Quick Review: Side Effects

- ➤ **Tetracyclines:** Phototoxicity and it may precipite in bones and joints. This is why I don't give tetracycline to <u>children</u>.
- ➤ Macrolides: Safe drugs; Virtually no side effects. This is why they are very common.
- **Aminoglycosides:** Nephrotoxicity and ototoxicity.
- ➤ Clindamycin: It has a bad reputation for causing pseudomembranous colitis.

Inhibition of DNA Gyrase:

Quinolones

- One of the best drugs used for gram negative bacteria. The attractive point in quinolones is that they are: *Oral* anti gram-negative drugs. In the old days there were no oral gram negative drugs!
- In the community when we talk about gram negativity; we are mostly discussing two problems:
- 1. UTI → Mostly caused by gram negative bacteria especially E.coli or Enteritis.
- 2. Any type of diarrhea (abdominal/traveler/severe) → mostly caused by Shigella, Salmonella and E.coli
- Quinolones are active against those gram negative bacteria and are taken orally.
- Therefore, the drug of choice for UTI or any type of diarrhea is always Quinolones, specifically the old types: **Ciprofloxacin**, a fluoroquinolone and a 2^{nd} generation quinolone \rightarrow Against gram negative.
- Nalidixic acid is a 3^{rd} generation quinolones, we took it in micro, forget about it.

o Respiratory Quinolones

- 3rd Generation
- We use them in the respiratory tract since we have improved their activity to include Strep. Pneumonia; which is gram positive.
- Ciprofloxacin (2nd generation) is not active against most gram positive bacteria, it has some activity but it doesn't include Strep. Pneumonia

o Levofloxacin

- Used in RTI caused by: Staph, Strep, H.Influenzae, and also by atypical microorganisms (it has better activity than cipro against atypical!)
- Covers everything in the respiratory tract! Used like Azithromycin; with community acquired pneumonia and can also be used in hospitals instead of (Gentamicin + Azithromysin).
- Ouinolones in general cover all Gram –ve bacteria: Pseudomonas, E-coli, Enteric, H.Influenza.
- Levofloxacin in addition covers some gram +ve bacteria. Respiratory flouroquinolones also have activity against atypical pneumonia agents (Legionalla, Mycoplasma, Chlamydia).

• Inhibition of DNA Gyrase

- DNA Gyrase (type two topoisomerase) that produces transient double strand breaks in DNA. Unzipping of the DNA causes coiling, this enzymes relieves coiling by cutting and recombining strands.
- Quinolones → inhibit Gyrase or Topoisomerase! They prevent the bacteria from rejoining the DNA strands together after being unzipped.
- The best example is the *Floroquinolones*, which trap the enzyme in its cleavable complex: When the Gyrase cuts the DNA, 3 types of drugs can cling to it (they trap the cleavable complex) → The DNA remains open → you produce strand breaks → bactericidal effect! The most important of these 3 drugs are quinololes. Another important drug is Adriamycin and is used in cancer treatment.
- It is a broad spectrum antibiotic active against all gram negative and some gram positive except for strep pneumonia → here we're talking about the basic/old quinolones.
- The first oral antibiotic effective against gram negative bacteria is *ciprofloxacin*. It is the most active against gram negative especially pseudomonas.
- Third generation: *Levofloxacin, Gemifloxacin, Moxifloxacin* have improved activity against gram positive organisms especially Strep and some Staph.

Uses of Quinolones:

• Gram negative UTI

- Most active against E. coli. E-coli produce ESBL which decreased amoxicillin activity (nowadays we usually do not use amoxicillin for UTI); the drug of choice for both the complicated and not complicated UTI is → ciprofloxacin.

• Bacterial Prostatitis and Cervicitis

- Caused by E.coli. Quinolones have good penetration into prostate fluids and cervix fluids.
- The patient will take the drug for 28 days which is very long (long term treatment)!!

• Bacterial Diarrhea

- Caused by: Salmonella, Shigella and E.coli.
- All quinolones can be used, but most importantly \rightarrow ciprofloxacin.
- Amoxcillin should not be given for shigella, Ampicillin can be given. But the drug of choice is the Quinolones!
- For those bacteria we usually give ciprofloxacin instead of Levo because we don't want to have a wide spectrum of bacteria eradicated. We don't need to eradicate the respiratory flora.

❖ The most common cause of pseudomembranous colitis is ciprofloxacin NOT clindamycin

• Infections of soft tissue, bones, joints and Intrabdominal infections

They have a good penetration for those areas (bones and joints)! They have activity against Staph, too, which always goes to bones and joints! Cipro acts against Staph, but doesn't act against Strep.

- Respiratory Infection in patients with Cystic Fibrosis
- FDA approval was granted for use of respiratory quinolones as a first choice drug for cystic fibrosis.
- Respiratory infections (upper and lower): We use third generation quinolones, but they are not the first choice:
 - o Atypical Pneumonia:
- Levo is used as a second choice after azithromycin.
 - o <u>Nosocomial Penupmonia</u>:
- In the hospital it is not the first choice to give IV or even oral *Levo* despite the fact that it has good activity against gram positive, negative and atypical bacteria, gives faster results, and doesn't require a peak and trough test. It is still the *second choice* because we don't want to lose it and it has some toxicity. Azithro + Genta are used as a first choice according to the FDA guidelines.

Side effects:

- Infrequent and usually mild.
- Consist of *GI disturbances* (nausea, vomiting, and diarrhea) and *skin rashes*.
- 13/10/2013: It was stated that the usage of these drugs might cause *peripheral neuritis* and a warning was issued stating that Quinolones may also cause other neural problems.
- The major drawbacks: cause tendon rupture *orthopathy* (damage growing cartilage causing orthopathy which is a bone disease). This happens particularly in young people and therefore contraindicated in children until 18 years of age except in special cases.
 - o Special cases: Cystic Fibrosis. Many cystic fibrosis patients have infections that are recurrent and so we must give Levofloxacin since CF is a huge problem! It is the only drug to be used with children under 18.
- Orthopathy is common is people over 60 years old: this is usually due to either Statins (decrease lipids level) or Cipro. The problem is with floroquinolones and it happens most frequently in prostatitis since they require long-term use; 10% of patients have cartilage problems or bone problems because it is used for a long time. Problems start showing as fatigue and usually after the second week of use.
- They used to say that neural problems are rare with quinolones, but now they are seen more frequently.
- **Phototoxicity** (like tetracyclines): They cause Steven John's syndrome which is a serious skin rash (especially in the face) after getting exposed to the sun.

At the end of the day, they are good drugs.

Sulfonamides

- Oldest drugs ever, they came even before Penicillins.
- They are very good drugs, but they lost the activity because of the frequent use. They had a broad spectrum but we lost them!
- Resistance was established by via upregulation of *PABA synthesis* (p-aminobenzoic acid) and by mutation in the *dihydropteroate synthetase*:
- PABA is used to synthesize purines and pyrimidines
- Sulfonamides are antimetabolites → We introduce false nucleotides to the DNA → Linking after the false nucleotide doesn't occur → We inhibited the synthesis of DNA!
- This effect is sometimes bactericidal and sometimes bacteriostatic (depending on the dose). But mostly bactericidal!
- There is another enzyme: *Tetrahydrofolate Reductase* (THFR): This enzyme also participates in folic acid synthesis needed for the production of purines
- Trimethoprim
- Also inhibits the pathway in addition to sulfonamides.
- We already mentioned that we lost the activity of the sulfonamides and most microorganisms became resistant. However, it was discovered that if you combine:

Trimethoprim 1 mg + 5 mg sulfonamide $(1:5) \rightarrow$ **Co-trimoxazole**

- Most microorganisms that have developed resistance are sensitive to this new drug (combination between trimethorpim and sulfonamides). This drug is active against many microorganisms (wide spectrum).

Uses of Sulfonamides

- Sulfonamides as drugs are used against things that are not related to infection. For example:
- Oral Nonabsorbable Agents
- Used in *inflammatory bowel disease* or *ulcerative colitis*, this is mostly an inflammation.
- **Sulfasalazine:** When in the bowel, it is broken down into two drugs:
 - o Sulfapyridine
 - o 5-amino- salicylic acid (Aspirin): Avery good anti-inflammatory drug
- It is used for Ulcerative colitis because it breaks down to form aspirin. We can't use aspirin directly because it doesn't reach the area of infection, where as Sulfasalazine can reach the colon.
- Topical Agents:
- **Silver Sulfadiazene**: this drug is not active unless it is mixed with silver. This cream is used to prevent infections caused by *burn wounds*. They may make healing slower but we need it for prophylaxis.
- Sulphonamides are *no longer used* for UTI because of resistance.

Side Effects:

- Mild to moderate side effects; *nausea*, *vomiting*, *headache* and *depression*.
- More serious side effects include *hepatitis, hypersensitivity reaction, bone marrow depression,* and *aplastic anemia.*
- It produces bone marrow depression (synthesis decreases) because it has a cross reaction with the purines that are synthesized in the bone marrow. We produce 13 billion cells per day in bone marrow! When you give an anti-metabolite, it might also inhibit DNA synthesis in normal cells such as those of bone marrow.
- Any sulfa-compound might produce hypersensitivity reactions, such as Furosemide (Lasix) and Sulfanomides. Some patients are hypersensitive to these drugs and this is why they are not great drugs.

❖ Oral Trimethoprim – Sulfametoxazol (TMP-SMZ):

We use them in two areas:

• UTI

- Can be given as another choice instead of Cipro.
- Their side effects are usually not adverse; this is due to the fact that we do not give a high dose of the drug.
- Ratio of TMZ to SMZ is always 1:5, for example \rightarrow we give 800 mg SMZ + 160 mg TMZ
- Active against E-coli. This is important since E-coli are starting to become resistant against Quinolones.
- FDA has allowed giving intramuscular Gentamicin (a last resort) for UTIs which are neither responsive to Quinolones (Cipro) nor TMP-SMZ. (In definitive therapy, we use the results from cell culture to determine if E-coli is resistant and which drug we should give).
- Many ladies have recurrent UTI's, therefore it might be used for prophylactic purposes. A low dose is taken over the course of 6 months. Prophylaxis does is 400:80. The frequency of UTI recurrence dictates the period of treatment.

• Pneumocystis Jiroveci (carinii) Pneumonia

- Co-tromexazol is the drug of choice;
- This illness is most common in immunocomprised patients (AIDS/cancer patients).
- **Toxoplasomosis, Nocardiosis:** Co-tromexazol is the drug of choice
- It can be used for atypical pneuomonia and URTI, BUT it usually <u>isn't</u> due to its side effects. It is the last resort!

❖ Vancomycin Resistant Enterococci (VRE) and More:

Teicoplanin

- Used in the prophylaxis and treatment of serious infections caused by Gram-positive bacteria, including *MRSA* and *Enterococcus faecalis* (also acts, to a lesser extent, on faecium).
- An alternative for vancomycin! A lot of pediatrics give it to children instead of Vanco when we're afraid that the child has meningitis caused by MRSA or if the bacteria is resistant to Vancomycin.
- Preferred in children over Linezolid since it is believed to be less nephrotoxic.

Linezolid

- Also approved for: Vancomycin-resistant E. faecium, Nosocomial Pneumonia, Community-acquired Pneumonia, Skin infections (complicated or noncomplicated).
- Linezolid is active on MRSA and VRE.

• Daptomycin:

- Active against MRSA and VRE but it gets destroyed in the respiratory tract.

- Last two slides are VERY IMPORTANT a summary of many diseases and the common prescribed drugs. The doctor read them.
- The most commonly used drugs against acne are tetracyclins.
- Note: we can also use Clindamycin for acne topically along with a with peroxidase as a cream.