Lec 3 **Antibiotics**

Cephalosporins

1) Cephalosporins are β-lactam compound in which the beta-lactam ring is fused to a dihydrothiazine ring.

2) They have low toxicity and broader spectrum than natural penicillins.

3) Cephalosporins compared with pencillins, they are in general less active against gram positive organism but more active against gram negative organisms.

4) Cephalosporins inhibit bacterial wall synthesis in a manner similar to that of pencillin.

5) Most cephalosporins are excreted through the kidneys**.**

Classification of cephalosporins

Cephalosporins may be classified by their:

1) Chemical structure

2) Clinical pharmacology

3) Resistance to β-lactamase.

4) Antimicrobial spectrum.

The well accepted system of classification is by generations and classification by generations is based on general features of antimicrobial activity.

1) First generation Cephalosporins

A) They are effective against staphylococci and streptococci such as: Cefazolin, Cephalothin, Cephalexin, Cefadroxil, Cephradine

B) Cefazolin, Cephalothin, Cephalexin have good activity against most gram positive cocci (*Streptococcus, Pneumococcus*) and they are more active against gram negative organisms (*E.coli*, *Klebsiella* and *Proteus*).

C) They are effective against some anaerobic cocci (*Peptococcus* and *Peptostreptococcus*).

D) They are not effective against *Enterobacter* and *Pseudomonas*.

2) Second generation Cephalosporins

A) They have a greater gram negative spectrum while retaining some activity against gram positive bacteria.

B) They are more resistant to β-lactamase and they are useful agents for treating upper and lower respiratory tract infections.

C) They are active against *E.coli*, *Klebsiella* and *Proteus* such as: Cefaclor, Cefuroxime, Cefonicid, Cefoxitin,

D) Cefuroxime, Cefamandole, Cefaclor are effective against *Haemophilus influenza*

3) Third generation Cephalosporins

A) They have a broad spectrum of activity and further increased activity against gram negative organisms.

B) The spectrum is extended to include: *Enterobacter, E.coli, Proteus mirabilis, Klebsiella, Pseudomonas*

C) Ceftriaxone and Cefotaxime have excellent activity against most strains of *Streptococcus pneumoniae*

D) Only Cetizoxime and moxalactum retain good activity against *Bacteroides fragilis*

E) Cefotaxime active against gram negative bacteria such as: *Pseudomonas aeruginosa,*

F) Ceftriaxone easily passes meninges and diffuses into CSF to treat CNS infections.

4) Fourth generation Cephalosporins

A) They have a greater spectrum of antimicrobial activity and a greater resistance to beta lactamases than the third generation cephalosporins.

B) Many of these cephalosporins can cross blood brain barrier and are effective in meningitis.

C) Cefepime has broad gram negative coverage with somewhat enhanced activity against *Pseudomonas.*

D) Cefpirome is more active against *Pneumococci* and has somewhat lesser activity against *Pseudomonas*.

E) Cefepime and Cefpirome are highly active against nosocomial pathogens such as: Enterobacter and Acinetobacter.

F) Both antibiotics have good activity against *Staphylococcus aureus* except for methicillin resistant strains and *Staphylococcus haemolyticus* which are of borderline sensitivity.

G) Both antibiotics have little useful activity against *Bacteroides fragilis* group or *Bacteroides oralis* group.

Therapeutic uses of Cephalosporins

A) Clinical studies have showm cephalosporins to be effective as both therapeutic and prophylactic agents.

B) The first generation Cephalosporins are excellent agents for skin and soft tissue infections owing to *Streptococcus pyogenes*.

C) For colorectal surgery, where prophylaxis for intestinal anaerobes is desired, and the second generation agent cefoxitin is preferred.

D) The third generation Cephalosporins is the drugs of choice for infections caused by *Klebsiella, Enterobacter, Proteus, Serratia*

Adverse reactions

A) Hypersensitivity reactions to the Cephalosporins are the most common side effects. The reactions appear to be identical to those caused by the penicillins.

B) Nephrotoxicity has been reported.

C) Diarrhea can result from the administration of Cephalosporins.

D) Serious bleeding related either to hypoprothrombinemia owing to the methylthiotetrazole (MTT) group, thrombocytopenia and or palettes dysfunction has been reported with several B-lactam antibiotics.

E) The cephalosporins that contain the methylthiotetrazole include Cefotetan, Cefamandole, Moxalactam and Cefoperazone.

Other β-lactam antibiotics

A) Carbapenems

They have a broad spectrum of activity than most other β-lactam antibiotics, such as: Imipenem, Meropenem

1) Imipenem

A) It is marketed in combination with cilastatin (Drug that inhibits the degradation of imipenem by renal tubular dipeptidase)

B) It is derived from a compound produced by *Streptomyces cattleya*

C) It binds to penicillin binding proteins and disrupts bacterial cell wall synthesis and causes death of susceptible microorganisms.

D) It is very resistant to hydrolysis by most β-lactam antibiotics.

Therapeutic uses of imipenem

A) Urinary tract and lower respiratory infections

B) Intra-abdominal

C) Skin, soft tissue, born and joint infections

Adverse reactions

A) Imipenem is not absorbed orally.

B) Nausea and vomiting are the most common adverse reactions.

C) Patients who are allergic to other β-lactam antibiotics may have hypesensitivity reactions when given imipenem.

2) Meropenem

A) It does not require co-administration with cilastatin because it is not sensitive to renal dipeptidase.

B) Clinical experience with meropenem demonstrated therapeutic equivalence with imipenem.

B) Monobactams

1) Aztreonam

A) It is isolated from *Chromobacterium violaceum*

B) It interacts with penicillin binding proteins of susceptible microorganisms.

C) It is resistant to many of β-lactamase produced by most gram negative bacteria.

D) It has activity only against gram negative bacteria

E) It has no activity against gram positive bacteria

F) Patients who are allergic to penicillins or cephalosporins appear not to react to aztreonam.

β-lactamase inhibitors

They are most active against plasmid encoded β-lactamases (including the enzymes that hydrolyze ceftazidime and cefotaxime)

1) Clavulanic acid

A) It is produced by *Streptomyces clavuligerus*

B) It is a (suicide) inhibitor that irreversibly binds β-lactamases produced by a wide range of gram positive and gram negative microorganisms.

C) It has been combined with amoxicillin as an oral preparation (Augmentin) and with ticarcillin as a parenteral preparation (Timentin).

2) Sulbactam

A) The combination Sulbactam with ampicillin has good activity against gram positive cocci, gram negative aerobes (but not resistant strains of *E.coli* or *Psedomonas*).