In this sheet we will talk about two cute drugs and a group of drugs, wish you a pleasant study...

First of all, we will talk about clindamycin, which is a protein synthesis inhibitor.

Remember >> protein synthesis inhibitor are tetracyclines, macrolides, aminoglycosides and lincomycin and clindamycin.

We talked about the first three drugs in the previous sheets.

We all visited dentists and most of us must have seen them prescribing two drugs a lot, which are lincomycin and clindamycin. Dentists like these two drugs a lot. These two drugs are actually used by dentist to treat oral infections... are they the drugs of choice in oral infections?? Not really. As we know the drug of choice must have the narrowest possible spectrum, so the drug of choice in oral infections is >penicillin V

But what is the spectrum of clindamycin??

This drug mostly acts on anaerobes; it will be active on Peptostreptococcus, some Bacteroides sp, Actinomyces, Prevotella sp., Propionibacterium, Fusobacterium and Clostridium sp. (not C. difficile). These anaerobes are mostly present above the diaphragm.

Clindamycin is mainly used in 2 situations: (mainly) against anaerobes and against some gram positive bacteria (staph and strep). It covers more anaerobes than Penicillin V, but Penicillin V still covers all oral anaerobes (narrower spectrum, so it is the drug of choice in oral infections). However, Clindamycin can be used in odontogenic infections in patients who are allergic towards the penicillins.

-clindamycin and lincomycin have other uses in bone infections (we will not discuss bone infections now because osteomyelitis are very complicated diseases and they need management rather than treatment, which means that the patient who has osteomyelitis or a diabetic foot needs a very long time of managing his case which may take years.

Still, you must keep in mind that lincomycin and clindamycin, especially clindamycin, have a good bone penetration and show a good activity in osteomyelitis.

Let's get back to oral infections and assume that you were asked the following:
A patient with a salivary gland infection (or any other oral infection) is allergic towards penicillins, which drug of these is the best choice in this case?

A) Penicillin V
B) Amoxicillin
C) Cefoxitin
D) Imipenem
E) Clindamycin

*clindamycin has a very common commercial name (Dalacin C).

*In Jordan, we have limited amounts of Penicillin V (Ospen) and only in certain places; not found in normal pharmacies.

*slide 100 which is titled (Dental pharmacologic features of clindamycin) was read rapidly by the doctor and he said that you can read it if you want to switch to dentistry (not important).

So Clindamycin is used in:

- dental infections
- bone infections

**Aspiration pneumonia!

When you eat something and a piece of food hinges in your throat (تشردقت) you start to take strong breaths from your mouth, during that some of the oral bacteria in your mouth might move to the lung and cause a lower respiratory tract infection (pneumonia).

We said in the first lecture that during treatment we do care about the source of the infection, so in “Aspiration pneumonia”, what is the source of the infection? It's not from the lung, not from the hospital, not Klebsilla and not Streptococcus pneumonia, it came from the mouth, it could be Strep, but most likely the infection was caused by anaerobes.
So, in **Aspiration pneumonia** we use clindamycin, WHY?
That is to cover all anaerobes in the mouth and the anaerobes over the diaphragm.

*Clindamycin is active against over the diaphragm anaerobes (Bacteroids), but it **isn't** active against all bacteroids (Cefoxitin and Cefotetan (2nd generation cephalosporins) which act in intrabdominal infections are active against all bacteroids), it is only active against some bacteroids (over the diaphragm bacteroids and it has a full coverage of these bacteroids).

So, in any infection over the diaphragm, which you think to be caused by anaerobes, you should give the patient clindamycin.

**A very important issue>>** Side-effects are generally limited to GI upsets. However, a potentially lethal pseudomembranous colitis can occur.

Many drugs with wider spectra cause pseudomembranous colitis, but this side effect is given a higher amound of consideration with clindamycin because in 1973 a patient taking Clindamycin died from pseudomembranous colitis (the first ever recorded death due to this disease). Due to that, doctors tend to be afraid from prescribing this drug to the patients, but, in reality, even if the patient died that doesn't mean that the incidence of pseudomembranous colitis in clindamycin is higher than that in other drugs (ciprofloxacin has a higher chance of causing pseudomembranous colitis than clindamycin).

**Summarising**
- Clindamycin a is drug with some gram-positive activity and (mainly) is active on the anaerobes above the diaphragm.

**The main uses of this drug are:** as an alternative to penicillin V in treating odontogenic infections and in **aspiration pneumonia**.

**The END of Clindamycin…**

**QUINOLONES**

(Ciprofloxacin, Levofloxacin, Gemifloxacin, and Moxifloxacin)

Quinolones are very important drugs, they are more important than the protein synthesis inhibitor.

They are DNA gyrase inhibitors and they are bactericidal drugs.
**Why they are bactericidal? (the mechanism of action..)**

In our cells, the DNA is unzipped (open the DNA), to make it available for transcription or translation. When the DNA is unzipped something called supercoiling happens, here the role of the topoisomerase enzyme (in human cells type 2. In bacteria it is type 4 or gyrase) comes, it will cleave the coiling and rejoin the DNA (watch this video and don’t care about the names of the enzymes, the types written above were according to what the doctor said, but there are more complications in the naming of these enzymes apparently: Video (press ctrl and click on the link to watch)).

Topoisomerase is a very important enzyme, so if this enzyme is inhibited the replication process will not happen or the DNA will break for many reasons..

To be clearer, there are two things that affect the enzyme’s activity negatively:

- enzyme inhibitors
- enzyme poisoners

In the case of quinolones and topoisomerase inhibitors we don’t cause a real inhibition of the enzyme, in reality what happens is that the drug will bind to it and inhibit it when it ends the cutting process before topoisomerase rejoins the cut DNA, so it will not be able to rejoin the DNA. The DNA in this case is said to be “trapped in a cleavable complex” (or a “tertiary cleavable complex” as it contains the enzyme, the drug and the cleaved DNA).

At the end, the bacterium gets its DNA cut and so it will die and that’s why this drug is bactericidal.

**WHAT is the value of Quinolones? (features)**

They are anti-gram negative drugs and are administered orally, so they were the first discovered anti-gram negative drugs to be administered orally.

*the first active anti-gram negative drug administered orally, was ciprofloxacin.

So Quinolones were active against *Pseudomonas, E.coli, Salmonella, Shigella & Serratia*.

So they are strong drugs and they are more active on gram negative than gram positive bacteria.
Now that we discovered an oral drug that has a gram negative activity, where can we use it???

Because it’s an oral drug, we can use it in the community (not necessary in the hospitals).

The gram-negative infections in homes are mainly two:
1. UTI >> caused by *E.coli, Proteus, Serratia and Staph saprophyticus*.
2. Gastroenteritis (GI tract infections) >> severe diarrhea, sometimes linked with bacteria >> caused by three >> *Shigella, Salmonella and E.coli*.

*All the causes of UTI and GI tract infections (EXCEPT *Staph saprophyticus*) are gram negative bacteria, so ciprofloxacin is active on them and, good news, it is also active on saprophyticus (its gram positive activity covers saprophyticus).

**SO the drug of choice in treating UTI and bacterial GI tract infections is ciprofloxacin, there is no drug better than it in these cases ,WHY?**

Because it covers all gram negative guys present in the abdomen and the urinary tract (slide 3).

Ciprofloxacin is a 2nd generation quinolone and it has a spectrum that covers many gram negatives, including pseudomonas and enterococci, in addition to staph and strep.

However, *Streptococcus pneumonia* is NOT covered by ciprofloxacin.

DON’T prescribe ciprofloxacin for the respiratory tract infections, because *Streptococcus pneumonia* is the main cause of upper and lower respiratory tract infections.

**big issue>> doctors and pharmacist prescribe ciprofloxacin for upper respiratory tract infections which is a major mistake.**

Ciprofloxacin works in
1. The lower abdominal area (in prostatitis and cervicitis) which are caused mainly by *E.coli, Proteus and Serratia*.
2. Complicated UTI
3. Bacterial diarrhea caused by *Shigella, Salmonella* and *E.coli*. 
Remember that ciprofloxacin is part of the Quinolones which cause arthropathy (one of the most important and most common side effects).

So it mustn’t be used with children, because it will cause problems in cartilage and bone building and linkage.

Q: A child with a UTI or a GI infection came to your clinic, what drug should you prescribe?

You are not allowed to give him ciprofloxacin so you should give him either Cefdinir or Cefixime (3rd generation oral cephalosporins).

You can give him Cefuroxime but it is not preferred, its preferred to give him Cefdinir or Cefixime because they are active in E.coli mostly and saprophyticus which cause UTI and on salmonella and shigella.

*In pharmacies, you will find a drug called Matador (levofloxacin, 3rd generation quinolones), which is a very strong drug, WHY is it so?

Because it’s active on gram positive bacteria, and on atypical pneumonia, so we added to the spectrum of ciprofloxacin the atypical pneumonia which means that we can use levofloxacin in treating respiratory tract infections (so they are called respiratory tract quinolones). So levofloxacin is active on everything, but its activity on anaerobes is weaker than clindamycin and imipenem.

So we can use certain types of quinolones in:

**respiratory infections in patients with cystic fibrosis**

Levofloxacin, gemifloxacin and moxifloxacin, the so-called respiratory Fluoroquinolones, with their enhanced gram-positive activity and their activity against atypical pneumonia agents (e.g. chlamydia, mycoplasma and legionella), are effective and used increasingly for treating upper and lower respiratory tract infections. (slide 105)

They are the drugs of choice in treating respiratory tract infections.. which infections?!.. Pneumonia…WHAT???

BUT In the last lecture the doctor said that Azithromycin is the drug of choice in pneumonia, what is he saying now???

Okay, the drug of choice is Azithromycin, but when the pneumonia is community acquired the patient does not need hospitalization and a bacteriostatic drug is enough.
However, if the patient has pneumonia and needs hospitalization, the drug of choice in this case must be a bactericidal drug so you must give him levofloxacin.

*remember ciprofloxacin is NOT active against pneumonia.

These drugs are NOT for children, we cannot give the children the respiratory quinolones, so we just use Azithromycin with them and if we need a cidal activity we can use other drugs to be discussed later.

When the child has pneumonia in the house and is going to school, nursery and so on, we give him Azithromycin

If he does not go to these places we give him respiratory drugs like, Cephalexin, Augmentin, Cefoxitin or Cefdinir.

*Arthropathy, Fluoroquinolones may damage growing cartilage and cause an arthropathy. Particularly in young individuals. So, they are contraindicated in children (under 18) except in special cases.(slide 106)

What are the special cases??
There is a (genetic) disease called cystic fibrosis, the problem of this disease is that the respiratory tract of the patient gets filled with mucus. The mucus may reach the lungs, so the patient is highly susceptible to upper and lower respiratory tract infections. HOW can we solve that? By giving the patient a prophylactic drug which is levofloxacin, even if the patient is young (under 18 years). We can give Azithromycin, but it’s weak and not enough for prophylaxis, because it’s bacteriostatic.

So the exception is: we can use levo, gemi or moxifloxacin in cystic fibrosis patients as prophylactic drugs, given frequently, daily and orally to prevent them from getting frequent respiratory infections >>frequent pneumonia, tonsillitis, sinusitis, and so on.

*Side-effects are infrequent and usually mild. They consist mainly of GI disorders (nausea, vomiting, and diarrhea) and skin rashes (very rare skin rashes).

*Ciprofloxacin causes pseudomembranous colitis more often than clindamycin.
-remember this paragraph when we talked about broad spectrum penicillins? (slide 36)

Although supportive clinical data are lacking for superiority of combination therapy over single-drug therapy, because of the propensity of P aeruginosa to develop resistance during treatment, an antipseudomonal penicillin is frequently used in combination with an aminoglycoside or fluoroquinolone for pseudomonal infections outside the urinary tract.

More than 50% of hospital infections are caused by pseudomonas aeruginosa, the worst thing about it is that it can form biofilms and cause green pus. It is a really bad infection, you can't treat it with a single antibiotic, you have to give the patient one of piperacillin, ceftazidime, cefamox (avoid using this drug), imipenem and aztreonam (cell wall inhibitors) and one of the aminoglycosides or fluoroquinolone.

If the patient is allergic to cephalosporins and penicillin, you can give him an aminoglycoside with a fluoroquinolone.

Always in pseudomonal infections you need two antibiotics (a dual drug) except in UTIs where you can give a single antibiotic.

Quinolones are more preferred over aminoglycosides, WHY?

Because of gentamycin toxicity (you need to trough), nephrotoxicity and ototoxicity (the side effects of aminoglycosides).

So we usually give ciprofloxacin (a gram negative drug) with an anti-pseudomonal penicillin, a cephalosporin or any other pseudomonal cell wall inhibitor.

We can prescribe aminoglycosides if pseudomonas developed resistance against the ciprofloxacin.

**The end of quinolones..**

**Sulphonamides**

The last group of antibiotics.

They are drugs that used to be used in treating skin infections, pain and in many other things, one of the oldest drugs in the world, older than
penicillin, but the usage of sulphonamides wasn’t wide spread like that of penicillin G.

We actually have lost these drugs (resistance developed), so we don’t have to know much about them.

You just need to know that they are antimetabolites and inhibit an enzyme called dihydrofolate reductase, this will make the tetrahydrofolate not able to transport the methyl group and will stop the purine synthesis, so they actually block the synthesis of DNA’s building blocks.

If there is no DNA synthesis the cell can choose to stay as it is (so sulphonamides are bacteriostatic drug).

However, this mechanism was not enough for the drug to remain active as the bacteria developed mutations in dihydrofolate reductase and developed resistance to these drugs.

By the end of the 70s, a scientist said that he could revive the sulphonamides by using another mechanism of inhibition.

Another antimetabolite from the sulphonamides group called Trimethoprim inhibits another enzyme called dihydropeptidase, so it causes inhibition of another purines and pyrimidines synthesis pathway and this drug is a bactericidal drug.

Cotrimoxazole is the commercial name of the drug that combines between trimethoprim and sulfamethoxazole. Cotrimoxazole is a very good drug on gram negative becateria and it’s a very good alternative for ciprofloxacin in UTIs.

It is administered orally and it’s active against gram positive and (mainly) gram negative bacteria, but it does not have a strong activity on atypical bacteria (pneumonia).

This drug is commonly used because now we have bacteria that developed resistance to ciprofloxacin. So it’s a good alternative for ciprofloxacin in the case of resistance or if the patient has developed arthropathy in response to ciprofloxacin (arthropathy can occur in adults, but it mostly occurs with children and affects the bone itself. For adults, it may cause tendonitis and pain in the bones).

In the exam, we will only be asked about cotrimoxazole from the sulphonamides (as it is the only still used sulphonamide).