**Note:**
Activity against G+ve decrease, and against G-ve increase while moving towards third generation. Fourth generation is active against both { G+ve and G-ve}.

- There is a fifth generation of cephalosporins but it hasn’t been approved for use yet and it’s not found in Jordan (will be mentioned at the end of cephalosporins but it’s NOT included in exam’s material )we Have a drug in this generation used to treat Pneumonia and skin infection caused by MRSA.

**First Generation:** Cefazolin,Cephalexin

- This group is Not heterogeneous (All the drugs of this group are the same).
- Low activity
- against G-ve
- Active against G+ve:
  - Streptococcus pyogenes.
  - Staphylococcus aureus.
    - Both cause Cellulitis,, SO: First generation is a drug of choice in case of Cellulitis.

*Does normal β-Lactamase (Not extended β-Lactamase), which is produced by Staph, destroy Cephalexin?*

No, it doesn't, It is active mostly against penicillin SO Cephalexin is the drug of choice for skin infection.

**The three most prescribed community drugs (against G+ve) mostly : Azithromycin,Amoxicillin, Cephalexin**

- Cephalexin:
  - It’s given PO (Orally).
  - We use it with Cellulitis.
  - We use it with Pharyngitis ; because 90% of Pharyngitis is caused by Strep
    - Is Cephalexin a drug of choice for Phayngitis?
      - No; It is alternative for Penicillin G and Amoxicillin (caused by streptococcal pyogens).
    - Cephalexin is NOT a good substituent, Why?
      - Because patients who have allergy toward Penicillins, some of them have allergy toward Cephalosporins .So when I know that my patient has allergy toward them, I have to avoid prescribing any of β-Lactamase Group WE DON’T RISK OUR PATIENT .
    - What should I prescribe for such patient?
      - We Use Macrolides instead (azethromycin\clarithromycin)
      - Azithromycin, It’s common prescribed drug, because it’s a substituent for Amoxicillin.
  - It’s common, at level of dermal infection (In USA, there is 25 million prescriptions of this drug,
which is high. [This number is half of Amoxicillin prescriptions].

✓ Cefazolin:
  ➢ It's given IV.
  ➢ It's a prophylactic drug before surgery.
    ▪ When doing a surgery and there is high susceptibility for having skin infection, we have to give the patient Cefazolin; because it's a coverage for skin flora (which are: Staphylococcus aureus AND Streptococcus pyogenes)
    ▪ The dose: 1 gram before 1 hour before the surgery.
✓ Cephadroxil: Is still used but whatever applied to cefadroxil is applied to cefazolin

**Second Generation:**

- this group is heterogeneous (Not all the drugs of this group are active against the same spectrum, there is differences between them)
- Some are active against Bacteroid fragilis (Anaerobes reside in our intestine) others are not
- More G-ve activity and A little bit less G+ve activity (means it is still active against S.Pneumonia and strep but Not highly active although we still use them) we increased the activity toward g-ve (H.influenza, Enterobactireae)
  
- Note: enteric bacteria developed resistance against Amoxicillin and Cefuroxime

✓ Cefuroxime

-Known as Zinacef.

- * the Brother of Amoxicillin* Cefuroxime ≡ Amoxicillin

What does that mean?

Cefuroxime is Like Amoxicillin active against: URTI: otitis media, sinusitis, pharyngitis (includes tonsillitis) and community acquired Pneumonia (typical one).
  ➢ NOT active against Bacteroides fragilis; NOT allowed to be used for prophylaxis in internal surgery.
  ➢ Is given orally.
    ▪ It's a community drug, very common:
      • It's a drug of choice for Community-acquired Pneumonia (the typical one), especially for children under 5 years.
        the drug in **UK** is: **Cefuroxime**
        but in **USA** and **Jordan** is: Amoxicillin.
      • How did they judge which one is better than the other?
        The spectrum is different; spectrum of bacteria in UK is different than the spectrum in USA. Due to the difference in environment.
In Adults 30% of community acquired pneumonia is Atypical (caused by mycoplasma and legionella)

- Intermediate penicillin-resistant Streptococcus pneumonia which causes Otitis Media are treated by: High dose of Amoxicillin
  - This type has intermediate resistance
  - There is another type of Streptococcus pneumonia which is not intermediate, It's penicillin-resistant (higher level), which is seen in UK, where they use Cefuroxime widely to treat it.
  - The percentage of this penicillin-resistant strep pneumonia in UK is HIGHER than in USA and Jordan, so we aren't allowed to prescribe Amoxicillin against Penicillin-resistant Strep pneumonia (as the intermediate one); because they have resistance against Penicillin; SO it's treated by Cefuroxime (but by time, there is another resistance again Cefuroxime, we are losing this drug).

- Cefoxitin and Cefotetan:
  - Are active against the anaerobes, the most important is:
    - Bacteroides fragilis:
      - In the intestine, internally.
      - When I want to do internal surgery; such as: Colectomy or Appendectomy, I have to give the patient a drug that covers gastrointestinal flora, which are anaerobes.
      - Example: When I want to do colectomy, I do NOT give the patient Cefazolin, I give him Cefoxitin OR Cefotetan to cover the anaerobic flora.
    - Picture in slide 40:
      - When doing a surgery on the skin: we use Cefazolin
      - When doing a surgery around the gastrointestinal area: we use Cefoxitin or Cefotetan.
  - Are given IV, 1 hour before surgery.

Dr read slide 41, with some notes(About the second generation):
- Cefmetazole: Is not used anymore
- Diverticulitis: Infection happens in the colon, from anaerobes (B. fragilis)
  - The cause of peritonitis and diverticulitis is the same cause of the infection which happens during internal surgery, SO we give the same drug, which is: Cefoxitin, cefotetan
    (Of course it has activity to some G+ve and some G-ve, BUT mainly on anaerobes internally)

- Klebsiella pneumonia will be taken in the next lectures independently.
- Enteric bacteria are a big problem, we are losing their susceptibility toward amoxicillin, second and thirds generations of cephalosporins. (will be discussed later)
- A simple story is H.influenzae that causes Pneumonia: still susceptible to Amoxicillin and second generation of cephalosporins.
Third Generation:

- It's heterogeneous (Like the second generation- Not all the drugs are active against the same microorganism eg Pseudomonas)
- This group is active against more G-ve, and less G+ve.
- Ceftriaxone
  - Brand name: Rocephin
  - IV administration
  - NOT active against pseudomonas
  - It's called: ملبّس المستشفى
    - In most cases, nosocomial infection is caused by G-ve, SO we want a drug that is active against G-ve, which is Ceftriaxone.

A drug that is similar to Ceftriaxone is Cefotaxime" Slide 45"

Meningitis >> it is caused by N.mengidititis and S.pneumonia NOT pseudomonas

The drug of choice For treating meningitis in non immunocompromised patients is Ceftriaxon and Cefotaxime, why? *immunocompromised have a different story*

- Both cover:
  - Neisseria meningitidis
  - Streptococcus pneumonia
    - These two organisms are the common cause meningitis
    - Ceftriaxone is a good coverage for them
    - Does Pipercillin cover them? And why we don’t use it?
      Yes, piprcillin cover them, but the problem is with building the concentration up of the drug in the brain; Ceftriaxone and Cefotaxime can cross the blood brain barrier easily, thus, building up a HIGH concentration above MIC to produce clinical outcome (which with pipercillin is difficult to do).

- meningitis is more in Children
  - We treat meningitis by; Ceftriaxone OR Cefotaxime WITH Vancomycin. why?

    Because meningitis can also be caused by MRSA specially if it was hospital acquired.

- They can be used against Penicillin-resistant strains strep pneumonia (NOT the intermediate type which we treat them by double dose of Amoxicillin).
  - How can I know what are the organisms that have resistance that are in the hospital? By the survey, every organism that affect patients are recorded in annual survey. In case of nosocomial infection we have to cover all G-ve and G+ve because of the resistance.

- They are used in Gonorrhea
- 20-30% are resistant to Penicillin G, so we use Ceftriaxone for all type of gonorrhea.
- N.gonorrhea is susceptible 80% to penicillin G But if I am afraid of serious infection I give Ceftriaxone

- Ceftriaxone is used to treat lyme disease "severe type":
  - Lyme: حشرة بتشبه حشرة أبو علي
  - Caused by :Borrelia (Rare in our country) carried by the lyme
  - Cause toxicities.
  - Clarethromycin might be also used for treatment

**Clinical Pharmacology:** If Cefotaxime is similar to ceftriaxone why we have both?

- Ceftriaxone should **NOT** be used in children under 28 days, especially children **who have high Bilirubin** or **Hyperbilirubinemia**:
  - Bilirubin is attached to **albumin** in the blood
  - When taking Ceftriaxone, It attaches to albumin according to *competitive antagonism* which depend on concentration and replaces bilirubin
  - **Free** Bilirubin's concentration increases in the blood
  - It goes to the brain, Passes the blood brain barrier
  - Increment of its concentration in the brain causes **encephalopathy**.
  - Why does this happen in babies under 28 days, not after 28 days?
    - Because:
      1) The **excretion** of Ceftriaxone, and ONLY Ceftriaxone, outside the body is **NOT** complete, SO; there will be build up of Ceftriaxone in 28-day-old baby or younger.
      2) Volume of the blood, in a 28-day-old baby or younger, is **LOW**; thus, the concentration of the drug become high, and then the competition on albumin is stronger.
  - Another problem of Ceftriaxone, is that we can **NOT** give it(to a 28-day-old baby) with a calcium product, why?
    - Ceftriaxone binds to the calcium product, the compound will **precipitate** in the **lungs** and **kidneys**, which will lead to **DEATH**.
  - If you search for Rocephin in FDA (Food and Drug Administration), you will find warning: "Never give to an infant under 28 days Ceftriaxone + Calcium Concomantly"
  - Where does this calcium come from?
    - We give the patient solutions by infusion, one of them is calcium.
    - SO; we give them for the infant **separated by 2 days** (Ceftriaxone,,, 2 days,,, calcium solution) to avoid precipitation.
  - There were reviews about this matter:
    - FDA decided **not to take** Ceftriaxone + calcium-containing solution **FOR ADULT**.
  - What can we do in this case?
    - We give this adult **two lines**; one for Ceftriaxone, and the other for calcium, and I try not to give them at the same time. If I have to give both of them in the same line, I give Ceftriaxone first, then I **flush the line with saline**, after that I give the calcium solution.
Any child under 41 weeks (36 weeks intra uteru[pregnancy period]+ 4 weeks after birth[28 days] +1week[for no reason]= 41 weeks) **SHOULD NOT** take Rocephin with calcium, there must be 2 days between them to avoid precipitation in lungs and kidneys, especially if he has hyperbilirubinemia , which will cause encephalopathy.

- **Ceftazidime** (and Cefoperazone) *called Pseudomonal cephalosporins*
  - **Active against pseudomonas aureginosa**
    - Example : A patient with nosocomial infection in the hospital, I must **NOT** give him Ceftriaxone, I give him Ceftazidime
  - **Remember pipercillin**:
    - Extended spectrum penicillin
    - Covers G+ve more than Ceftazidime
    - Its spectrum:
      - G+ve
      - G-ve
      - **Pseudomonas**
        - NOT active against MRSA (treated ONLY by Vancomycin)
    - Ceftazidime is more **similar to Ticercillin**, Ticercillin is:
      - Active on G-ve, but less on G+ve(This is why we aren't using it so much)
      - Strong on **Pseudomonas**
  - SO, when I want to treat Pseudomonas, I use either Pipercillin, or Ceftazidime, in nosocomial infections.

Dr read slide 43, with these notes (about third generation):
- **ALL OF THEM** are active against G-ve
- When I want to treat Psuedomonas I use **CEFTAZIDIME**, not Ceftriaxone.
- Some of G-ve give **ESBL** (Extended-spectrum β-Lactamases) *Klebsiella and E.coli*
  - **Klebsiella pneumonia**(There are some hospitals that have a machine that you put the microorganism in it, and the machine make a susceptibility test and tell you whether this microbe produce ESBL or not). Common in USA, Israel, and we Have a good percent of ESBL K.pneumonia here in Jordan (around 10% -the # is Not accurate-)
  - Those microorganisms make a problem, why?
    - Because this type (which produce ESBL) does **NOT** respond neither to the third generation, From where this ESBL came from ?
    - Due to the abuse of Rocephin \ceftriaxone in hospitals
  - *The treatment of such organisms is difficult, and depend on susceptibility test*

An example >> the Dr once asked a dermatologist what does she prescribe for treating cellulitis ? "remember cellulitis is caused by 1- S.pyogens 2-Staph.aureus"
  - We know that the first generation is excellent in treating cellulitis but this Dermatologist used to give the patient ceftriaxone with 1st generation cephalosporins ! **THIS IS WRONG**!
- What is the problem of Rocephin?
Rocephin was used ALOT; so many Klebsiella and E. coli start producing extended spectrum Beta lactamases ESBL (slide 43, last paragraph is IMPORTANT).

When I give third generation to cover G-ve, I have to keep in mind that these G-ve in few years they will be resistant to third generation cephalosporins. In this case I have to use the fourth generation cephalosporins.

❖ To sum up:
  ➢ Third Generation:
    ▪ In case of Pseudomonas: Cefazidime (Like Ticercillin)
    ▪ Good coverage to G-ve: Cefazidime or Ceftriaxone
    ▪ In case of Meningitidis (Neisseria Meningitidis) I don't afraid of Pseudomonas, so I use Ceftriaxone or Cefotaxime, to build up concentration in the brain, also in case of penicillin-resistant strep pneumonia (Strep Pneumonia), Lyme disease and Gonorrhea.

Fourth Generation:

❖ When do I use them?
  When Third generation cephalosporins become inactive (They are still active)
  What is the advantage of fourth generation?
  They cover EVERYTHING.
  ➢ Like Pipercillin:
    ▪ It covers Pseudomonas
    ▪ Covers G+ve
    ▪ Covers G-ve: (EVEN THE EXTENDED ONES)
      • Klebsiella
      • E. coli
      • Serratia
      • Proteus >> UTI
      • Enterobacter
      • Shigella
      • H. influenzae
  ➢ It's a drug of choice, BUT NOT NOW, like the Pipercillin, last drug resort, used in ICU, ONLY when there is life threatening, WHY?
    We do NOT want to lose it (Like Imipenem, we lost it)

❖ Cefepime:
  ➢ We didn't lose it.
  ➢ It's active against: G+ve, G-ve, and Pseudomonas (extended spectrum)
  ➢ Brand name: Cefemax (means: max coverage)
  ➢ Dr read slide 46, with these notes:
We use it when third generation drugs are **NOT** active anymore.

Useful against : G+ve, enterobacteriaceae (G-ve), Pseudomonas, which are potential causes.

Dr read slide 47, with these notes:

- Which one is better than the others: Cefepime, pipercillin or Ceftazidime?
  - **Cefepime is the best** .. why? because its not susceptible to ESBL produced by some G-ve

- Does it cross Blood brain barrier?
  - Yes, it does. **BUT** we do not want to use it now (it's the last drug resort). for meningitis, we use Rocephin.

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لا تخشِ أن حياتك سيكون لها نهاية... ما يجب أن تخشاه هو مضي حياتك دون أن تنجز فيها شيئاً عظيماً...

- عشاق القمم

Done by:
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