PHARMACOLOGY

◉ Sheets ○ Slides

Number: 15

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Subject: Penicillins & Cephalosporins

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In the previous lectures, the following points were tackled:

- ✓ Definition of antibiotics
- ✓ Difference between empirical, definitive, & prophylaxis therapies
- ✓ Difference between narrow, broad, & extended spectrums
- ✓ Importance of using narrow spectrum antibiotics
- ✓ Importance of microbiological culture for microorganism identification
- ✓ Categorization of bacteria according to gram stain
- ✓ Problems arising from antibiotic misuse
- ✓ Main molecular targets of antibiotics
- ✓ Mechanism of action of cell wall inhibiting antibiotics

- **Amoxicillin and ampicillin** are very important antibiotics. They are active against bacteria causing upper respiratory tract infection like *Staphylococcus aureus*, *Streptococci*, *Haemophilus influenza*, & *Moraxella catarrhalis.* However, Penicillin G is the drug of choice for streptococcus pharyngitis (also called strep throat) because amoxicillin and ampicillin are broad spectrum drugs.

- Always prioritize the use of narrow spectrum drugs (like penicillin G) over broad spectrum drugs for treatment of infection.

- Amoxicillin and ampicillin are also used against enterococci. Penicillin G and V have some activity against enterococci, but it's not really great compared to amoxicillin and ampicillin.

- **Endocarditis** is an inflammation of the inner layer of the heart, the endocardium, due to an infection. It mainly affects the heart valves. Endocarditis is caused by:

    1. *Streptococci*
    2. *Staphylococcus aureus*
    3. *Enterococci*

- **Amoxicillin and ampicillin** are drugs of choice, for treatment of endocarditis. These drugs should be given as an injection (IV) in order to reach the valves (site of endocarditis) easily and quickly because endocarditis is a life-threatening situation.

- **Augmentin** (amoxicillin + clavulanic acid) is employed prophylactically, for patients with abnormal heart valves (to protect them from infectious endocarditis) who will undergo extensive oral surgery (such as the removal of the wisdom teeth). 2 grams of Augmentin are given 2 hours prior to the oral surgery (because absorption of the drug through the oral route takes time).

- Hospitalized patients with endocarditis are treated with ampicillin.

- Augmentin is used empirically for the treatment of acute otitis media in children. The dosage is increased 80-90mg/kg/day.

- **Streptococcal pneumonia** (causing otitis media) is in a state of intermediate resistance so instead of changing the drug, the dose is increased. Therefore, there are various doses of Augmentin in the pharmacy: 375mg, 625mg, 800mg in a syrup form. There are used according to the severity of the infection. However, the child must be given a high dose in case of otitis media because amoxicillin penetration to the ear is poor, so you either give 625mg three times daily or 800mg just twice.

- A low dose of 375mg of Augmentin is sometimes used for sinusitis. Bacteria are not really resistant to antibiotics in the case of sinusitis.

- Now let's move into the "Extended Spectrum".
  Note: in the slides the doctor made a mistake; the headline for what we'll next talk about is "extended" not "broad". Because the broad spectrum is what we just talked about above.

- Extended Spectrum β-Lactamases are drugs invented to deal with hospitalized infections, you don't see them a lot in the community.

- **The main cause of hospitalized infection is that the patients are immunocompromised**.

- Acinetobacter is one of the most problematic bacteria in immunocompromised patients. It does not cause any harm in normal healthy individuals.

- Acinetobacter is resistant to all antibiotics and it is very difficult to restrain its reproduction in immunocompromised patients.

- The problems associated with hospitals are increased risk of infection for immunocompromised patients, and some patients are in life-threatening situations, because in life threatening situations highly resistant bacteria increase in number due to the usage of very strong antibiotics.

- Highly resistant bacteria include: the 2 worst gram negative bacteria: *Pseudomonas aeruginosa* and *Enterobacter*, as well as gram positive bacteria like: *MRSA* and *vancomycin resistant enterococci*).

- Antibiotics were developed to combat the highly resistant gram negative bacteria (like Pseudomonas aeroginosa) and gram positive bacteria (Streptococci and enterococci *but* not staphylococci since they produce β-lactamases), and they have some activity on anaerobes. These antibiotics are called "**Extended Spectrum Antibiotics**".

- **Extended Spectrum antibiotics** have an increased activity against gram negative bacteria including:

  1. *Proteus mirabilis*
  2. *Salmonella*
  3. *Shigella*
  4. *E. Coli*
  5. *βL- H. Influenzae*
  6. *Enterobacter sp.*
  7. *Pseudomonas aeroginosa*
  8. *Serratia marcescens*
  9. *Klebsiella sp.*

- **Piperacillin**, an extended spectrum antibiotic, needs a β-lactamase inhibitor which is tazobactam (similar to amoxicillin which needs clavulanic acid).

- **Tazocin** is an injection which is a combination of pipercillin and tazobactam.

- Target Question: Which of the following antibiotics is used for hospital acquired pneumonia?
  a. Penicillin G
  b. Penicillin V
  c. Flucloxacillin
  d. Amoxicillin/Ampicillin
  e. Piperacillin

- **Pipercillin** is the only extended spectrum antibiotic available in Jordan.

- Extended Spectrum antibiotics like **piperacillin** and ticarcillin are:

  1. Poorly absorbed in the GI tract. Thus, they are given as injections.
  2. They are susceptible in β-Lactamases
  3. Their antibacterial spectrum is the same as the broad spectrum drugs plus pseudomonads and enterobacter.
  4. Used in intensive care medicine. (The worst place in the hospital is the ICU, or the intensive care unit, because ICU patients are given a lot of strong broad spectrum antibiotics, thus increase bacterial resistance).

- Due to propensity of Pseudomonas aeruginosa to develop resistance during treatment, antipseudomonal penicillin is frequently used in combination with an

aminoglycoside or fluoroquinolone for pseudomonal infections outside the urinary tract (this theory still lacks supportive clinical data).

- In general, antibiotics have no side effects but they can cause:
  1. ***Alteration of normal body flora*** and can be associated with GI disturbances, such as diarrhea (this effect increases by increasing spectrum).
  2. ***Allergy***, or hypersensitivity, is a common side effect. 10% of people are allergic towards penicillin.
     How does an allergic reaction towards penicillin occur?
     When penicillin is metabolized in the body, a chemical compound is released which binds to a protein and forms haptin. Haptin is perceived as an antigen by the immune system so the next time the drug is taken, antibodies are formed against haptin.
     The main sign for allergy is rash. The worse signs of allergy are bronchospasm with hypotension because of histamine.
     To resolve this allergic reaction (anaphylactic shock), drug consumption should be stopped and adrenaline (epinephrine) in the form of an injection called "EpiPen" is used.
  3. ***Nephritis by methicillin*** happened once and now methicillin is no longer used. Due to this incident, there is a note in all penicillin drugs' leaflets warning consumers that such drugs can cause acute nephritis. However, this is not true because nephritis occurred only when methicillin was taken so it is referred to as "drug-specific" nephritis. In the end, <u>not only did methicillin cause nephritis but it also resulted in the emergence of MRSA.</u>

- All oral penicillins are best given on an empty stomach to avoid the absorption delay caused by food. Nevertheless, **Amoxicillin** (Augmentin) can be given with a meal.

Cephalosporins

- The next group of β-lactam antibiotics is Cephalosporins. Their mechanism of action is the same as penicillins (i.e. cell wall inhibition).

- There are 5 generations of Cephalosporins, but only the first 4 generations are required.

- Moving from the 1st to the last generation, activity against gram negative bacteria increases. Nonetheless, gram positivity varies going backwards from the last generation to the 1st.

- The drugs of each generation of cephalosporins are not homogenous.

- **None** of the 4 generations are active against Enterococci. Therefore, they are not the drugs of choice for endocarditis or urinary tract infections.

- In Jordan, 90% of urinary tract infections are caused by E. coli. In western countries, urinary tract infections are caused by E. coli or Enterococci.

- **1st Generation Cephalosporins**:
  1. Cefazolin (injection)
  2. Cephalexin (oral tablet)

  They are the narrowest spectrum antibiotics covering *Streptococcus pneumoniae* and Staphylococci. They by nature cover Strep and Staph, meaning there's no need to add any β-lactamase inhibitors.

- They act on all the Streptococci and all the Staphylococci, except MRSA.

- They have nice activity on gram negative bacteria: E.coli, Klebsiella pneumonia, and Proteus mirabilis. But it doesn't act on H-Influenza, so it's not a great drug on upper respiratory tract infections.

- So we don't use 1st generation Cephalosporins in case of: endocarditis, and upper respiratory tract infection.

- Cellulitis, dermatitis and other skin conditions are usually caused by Streptococci and Staphylococci (present on skin). Augmentin is not used because it has a broad spectrum so cephalexin, which has a narrower spectrum, is chosen.

- **1st generation cephalosporins** are excellent agents for skin infections empirically, prophylactic and even definitively after the lab results pinpoint the cause of the infection which is usually streptococcal and staphylococcal infections.

- Wounds due to surgery incisions may result in skin infections. Patients, who do not have endocarditis, are given 1g cefazolin 1 hour prior to surgery.

- **2nd generation cephalosporins**:
  1. Cefoxitin
  2. Cefuroxime

  They cover the same gram positive bacteria as the 1st generation.

- Cefuroxime is the drug of choice for upper respiratory tract infections in England. Augmentin is used for upper respiratory tract infections in the USA. (Conclusion: Cefuroxime and augmentin are equally active against upper respiratory tract infections.)

- **Cephamycins** (like cefoxitin and cefotetan) are the only second generation Cephalosporins that have activity against anaerobes. The most important anaerobes we encounter are **bacteroides fragillus**.

- For colorectal surgery, where prophylaxis therapy for intestinal anaerobic bacteria is desired, cephamycins are given. **Why?**
  Because Cephamycins (cefoxitin and cefotetan) cover Strep, Staph, and fragillus; when you make a cut during the surgery you look out for Strep and Staph, and then when you get in you look out for fragillus. So we give high dose of cefoxitin and cefotetan before the surgery by one hour.

- Cefuroxime is used to treat community-acquired pneumonia because it is active against beta-lactamase-producing H. influenza or K. pneumonia and penicillin-resistant pneumococci.

GOOD LUCK!