بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 13

Antibiotics Pt.5

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Cephalosporins

1st gen

- Cefadroxil
- Cefazolin
- Cephalexin
- Cephalothin

2nd gen

- Cefaclor
- Cefoxitin
- Cefuroxime

3rd gen

- Cefnidir
- Cefixime
- Cefotaxime
- Ceftazidime
- Ceftibuten
- Ceftriaxone

4th gen

Cefepime

A Recap of Cephalosporins from the last lecture:

There are five generations of cephalosporins, but you are only required to know the first four for the exam:

First Generation Cephalosporins:

The first generation includes **Cefalexin**, which is taken orally. It is used as prophylaxis for skin surgeries in both the hospital and the community because it targets **Staphylococcus and Streptococcus**. It is also a good oral choice for people who are allergic to penicillin.

Second Generation Cephalosporins:

Cefoxitin and Cefotetan are used as prophylaxis for abdominal surgeries because they target **anaerobic bacteria like Fragilis**.

Cefuroxime is another drug in this group that works similarly to **Augmentin**. We give Cefuroxime to patients who are allergic to penicillin as a substitute for Augmentin.

Third Generation Cephalosporins:

Ceftazidime targets Gram-negative bacteria like **Pseudomonas aeruginosa**, but it has very low activity against Gram-positive bacteria. It is used as an alternative to **Tazosyn for hospital-acquired infections** caused by bacteria such as **Pseudomonas, Enterobacter, Klebsiella, and Serratia.**

Ceftriaxone is effective against both Gram-positive and Gram-negative bacteria, but unfortunately, it does **not cover Pseudomonas**. It is used to **treat meningitis** because it can cross the blood-brain barrier. However, you should not use Ceftriaxone for children under 42 weeks who have hyperbilirubinemia. This is because it can cause bilirubin to precipitate and lead to toxicity; in this case, **Cefotaxime** is the safe alternative.

Additionally, **Cefnidir and Cefixime** are oral options for children with urinary tract infections.

Overuse of the third generation has caused resistance known as **Extended Spectrum Beta-Lactamases (ESBL)**, especially in Klebsiella, E. coli, and Proteus. We now use **Avibactam** combined with Ceftazidime to inhibit these enzymes and help kill ESBL bacteria.

Fourth Generation Cephalosporins:

The fourth generation includes Cefepime, also known as Cefemax. It has an extended spectrum that covers Gram-positive, Gram-negative, and Pseudomonas aeruginosa bacteria. Unlike the third generation, it does not induce ESBL resistance. We must be careful not to overuse it so that it does not become ineffective. It is used for severe, mixed infections involving multiple organs and multiple types of bacteria.

Fifth Generation Cephalosporins:

The fifth generation is not required for the exam. However, as a physician, you should know that it is active against **MRSA and Enterococcus.**

Fourth-generation cephalosporins

- ***cefepime,*** **have an extended spectrum of activity compared with the third generation.**

- **The fourth-generation cephalosporins are indicated for the empirical treatment of nosocomial infections (hospital acquired).**

  particularly useful when gram-positive microorganisms, Enterobacteriaceae and *Pseudomonas* all are potential etiologies.

Fourth Generation Cephalosporins

- 4th generation cephalosporins for 2 reasons
  - Extended spectrum of activity
    - gram-positives: similar to ceftriaxone
    - gram-negatives: similar to ceftazidime, including *Pseudomonas aeruginosa*; also covers beta-lactamase producing *Enterobacter* sp.
  - Stability against β-lactamases; poor inducer of extended-spectrum β -lactamases
- Only cefepime is currently available

Clinical uses

- **For example, cefepime has superior activity against nosocomial isolates of *Enterobacter, Citrobacter,* and *Serratia* spp. compared with ceftazidime and piperacillin (Jones *et al.*, 1998).**

- **Cross blood-brain barrier and are effective in meningitis (Ceftriaxone).**

Cephalosporins adverse effects

Explained in the next slide:

- **Hypersensitivity, patient who has an anaphylactic response to penicillin should avoid cephalosporins.**

- **N-methyl-thiotetrazole-containing cephalosporins**
- **cefamandole, cefotetan, cefditoren, cefoperazone, and only**

1) A disulfiram-like effect: happened when some cephalosporins is indigested with alcohol, because of the blockade to the alcohol metabolism, which result in accumulation of acetaldehyde.

2) Bleeding: some cephalosporins have an anti vitamin K effect, and may cause bleeding (hypoprothrombinemia).

Cross-Sensitivity:

About 10% of people who are allergic to penicillin (which are 10%) are also allergic to cephalosporins. This crossover hypersensitivity means that, in total, roughly 1% to 2% of the population is hypersensitive to both types of antibiotics, so we must be aware of this risk.

Side Effects of Cephalosporins:

1. Disulfiram-like Effect (Ceftriaxone):

Ceftriaxone can cause a reaction similar to the drug Disulfiram, as it contains N-methyl thiotetrazole. Because Ceftriaxone is similar to the enzyme **aldehyde dehydrogenase (ALDH)**, it can inhibit this enzyme. If a patient drinks alcohol while taking this medication, the inhibition of ALDH causes toxic acetaldehyde to **accumulate** in the body, because Cefatriaxone binds to acetaldehyde preventing ALDH working on it. This accumulation leads to severe **nausea and vomiting**, which discourages the patient from drinking alcohol and can help **stop addiction**.

2. Bleeding Risk:

Ceftriaxone can also lead to bleeding issues. It binds to prothrombin and inhibits it, causing a condition called **hypoprothrombinemia**. This lowers the body's ability to clot blood effectively, which can result in excessive bleeding.

Cephalosporins interactions

- **Ceftraixone and calcium product , FDA warning.**

- ***Note***

cefoperazone and ceftriaxone are exceptions because they are excreted predominantly in the bile.

FDA Warning for Ceftriaxone:

Ceftriaxone has a warning from the Food and Drug Administration (FDA). You must be very careful when administering **calcium** products at the same time as Ceftriaxone.

Ceftriaxone Excretion:

Ceftriaxone and Cefoperazone are **exceptions as they are excreted through the bile and feces** rather than the kidneys. This makes them excellent choices for **patients with kidney failure**. You do not need to adjust the dose of Ceftriaxone for these patients because the drug does not build up in the kidneys, so toxicity will not occur.

Ceftobiprole – Injectable Anti- MRSA Cephalosporin Antibiotic

These 5th generation cephalosporins are not required.

Ceftobiprole coverage and pharmacokinetic

These 5th generation cephalosporins are not required.

- ✓ Ceftobiprole, a novel, broad-spectrum, parenteral cephalosporin, inhibits the cell-wall synthesis of penicillin-binding proteins (pbps) pbp2a and pbp2x, responsible for the resistance in staphylococci and pneumococci, respectively.
- ✓ Ceftobiprole has good activity against :
- Gram-positive aerobes and anaerobes; methicillin-resistant staphylococcus aureus (MRSA) and methicillin-resistant staphylococcus epidermidis (MRSE), penicillin-resistant streptococcus pneumoniae, enterococcus faecalis as well as many gram-negative bacilli
- Ceftobiprole is relatively inactive against *acinetobacter* species.
- Its ability to bind relevant pbps of resistant gram-positive and gram-negative bacteria indicates ***its potential use in the treatment of hospital-acquired pneumonia and complicated skin and skin-structure infections (CSSSIS).***

Carbapenems:

Carbapenems: are considered some of the best drugs available. This group includes **Imipenem (Tinam), Meropenem, and Ertapenem**. They have the broadest spectrum of activity and include coverage for **Enterococcus**. However, they do not work against Methicillin-Resistant Staphylococcus Aureus (MRSA) because the **penicillin-binding protein in MRSA is altered,** which prevents the drug from binding.

Carbapenems spectrum:

Carbapenems are more effective than Cefepime (Cefemax) against aerobic bacteria, anaerobic bacteria, and bacteria that produce ESBL. Despite their broad range, Carbapenems do not cover MRSA, Vancomycin-Resistant Enterococci (VRE), Coagulase-negative Staphylococcus, Clostridioides difficile, or Nocardia.

Note: Ertapenem is an exception in this class because it is **not active against Pseudomonas or Enterococcus**. While Carbapenems are generally good for mixed infections involving pus and biofilms, Ertapenem is not used for these specific cases.

Carbapenem

- **Doripenem, ertapenem, imipenem, and meropenem are licensed for use in the USA.**

- **Imipenem has a wide spectrum with good activity against many gram-negative rods, including *P aeruginosa,* gram-positive organisms, and anaerobes.**

- **Imipenem is inactivated by dehydropeptidases in renal tubules, so administered together with an inhibitor of renal dehydropeptidase, cilastatin, for clinical use:**

Imipenem is always given in combination with **Cilastatin**. Cilastatin **inhibits** an enzyme called **dehydropeptidase**, which prevents the metabolism and breakdown of Imipenem. This allows Imipenem to stay in the body and work effectively. This interaction is known as **potentiation or synergism**, where the helper drug significantly boosts the effect of the antibiotic.

Carbapenems

Explained in the previous slides:

(Imipenem, Meropenem and Ertapenem)

- Most broad spectrum of activity of all antimicrobials
- Have activity against gram-positive and gram-negative aerobes and anaerobes
- Bacteria not covered by carbapenems include MRSA, VRE, coagulase-negative staph, *C. difficile*, *Nocardia*
- **Additional ertapenem exceptions:**
  - ***Pseudomonas and Enterococcus***

Carbapenem

- **A carbapenem is indicated for infections caused by susceptible organisms that are resistant to other available drugs, eg, *P aeruginosa*, and for treatment of mixed aerobic and anaerobic infections.**

- **it is also the treatment of choice for infections caused by extended-spectrum beta-lactamases–producing gram-negatives.**

Example:

A carbapenem is the beta-lactam antibiotic of choice for treatment of enterobacter infections because it is resistant to destruction by the lactamase produced by these organisms; They aren't affected by lactamases produced by some bacteria.

Carbapenems:

- Its side-effects are similar to those seen with other b- lactam antibiotics,

- Nausea and vomiting been the most frequently encountered.

- At high doses neurotoxicity can occur.

Side Effects of Carbapenems:
High doses of Carbapenems can cause **neurotoxicity**, which leads to **seizures, nausea, and vomiting**.

Note: Imipenem is the specific drug in this class that is **most likely** to cause nausea and seizures.

Class A Carbapenemases

See next slide:

- Most common in Klebsiella pneumoniae (KPC)
- Also seen in E. coli, Enterobacter, Citrobacter, Salmonella, Serratia, Pseudomonas and Proteus spp.
- Very often with multiple other drug resistance mechanisms, resistance profile similar to ESBL but also carbapenem resistant
- Became problem in New York City first in 2002-2003 and is being increasingly recognized in Mid-Atlantic US.
- Spreading across species to other gram-negatives and enterobacteriaceae

Carbapenems:

Imipenem (Tinam):

The overuse and misuse of Imipenem (Tinam) have caused resistance. **Klebsiella pneumoniae now produces Class A Carbapenemase**, which breaks down the drug. This resistance has also spread to other bacteria, including E. coli, Serratia, and Enterobacter. As a result, Imipenem has become useless against many of these resistant bacteria.

Meropenem:

Meropenem is **not susceptible to this specific carbapenemase**. However, we must use it correctly and carefully to ensure we do not lose its effectiveness like we did with Imipenem.

Note: Mistakenly prescribing Imipenem instead of Meropenem for a patient increases the death rate by three times.

رسالة من الفريق العلمي:

أصعب شيء على المجاهد في سبيل الله أن يعيش عمره مجاهدًا بين الخنادق والجبهات، ثم يموت على فراشه، وليس في المعركة شهيدًا،
وأجمل ما ينتظره المجاهد بعد مسيرته العظيمة: أن يكرمه الله بالشهادة في سبيله.

والنبي ﷺ بنفسه تمنى أن يُقتل في سبيل الله مرارًا كما ثبت عنه في صحيح البخاري أنه قال:
"والذي نفسي بيده، لوددت أني أُقتل في سبيل الله، ثم أُحيا ثم أُقتل، ثم أُحيا ثم أُقتل".

تقبّل الله خيار شباب أمتنا الذين قضوا شهداء في معاركها العظمى، وعوّض الأمة خيرًا بفقدهم.

-الشيخ أحمد السيّد

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			