Aminoglycosides

Notes:

- Ampicillin is not used for treatment of atypical pneumonia.
- Ampicillin + Clavulanic acid /Sulbactam = H.Influenza (many species of H. influenza produce beta lactamases)
- Ampicillin doesn't cover staph, E. Coli, or H.Influenza since they all produce beta lactamases.
    - Amoxicillin must also be used with another drug.
- Enterococci: Ampicillin; but resistance is increasing. We need to use Vancomycin if we suspect resistance. We no longer use cephalosporins. Fifth generation cephalosporins are active against Enterococci
    - Fifth generation cephs are still not approved
- Penicillin V: pharyngitis, because it is caused by streptococcus pyogens.
- Tetracyclins:
    - Used for Mycoplasma and Chlamydia (Azithromax).
    - Combination therapy with aminglycosides for Brucellosis.
    - Used against H. pylori.
    - Used against acne.
    - Used against syphilis.
    - Tigecycline (a new drug, tetracycline) and Calithromycin (a new drug, macrolide)

For reading Only:-

Tigecycline (Tetracycline):

- Approved in 2007
- When it was first released it had many problems.
- A new warning was released in 2013. It increases the incidence of death with pneumonia patients and sepsis patients.
- Broad spectrum
- Active against most bacteria: aerobic, anaerobic, Gram-positive, and Gram-negative.
- Not active against Pseudomonas and Proteus.
- Only used when benefit outweighs risk.
- You can use it with multi-drug resistant microorganisms
- It is not a good drug, because it is linked to high levels of mortality.

Calithromyocin (Macrolide):

- Liver toxicity
- Liver failure causing death
- Approved in 2007.
    - David Ross: "How does one justify balancing risk of fatal liver failure against 1 day less of ear pain?"
- Used against community acquired pneumonia (all its forms)
- Used against sinusitis and otitis media!
- In 2013 a warning was released (3 months ago): "you are not allowed to use it with otitis media or sinusitis, because we don't want to risk liver toxicity". Sinusitis can be treated with many other drugs. It still has approval for community acquired pneumonia.

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Telitromysin :-

- It is just like azithromysin, but a bit stronger.
- Azithromyocin resistant microorganisms are more susceptible to Telitromysin than Azithomysin.
- Causes liver failiure.

Protein synthesis inhibitors:

- Macrolides: Gram-positive
- Aztreonam: active against aerobic gram negative rods: Pseudomonas, Proteus, Seriata, Cerrus bacilaita, and E. Coli (all enterobacteriaceae)

Aminoglycosides:

- One of the few drugs that were active against gram negative in old days.
- Bind to ribosome 30s subunit
- Inhibit initiation of peptide synthesis and cause misreading of the genetic code.
- Streptomycin is the oldest. It was the first to be used against tuberculosis. it is the best known member of the group which includes: Amikacin, Gentamicin, and Tobramycin ***memorize them***
- Netilmycin and Neomycin for topical use
- Aminoglycosides are used against aerobic Gram-negative bacteria and some Gram-positive.
- Their greatest use is against gram negative enteric organisms and in sepsis. We still use them in sepsis, especially when we want strong coverage against Gram-negative.
- We use them against Gram-negative, especially against Pseudomonas.
    - Pseudomonas cannot be treated with one antibiotic. You need to use more than one drug due to fast mutation rate during treatment.
    - Gentamicin (mostly) or Aztreonam with Pipercillin

- Gram negative bacilli in **septicemia**, pelvic and abdominal sepsis
- If you have sepsis or **abdominal sepsis** you need to give gram negative antibiotic
- we usually combine gentamicin and pipercillin to increase the coverage of gram –ve bacteria especially against pseudomonas
- **Endocarditis**: usually caused by gram positive (staph , enterocci or strep), we use Ampicillin against them along with clavulinic to cover staph, although the most usual causes are either strep or enterococci. Sometimes staph is resistant we have to use Vancomycin.

We combine either **Ampicllin** + **Gentamycin** if we are not worried about MRSA, or **Vancomycin** + **Gentamicin**. This is to increase synergistic activity! They don't cover bacteria that cause endocarditis along with gentamicin or aminoglycosides, they are only added to increase the effectivity of cell wall inhibitors used, mostly penicillins, vancomycin or teicoplanin (similar to vancomycin) are used in cases where there is resistance (for MRSA). Cephalosporins are not used since none are active against enterococci.

Aminoglycosides

- **Streptomycin** is one of the alternative drugs used for tuberculosis. Rifmapicin and other drugs are now used.

- **Nosocomial Pneumonia**:

- There is a difference between it and Community Acquired which is caused by: Strep, Staph sometimes, H.influenza. Atypical: Mycoplasma, Legionella and Clamydia → Azithromycin or Doxycyclin are the drugs of choice for community acquired pneumonia.

- Hospital acquired (nosocomial) pneumonia: Pseudomonas, Enterobactar origins, E.coli, H.inffluenza. We have to cover gram negative bacteria.
- Atypical types are also found in the hospital. This is why we need to combine two drugs: **Gentamicin** (one of the most used drugs, since it strongly covers gram -ve) or **Pipercillin** and I need to give **Azithromycin** to cover atypical types or clarithromycin (macrolides).

- Hospital acquired pneumonia is treated with a combination of *macrolides* and *aminoglycosides*.

- IT IS WRONG to give gentamicin + azithromycin for community acquired pneumonia, there is no need for gentamicin.

- **Brucellosis** (الحمى مالطية) we give *Tetracycline/Doxycycline* + *Gentamyocin/Streptomycin* (Dual therapy)

- **Sterilizing Agents** (a weird use): we give them to patients who are about to go for a surgery to sterilize the GI tract. We give patients a drug that is not absorbed from the mouth (we usually use neomyocin for this case).

    - Used with hepatic coma:

Patients with liver cirrohsis: there will be a buildup of urea in the body. Some bacteria also produce urea and some patients might develop encephalopathy due to that. Hepatic coma results from the buildup of toxic materials in the brain! This is since the hepatic system is not working well on detoxification and the liver is responsible for detoxifying urea. We give drugs that kill urea-producing bacteria to decrease the amount of urea reaching the brain. This is to avoid encephalopathy!

- Surgery: If I want to perform a surgery that is related to the GI and I am afraid of infection during/before surgery due to the bacteria there I use aminoglycosides for strelization.

- Urethral Irrigation (washing): we use Aminoglycosides since gram negative bacteria are found in GI and urinary tract!

Aminoglycosides

- **Gentamicin:** it is the first choice due to: low cost, we have a long experience of using it. We know a lot about it and we know how to use it. It is both cheap and effective.

* Examples of how cost can be a problem: -

- Prices: Warfarin == 5 JDs/month, Depectran == 100 JD/month

the second is better but money talks

- Pediatricians:

They give teichoplanin instead of linzoled because of the higher cose of linzoled. Linzoled is better.

- Used in infected burns, otitis externa and pyelonephritis

- For otitis externa we use it topically (eye droplets and creams)! Otitis externa is mostly caused by gram –ve pseudomonas arigonsa.
- For burns, it is mostly used for prophylactic purposes.

- In relation to pseudomonas: **Tobramycin** is stronger than Gentamicin! But they both act on it.

- In some cases, some of the microorganisms in the hospital are resistant to genta and tobra → we use **Amikacin**

- In the hospital → gram negative bacteria: ESBL → we can no longer use amoxillin and ampicillin, *pipercillin + tazobactam* are still active against them in addition to *imepenim* and *cefepime*.
- One of the LAST choices would be gentamicin because ESBL are usually susceptible to aminoglycosides.
- Why do we use aminoglycosides → active against multidrug resistant patients, even if bacteria is resistant against the three strong drugs (mentioned above) it might respond to aminoglycosides!!
- We use aminoglycosides to cover multi drug-resistant microorganisms. If those MOs develop resistance against gentamicin and tobramicin, we still have amikacin too!

    - Gentamicin and tobramysin are inactivated by phosphorylation; amikacin is resistant towards this phosphorylation. Amikacin works as the absolute last drug choice!

- Amikacin has the broadest antibacterial spectrum. It is used in serious nosocomial infections especially those caused by gram negative bacilli where tobra and genta have developed resistance.

(We usually do a survey and we need to go through the number of microorganisms that cause nosocomial infections. We classify them. For example we find that we have pseudomonas in the hospital, we must determine if it is resistant to tobra and genta? If it is resistant we use amikacin.)

Aminoglycosides

◆ **Toxicity of Aminoglycosides:**

- It is a serious issue; why do we still use them? They are the best against multidrug resistant bacteria.

  - *Nephrotoxicity* and *Ototoxicity*

- Nephrotoxicity is a dose related issue. As a greater dose accumulates in the tissue the greater is the incidence of nephrotoxicity. This will lead to us prescribing the drug for a short period of time because of the accumulation of dose! We are not allowed to give it for more than 5-7 days or in a different setting we need to wait for the culture and see whether the organism really needs this drug! You need to change the drug after seeing the lab result if you don't really need it.

- We learned about nephrotoxicity with vancomysin, though strong toxicity in relation to vancomycin is only a myth, meaning that gentamicin is the cause of nephrotoxicity; since it was usually added to vancomycin and this causes the toxicity ; not vancomycin by itself.

    - Trough and Peak tests for nephro and ototoxicities.

- These indicate the amount of drug after 60 minutes of administering the drug!

- Peak: peak is defined as the maximum concentration of the drug in the blood. We test for the peak to make sure that our drug is reaching the suitable concentration in the blood (over MIC 4-8 times).

- Trough: trough is defined as the lowest amount of drug that can be present in the body just before giving the next dose. We use it to test for the accumulation to see if the patient doesn't have problems with the nephron or with excretion.

- All patients taking gentamicin: we need to measure trough and peak.

- In the case of vancomycin we don't worry about the peak because we generally give high concentration of it, trough is what we worry about!!

- Let us agree tha the issue of nephrotoxicity is caused by gentamicin and patient must be monitored.

A real story: a Dr. prescribed gentamycin for the patient and took a vacation! The nurse kept giving the patient the drug for 3 weeks, the patient ended up with kidney failure and started having dialysis! You have to follow your order; you cannot depend on the nurse or anyone else.

- Gentamicin is given once daily over 30-60 minutes. We don't divide the doses a lot (for example every 8 hours, instead we give the whole dose once for 30-60 minutes) because we don't want to have many peaks! This is done to reduce the dose accumulation.

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◆ **Gentamicin:**

- Inhibits bacterial protein synthesis by binding to bacterial 30s ribosome
- The only protein synthesis inhibitor that is bactericidal
- Used in sepsis and synergistic activity
- 5-7 mg per kg body weight
- May have less toxicity than conventional dosing toxicity (conventional: dividing doses). Given as one dose daily (no multiple doses). This dosing regimen makes the drug less toxic than the regular dosing system.
- Irreversible ototoxixity (hearing might be lost) and reversible nephrotoxicity!
- The side effects are serious but there is no other drug choice, especially in sepsis/abdominal sepsis.
    - With sepsis → aminoglycosides (rule of thumb!) → sepsis might be life threatening

- Tobramysin: IV, more active against pseudomonas than genta. Less nephrotoxicity.
- Amikacin: broad spectrum, IV. Resistant to many enzymes that inactivate genta and tobra.
- Neomysin: oral or topical. Poor bioavailabilty. Used before bowel surgery to decrease aerobic flora. Used to treat hepatic encephalopathy (hepatic coma).

Refer to slide #82: the table is a summary .. and has most of the information said before according aminoglycosides.

- Why is gentamicin active only against aerobic and not anaerobes?

Because we need oxygen to pump gentamicin to the cell; if there is no oxygen, the pumping mechanism is inactive. Then there is no activity! Aztreonam also uses the same mechanism.

◆ **Clindamycin**

- Anaerobic, "dentists love it!" they don't like using penicillin V for dental and oral infections (because it is weak); they usually use Clindamycin! Amoxicillin has activity against anaerobes too and some dentists use it although it is not preferable.

- Binds to 50s subunit of ribosome/

- Active against gram positive cocci: staph and strep including penicillin resistant staph but not MRSA!!! and many anaerobic bacteria.

- Clinical use in infections caused by bacteroides organisms "fragellus" and all of the bacteroides in the mouth. As well as staph infections of bones and joints since it has a very good penetration and can penetrate through to bones and joints.

- Why do I use it in bones and joints diseases? For staph, because staph is the main cause for them.

- Also used for anaerobes in the oral cavity and other anaerobes that cause mixed infections such as: lung abscess which has both aerobic and anaerobic bacteria (mixed infection). I give clindamycin to cover the anaerobes.

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- Doctors nowadays give tienam (imepinim) for lung abcess since it is has a broad coverage for aerobic/anaerobic or any type of bacteria and this is WRONG since we are losing it!

- Older drugs like clindamycin can be used to cover anaerobes along with other drugs to cover both gram positive and negative in lung abscess.

- For Lung abscesses:

Clindamycin (gram +ve & anaerobes) + *Aminoglycosides* or 3rd generation *Cephalosporines* (gram –ve)

- Clindamycin + Cefuroxime/Gentamycin or Amikacin, can be used for:

- Penetrating wound of abdomen or gut

The wound can be caused by a bullet or it can be a stab wound. It may lead to microorganism on the skin entering into the blood. This can cause sepsis or infection.

The wound mostly has anaerobes because the abdominal area has anaerobes mainly as well as gram negative bacteria and enteric bacteria. This is why we need to combine drugs active against both anaerobes and gram negative.

- Infection of the uterus or the female genital tract

Septic Abortion: sometimes during pregnancy an infection occurs in the uterus which could be caused by anaerobes or gram –ve bacteria. This drug combination reduces the septic abortion and premature labor rate.

- Aspiration Pneumonia

Bactroides of the mouth go towards lung (lower respiratory tract) causing an infection pneumonia. The cause is Bacteriodes (fragellus is an example) NOT typical or atypical.

We need to cover bacteriodes and we need good coverage! We can give gentamicin but we have to give something else with it. Clindamycin must be given to cover the bacteriodes in aspiration pneumonia and in lung abscess too!

- Clindamycin is said to cause pseudomembraneous colitis. However, this is not very true. It causes pseudomembranous colitis but not more than any other drug.