◉Sheet ○Slides

number : 12

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Please note that everything marked **EXTRA** in this sheet is not for memorization, but the doctor explained it as additional information.

RECAP: In the last lecture we started talking about cephalosporins, and that they are subdivided to generations. These generations are solely based when the drug was discovered, and does **not** mean the larger the generation the wider spectrum.

EXTRA: For example, first generation cephalosporins were first discovered in 1964, second generation cephalosporins were discovered in the 1970s, third generation in 1980s…etc.

First generation: skin infection patients allergic to penicillins are treated with first generation cephalosporins. We either give them cephalexin or cefadroxil orally, or an injection of cefazolin. These drugs are used as prophylactics before surgeries, when the microflora of the skin is the risk of infection. Usually, 1gm is usually given one hour before the surgery.

Second generation: We divide them to two groups:

1. Cefuroxime: it is like Augmentin(amoxicillin +clavulanate), because it is active against streptococcus pneumoniae, staphylococcus aureus, and H influenza. It is used to treat upper respiratory tract infections. A popular trade name for cefuroxime is Zinnat.
2. Cefoxitin: it has little activity against gram positive and gram negative, but it has great activity against Bacteroides fragilis group, which is a part of the normal flora in the abdomen. It is used for treatment of diverticulitis and peritonitis. So if there is a patient that will undergo colorectal surgery, he is given cefoxitin before the surgery instead of cefazolin.

Third generation cephalosporins:

Third generation cephalosporins are divided to three groups:

1. Cefnidir and Cefixime.
2. Ceftazidime.
3. Ceftriaxone and Cefotaxime.

1. Cefnidir and Cefixime:

Both have good activity against gram positive and gram negative. However, their spectrum doesn't cover Pseudomonas. They are used in case of respiratory tract infections (active against S. pneumoniae, S. aureus, H. influenzae, E. coli…etc.). They have the same properties of cefuroxime , so why are they in the 3rd generation? Simply because they were discovered after the 2nd generation cephalosporins were.

- To treat upper respiratory tract infections we use: 1.Augmentin 2.Cefuroxime 3. Cefnidir 4. Cefixime.

2. Ceftazidime:

   Ceftazidime is active against and generally every type of gram negative, but it is not active gram positive. It is similar to tazocin (piperacillin and tazobactam injection), but is not the same. Tazocin is active against gram positive and negative.

   Ceftazidime covers Pseudomonas, so it is used when the patient has hypersensitivity towards penicillin, and has a pseudomonal infection.

- Until now there are only two drugs that cover pseudomonas: 1. Tazocin (piperacillin and tazobactam) 2. Ceftazidime
- What drug is used when the patient has an allergy to penicillins, and I don't know if he is infected with gram positive or negative?

  Gram negative is treated with ceftazidime, and we cover gram positive with another drug that we'll take later (vancomycin).

  STUDENT'S QUESTION: How do you choose an antibiotic for someone infected with H influenzae?

  Firstly, if the patient has any type of upper respiratory tract infection , he is treated with Augmentin unless he has an allergy, we use cephalosporins. Which one exactly? We use cefuroxime (because it is older). If the patient did not respond to it we use cefnidir or cefixime.

  Or we use the drugs depending on the community. Here in Jordan, a lot of S. pneumoniae has started to build resistance to Augmentin and cefuroxime, but they're not resistant to either cefnidir or cefixime. It is predicted that after five years we won't be able to use cefnidir or cefixime.

The reason we don't use them immediately is because we don't want bacteria to build resistance against them.

However, in some cases regarding children only cefnidir is used, because the percentage of S. pneumoniae causing otitis media that has built resistance to it is very little. But you always have to start with Augmentin.

3. Ceftriaxone and Cefotaxime.
   Ceftriaxone is used for initial treatment meningitis in nonimmuno-compromised patients (the only drug used for treatment of meningitis, because of their antimicrobial activity). It can penetrate into the cerebrospinal fluid (CSF), and a record for clinical success. It is active against gram positive and negative, S. aureus, S. pneumoniae, H. influenzae, and Neisseria meningiditis. It does not cover pseudomonas, but it is not a problem because it does not cause meningitis.
   Meningitis is a very risky infection. If it ended up with a child and it was not treated, he will develop mental retardation. If an adult was infected, he may suffer from delirium, amnesia and dizziness.
   The most important thing in treating meningitis is the fast intervention, and using a drug that can reach the brain in high concentrations, that drug is ceftriaxone (Rocephin is its trade name). Rocephin was overused, it was prescribed wrongly to patients with any type of infection.

- What does 'a record for clinical success' mean?
  It means it has great penetration, great activity, and it is cheap.

- There is a small problem concerning the Rocephin drug (ceftriaxone) when treating young patients. Let's say that we have 28-day-old or less infant, and his skin was a bit yellow but not to the extent of jaundice (has hyperbilirubinemia), his skin will turn back to normal after a certain period of time without treatment. The problem is when we give him ceftriaxone, because it interferes with the metabolism of bilirubin, and it displaces bilirubin from the albumin (bilirubin is carried in the blood by albumin). In this case bilirubin will accumulate in the brain causing encephalopathy. That's why it is contraindicated to give ceftriaxone to babies under 28 days or even to jaundice patients.

EXTRA: Some books say that ceftriaxone should not be used on child aged 42 weeks or less, this means after 4 weeks of birth (most children are born on the 38^{th} week). It is written this way to include premature babies, if a baby was born, for example, on the 30^{th} week, we don't give them any ceftriaxone unless after 12 weeks.

So what do we use in cases of babies with hyperbilirubinemia or jaundice patients? We use cefotaxime. Cefotaxime is not preferred to be used on all patients, because the half-life of ceftriaxone is longer (6 hours), it stays longer in the brain without being broken down, while the half-life of cefotaxime is 1.5-2 hours.

- Some of the reasons we prefer some drugs over others:
  1. The half-life of the drug.
  2. Side effects.
  3. Contraindications
  4. 'Keep it until you need it'. Especially antibiotics. We don't jump to the widest spectrum or most recent drug.

  Also, Ceftriaxone and cefotaxime are the most active cephalosporins against penicillin-resistant strains of pneumococci. And it is the therapy of choice for all forms of gonorrhea and severe forms of Lyme disease.

Fourth generation cephalosporins:

Why is there fourth generation of cephalosporins? Because third generation is going away, this means that although in a time they were very good drugs, there are a lot of resistance being built against them, because they are strong inducers of extended spectrum β-lactamase (ESBL).

Cefapime is the only drug in this generation, and it is a great drug, because it has stability against ESBL, and it is a poor inducer of it, and has a wide spectrum of activity that covers gram positive, gram negative, pseudomonas aeruginosa. But it does not cover MRSA nor Enterococci.

Enterobacteriaceae (which are gram negative and includes: Shigella, Salmonella, Serratia, Proteus, and Klebsiella) and E. coli might produce ESBL, but cefapime is not susceptible to ESBL like third generation cephalosporins. Most of enterobacteriaceae has built resistance to 3rd generation but not to cefapime.

Also, cefapime can cross the blood brain barrier and is effective in treating meningitis, but we still use ceftriaxone, because S. pneumoniae, H. influenzae, and N. meningitidis have not developed resistance against it yet. When they do

build resistance against ceftriaxone we will start using cefapime to treat meningitis.

- Fourth generation cephalosporins are indicated for the empirical treatment of nosocomial infections, particularly useful when gram positive microorganisms, enterobacteriaceae, and pseudomonas are all potential etiologies. That means if your patient developed a nosocomial infection, and you know that the hospital is full of gram positive ad gram negative (which include enterobacteriaceae), you either give them piperacillin with tazobactam (tazocin), or you give them cefapime if they have an allergy.
- What do we do if someone was infected with gram negative bacteria? Do we skip third generation cephalosporins and immediately give them cefapime? No, we examine the gram negative bacteria, if it produces ESBL, we give them cefapime, if not, we give them third generation cephalosporins.

EXTRA: Fifth generation cephalosporins:
They are not very well known in Jordan. One of them is ceftaroline, it is a great new drug, but it is not active against ESBL producing enterobacteriaceae.
They are active against pseudomonas, MRSA, penicillin-resistant S. pneumoniae and enterococci which mainly causes endocarditis.

- Fifth generation cephalosporins are the only cephalosporins active against MRSA and enterococci.

Cephalosporins' adverse effects:

1. Hypersensitivity: patients who have the anaphylactic response to penicillins should avoid cephalosporins (10% of the patients who have allergy to penicillins are allergic to cephalosporins)
2. N-methyl-thiotetrazole-containing cephalosporins produce a disulfiram-like effect. Disulfiram is a drug used to treat alcoholics by inhibiting the metabolism of acetyl aldehyde, thus resulting in accumulation of acetyl aldehyde. This results in nausea, vomiting, and delirium when the patient drinks alcohol.
3. N-methyl-thiotetrazole-containing cephalosporins can cause bleeding. They have anti vitamin K effect and may cause bleeding (hypoprothrombinemia)

EXTRA: N-methyl-thiotetrazole-containing cephalosporins are cefamandole, cefotetan, ceftidoren, ceftoperazone.

EXTRA: This may be a bit complicated, that is why there is an 'infectious diseases specialist'. This specialist's job is to make surveys and to know the types of bacteria that are present in the hospital, and to know their properties and determine how to deal with them, because the bacteria that are in the environment are different than those in the hospital and they are not so threatening.

They know all of this information by counting how many in-patients were infected (hospital acquired, nosocomial infections) with a certain bacteria. MRSA and pseudomonas are the most important to look out for. And they classify the bacteria that infected the patients according to their sensitivity. At the end, they know which type of antibiotics they are and are not resistant to.

"The good physician treats the disease; the great physician treats the patient who has the disease."

Sorry if there were any mistakes.