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Thanks to Saad Qamar for providing me with his class notes.

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Cephalosporin pharmacology:

Introduction:
Cephalosporins are beta-lactam antibiotics like penicillins.

They are cell wall synthesis inhibitors. And are found in their natural and semisynthetic forms.

Cephalosporins are of variable spectrum, possessing bactericidal action.

They have a wide margin of safety (high therapeutic index).
The official generic names of cephalosporins end with prefix ‘ceph’ or ‘cef’.

**Natural source and discovery:**
Cephalosporin was isolated for the first time from fungi “*Cephalosporium acremonium*” by an Italian scientist Brotzu. There are three types of cephalosporins cephalosporin P, N and C. cephalosporin-C is the important prototype and the derived semisynthetic analogues use it as starting substance.

**Chemistry:**
Cephalosporin has two rings similar to penicillin. The primary ring is 7-amino cephalosporinic acid (beta-lactam ring) and the secondary ring is di-hydro thiazine ring.

**Classification of cephalosporins:**
There is a generation based classification of Cephalosporins, namely;

- 1\(^{st}\) generation
- 2\(^{nd}\) generation
- 3\(^{rd}\) generation
- 4\(^{th}\) generation

There are further subclasses in each of these generations which will be discussed.

**1\(^{st}\) generation cephalosporins:**
First generation cephalosporins are highly susceptible to beta-lactams. They are narrow spectrum (gram +ve and few ‘gram–ve’. They cannot cross blood-brain barrier.

1st generation cephalosporin antibiotics may be administered orally or parenterally.

*oral:*
cephalexin (ciporex), cephradine (velosef) and cefadroxil (buracef) are orally administered 1\(^{st}\) generation cephalosporins.

*Parenteral:*
Cefazolin (kefzol, Ancef), cephalothin, cephaloridine, and cephapirin are parenterally administered 1\(^{st}\) generation cephalosporin.

**2\(^{nd}\) generation cephalosporin:**
2\(^{nd}\) generation cephalosporin is intermediate spectrum antibiotics. With exception of few most cannot cross the blood-brain barrier. Cephalosporin is susceptible to beta-lactamases with exception of few members.

*Oral:*
Orally administered 2\(^{nd}\) generation cephalosporin antibiotics are;

- Cefaclor
- Cefprozil
Cefuroxime axetil
Lorocarb f

**Parenteral:**
- Cefamandole
- Cefonicid
- Cefuroxime sodium
- Cephapirin (7 amino analogues of cephalosporin).
- Cephamycin (cephalosporin+cephamycin)

Cefmetazole, cefotetan, cefoxitin; these three antibiotics are highly effective against anaerobic bacteria.

**Third generation cephalosporin antibiotics:**
These are extended-spectrum antibiotics.

Most of them cannot cross blood-brain barrier

These are resistant to beta-lactamases.

The oral and parenteral antibiotics included in this class are as under.

**Oral:**
Orally administered 3rd generation cephalosporin includes;
- Cefixime
- Cefdinir
- Cefpodoxime
- Ceftibuten
- Cefditoren

**Parenteral:**
- Cefotaxime
- Ceftriaxone
- Ceftizoxime
- Ceftazidime
- Cefoperazone
- Moxalactam

Are parenterally administered 3rd generation cephalosporin.

**4th generation cephalosporin:**
These are reserve drugs used in case of resistances to the antibiotics discussed earlier.

4th generation cephalosporins are broad spectrum including cefepime, cefpirome as examples.
Spectrum of cephalosporins:
The spectrum of a particular antibiotic means the range of microbes against which the antibiotic will be useful. Cephalosporins are with a very diverse spectrum. For easy differentiation we’ve further classified this topic into individual generation based.

Spectrum of first-generation cephalosporins:
1st generation cephalosporins are effective against a wide range of microbes including gram-positive and few gram-negative microbes.

Their spectrum includes streptococi pyrogens, streptococcus pyogens, streptococcus pneumoniae, streptococcus mutam, streptococcus agalactae and streptococcus viridian.

Staphylococcal aureus, staphylococcal saprophyticus, and staphylococcal epidermitis.

And estredia.coli.

The spectrum of second-generation cephalosporins:
The spectrum of second-generation cephalosporins includes most those of 1st generation plus some other microorganisms especially gram negative.

These include; Enterobacter aerogenes, Haemophilus influenzae, moraxilla catarahalis and Neisseria spp.

Spectrum of 3rd generation cephalosporins:
3rd generation cephalosporins have an even broader spectrum that the first two discussed earlier.

Their spectrum includes all those of 1st and 2nd generation with an addition of some other microorganisms including salmonella typhi, Pseudomonas aeruginosa, Vibrio cholera and other gram-negative organisms.

4th generation cephalosporins spectrum:
The spectrum of 4th generation cephalosporins is same as that of the 3rd generation which we discussed earlier but they are more effective and with increased toxicities, so they are used in case of resistance.

Clinical uses of cephalosporins:
The clinical uses of cephalosporins can be easily guessed from the spectrum we’ve discussed earlier;

In this section, I will discuss their spectrum generation vise.

1st generation:
1st generation cephalosporins are clinically effective for skin and soft tissue infections esp cefazolin which is also used prophylactically for surgical infections.
2\textsuperscript{nd} generation:
This can be useful in mixed abdominal and pelvic infections of anaerobic origin.

Cefoxitin and cefotetan is an example.

2\textsuperscript{nd} generation drugs are also effective in respiratory infections.

3\textsuperscript{rd} generation cephalosporins:
Third generation drugs of this class are effective for a considerable range of microbes infections.

For instance, typhoid fever can be treated with ceftriaxone (drug of choice) and cefoperazone. Ceftriaxone is also the drugs of choice for gonococcal infections.

Similarly, meningitis caused by H influenza can also be treated with ceftriaxone and cefotaxime. Ceftriaxone is also used for another mix aerobic and anaerobic infections in malignancy, for nosocomial (hospital acquired infections) and for urinary tract infections.

4\textsuperscript{th} generation:
As we’ve studied earlier in this article that these are not quite commonly used drugs and are reserved drugs used when there is severe drug resistance to the former discussed drug classes.

Side effects:
The side effects of cephalosporins are extended over a wide range in acute, moderate and less common side effects.

Majority of its side effects are associated with hypersensitivity reactions including skin rashes, skin rashes urticaria, serum sickness, anaphylactic shocks etc.

Cephalosporins should not be used in individuals which are allergic to penicillins.

Hematological side effects of cephalosporins include hypoprothrombinemia which is a bleeding disorder encountered in vit. K deficiency.

“methyl, thio, tetra, and azole containing antibiotics are responsible for causing neutropenia, thrombocytopenia, hemolytic anemia and blood dyscrasias etc.

GIT related side effects include diarrhea, superinfections, disulfiram-like reactions due to increase aldehyde characterized by flushing , tachycardia, git problems etc.

Other side effects include phlebitis (inflammation of a vein in the leg) with iv administration, interstitial nephritis etc.

For most of the side effects dose adjustments are needed to get rid of them or to lessen the severity
Resistance of microbes toward cephalosporins:

A pathogen may show resistance to cephalosporin by any of the following general mechanisms of antibiotic resistances:

The major mechanism of resistance is by enzymatic degradation of cephalosporins by cephalosporinase enzymes.

Another mechanism that can play a role can be a decrease of the cell permeability of bacterial cell toward cephalosporins.

Similarly, the bacteria may alter its binding sites (cephalosporin binding protein).

A pathogenic bacteria may even develop an efflux pump for cephalosporins that flushes them out of the cell.

Following are some pathogenic microbes that have shown resistance towards cephalosporins by the mechanisms described earlier.

These microbes include;

- Listeria monocytogenes
- Legionella pneumophylla.
- Mycoplasma
- Mycobacterium spp.
- MRSA (methicillin resistance streptococcus aureus).
- Enterococcus liquifaceous etc.

This list can be tricked to remember by the pneumonic “LAME”.