori** (The bacteria that causes Peptic Ulcers) with **Tetracyclines**. The rest will be explained in the GI System course.

➤ Brucellosis (الحمى المالطية)

How to treat Brucellosis? What's the difference between the treatment of Brucellosis and other infections? Brucella is a bit different from other bacteria. It lives **intracellularly**, so the treatment will be a bit different as well. Brucellosis is treated not for 3, 5 or 7 days; it's treated in **1 month with Doxycycline**, and that is because the bacteria lives intracellularly. Not just that, we also combine **Aminoglycosides** with it. Therefore, Brucellosis is treated with **combination therapy**:

IM injection of Gentamycin (an aminoglycoside) + Doxycycline for 7 days. After that we remove gentamycin injection and keep Doxycycline for 1 month.

The problem with Tetracyclines is that resistance to them is common and it's mainly due to the **plasmic mediated energy dependent pump typically of multi-drug-resistance type**. However, there's a new drug called **Tigecycline (aka tygacil)** (it was introduced to the market in 2007). What happened is that Pharmacists brought the **Minocycline**, improved it a bit and introduced a new drug out of it that **is not** a substrate for the pump (P Glycoprotein) in Gram +ve and Gram -ve bacteria. In other words, this drug **retained** the activity of Tetracyclines by not being a substrate for that pump. So now this drug is now active on **Gram +ve and Gram -ve (URTI and LRTI)**, but doctors and pharmacists don't like it because of its lethal side effects which will be mentioned in the next lecture.

➤ Tetracyclines Side Effects:

1- Food-Tetracyclines should not be taken with **Milk or Antacids which are sources of di or trivalent ions** (Aluminum Hydroxide, Magnesium Hydroxide, Iron) because together they'll create **insoluble complexes** that cannot be absorbed. If it's taken with Milk it's called **Food-Drug interaction**, while if it was taken with Antacids it's called **Drug-Drug interaction**.

2- The most common Side Effect of Doxycycline is that it is **very irritant** to the GI Tract (Burning Sensation). Later, it might lead to the modification of the gut flora.

3- They **shouldn't be used in Children, pregnant ladies and nursing mothers**. Why? Because it is deposited in growing bones and teeth causing staining and, sometimes, **dental hypoplasia** and **bone deformities**. It may also cause **hepatotoxicity** in pregnant woman.

4- **Photosensitivity**: Severe sunburns occur when the patient is receiving tetracyclines and gets exposed to sunlight or ultraviolet light. So for anyone who's on treatment with Doxycycline and planning to go tanning, he/she should think twice because it's not a good idea.

To summarize, Doxycycline is used to treat

1- pneumonia caused by mycoplasma and chlamydia (definitive) 2- cholera

3- acne (in the past) 4- brucellosis (in combination with gentamycin)

5- syphilis 6- gastric and duodenal ulcers (triple therapy)

7- rickettsia 8- Lyme disease

➤ **Macrolides:**

Four drugs in this group:

1- **Azithromycin** (Azithromax) 2- **Erythromycin** 3- **Clarithromycin** 4- **Telithromycin** (New)

But for now we'll talk about the first three: Azithromycin, Erythromycin and Clarithromycin.

Let's first talk about the spectrum for each one of those drugs:

Azithromycin, Erythromycin and Clarithromycin most of them are active on:

- A) Gram +ve : Staphylococcus, Streptococcus, (example: Streptococcus Pneumoniae).
- B) Gram -ve : Moraxella, Neisseria Gonorrhoeae, H. Influenza, Legionella Pneumophila
- C) Mycoplasma, Chlamydia and treponema pallidum (spirochete)

So in reality, 99% of the causes of **URTI & LRTI** are covered by **Azithromycin, Clarithromycin** (and tigecycline). (exclude **Klebsiella Pneumoniae**, the reason is in next lectures)

*****Erythromycin** covers URTI and LRTI but to lesser extent (no action on legionella and chlamydia) and it is a bad drug.

In Empirical treatment, when your patient has a **community acquired Pneumonia (CAP)** and he/she doesn't need a Bactericidal activity, instead he/she needs a bacteriostatic, the drug of choice is **Azithromycin**.

*****Macrolides** are 'respiratory drugs' for URTI and LRTI. Especially for community acquired Pneumonia

- 1- because it's spectrum activity includes Pneumococci, Mycoplasma and Legionella
- 2- because they got high penetration.

Q. When do we use Macrolides for URTI?

A. When we can't use "the four guys" due to sensitivity/allergy towards Penicillins & Cephalosporins. (The four guys: Augmentin, Cefuroxime, Cefnidir, Cefixime)

Q. What do I give my patient then?

A. Azithromycin

Azithromycin, Erythromycin and Clarithromycin are the drugs of choice for the treatment of choice for **Urogenital Infections** due to **Chlamydia infection**. For **Mycoplasma**, **Erythromycin** and **Tetracycline** are effective for **definitive treatment**. And for **Legionella**, **Azithromycin** is the drug of choice because the Macrolides are more active on Legionellosis.

Macrolides' antibacterial spectrum is very similar to that of **Penicillins** and it is proved to be a very useful substitute in patients allergic to Penicillin.

Azithromycin is now the preferred therapy for **Urethritis. Urethritis** and **Chlamydia** are either treated by
1) 5 days of 25mg twice daily **doxycycline** 2) 1gram of **Azithromycin** once a day.

***Why do we treat Chlamydia with only 1gram of Azithromycin while on the other hand, 5 days with Doxycyclines? Azithromycin treats most tissues (high penetration) except cerebrospinal fluid with a tissue concentration exceeding the serum concentration by 10-100 folds. The drug is **slowly released from the tissue to produce an elimination half-life approaching 3 days**. So this 1gram goes the tissue and the tissue acts as a **reservoir** and this reservoir will release the drug over a long period (At least 3-4 days). So if you take 3 grams it will take a very very long time to get out of your system (At least 10 days). Therefore, the 3 grams of Azithromycin that you'll use in URTI will cover 10 days.

Erythromycin has the worst side effects of the three Macrolides:

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|----------------------------------|--|
| 1- Ototoxicity | 2- Cholestatic Jaundice (blockage of the bladder, increase of bilirubin) |
| 3- Gastrointestinal Disturbances | 4- Skin Rash |
| 5- Fever | 6- transient hearing disturbances. |

THE END

"في كل صباح لديك خياران: إما أن تنام لتكمل أحلامك، وإما أن تستيقظ لتحقيق أحلامك"