CEPHALOSPORINS

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CEPHALOSPORINS

-- Derived from Cephalosporin-C

--Beta-lactum ring fused with Dihydrothiazine ring.

--Modification at side chain at position 7 of beta lactum ring alters antibacterial spectrum while alteration at position 3 of dihydrothiazine ring alters P/K profile

-- acid stable

-- spectrum of activity against Gm+ve,–ve bacteria and anaerobes

-- not active against MRSA (Methicillin Resistant Staphylococcus Aureus).

First generation cephalosporins

Parenteral

- Cephalothin (I.V.), Cefazolin(I.V.)

Oral

- Cephalexin
- Cephradine
- Cefadroxil

Second generation cephalosporins

Parenteral (i.v.)

- Cefuroxime
- Cefoxitin
- Cefamandole

Oral

- Cefuroxime axetil
- Cefaclor

Third generation cephalosporins

Parenteral

- Cefotaxime
- Ceftizoxime
- Ceftriaxone
- Ceftazidime
- Cefoperazone

Oral

- Cefixime
- Cefpodoxime proxetil
- Cefdinir
- Ceftibuten

Fourth generation cephalosporins

Parenteral

- Cefepime
- Cefpirome

MECHANISM OF ACTION

- Bacterial cell wall synthesis inhibition like Penicillin.

Penicillin –G (Mechanism of Action)

Penicillins

↓

Bind and Inactivate PBP's (Penicillin Binding Proteins) on the cell wall of suceptible bacteria

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Inhibit Transpeptidase Enzyme

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Prevent synthesis of Peptidoglycan

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Cell Wall Deficient Forms (Spheroplasts and Filamentous Forms)

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Autolysis

↓

Cell Death Occurs (Bactericidal Effect)

FIRST GENERATION CEPHALOSPORINS

- high activity against gram-positive but weaker against gram-negative bacteria.
- Ineffective in meningitis
- All are sensitive to B-lactamase enzyme.

Cefazolin

- Streptococci (pyogenes as well as viridans), gonococci, meningococci, C. diphtheriae, H. influenzae, clostridia and Actinomyces.

- **Klebsiella and E. coli**
- **i.m. (less painful) as well as i.v.**
- **90% bound to plasma protein**
- Cefazolin used for :-
- *Surgical prophylaxis* :-
- **--Effective -> microbes causing wound infs.; longer Pl. t1/2; good tissue penetrability**

- Cephelexin and Cefadroxil used for :-
- URTIs, ENT infections in children & adults.
- Minor Skin & Soft Tissue Infections (SSTIs) like Abscesses or Cellulitis.

Cephalexin :

less active against penicillinase producing Staphylococci and H. influenzae.

0.25-1 g 6-8 hourly

Cefadroxil

Attains Good conc. in Plasma & urine

Used in UTIs, RTIs & SSTIs.

- given 12 hourly despite a t ½ of 1 hr.
- 0.5-1 g BD.

SECOND GENERATION EPHALOSPORINS

- more active against gram-negative & some Gm +ve & anaerobes (B.Fragilis) organisms
- More Resistant to Beta-Lactamases
- none inhibits P. aeruginosa.

Cefuroxime (I.M,I.V.); Cefuroxime axetil (Oral)

resistant to gram-negative β-lactamases:

- retaining significant activity on gram-positive cocci and certain anaerobes.
- attains relatively higher CSF levels *(effective against H.Meningitis, N.Meningitis & S.Meningitis)*
- employed for single dose i.m. therapy of gonorrhoea due to PPNG.

Cefaclor

- more active than the first generation compounds against H. influenzae, E. coli
- Orally effective in RTI,UTI,SSTIs.

THIRD GENERATION CEPHALOSPORINS

- highly augmented activity against gram-negative Enterobacteriaceae, anaerobes
- some inhibit Pseudomonas
- Higher conc. in CSF → Meningitis

- All are highly resistant to β-lactamases from gram-negative bacteria.

- less active on gram-positive cocci

Cefotaxime

- potent action on aerobic gram-ve ; +ve bacteria
- Resistant to Beta-lactamases
- Metabolized to active metabolite
- Higher conc. In CSF → Meningitis
- not active on anaerobes , Staph. aureus and Ps. aeruginosa

indications of Cefotaxime (i.v. ; i.m.)

- meningitis caused by gram-negative bacilli (attains relatively high CSF levels)
- life-threatening resistant / hospital-acquired infections
- speticaemias
- infections in immuno-compromised patients (AIDS, Cancer , on Corticosteroid therapy).
- Dose : 1-2 g i.m/i.v. 8-12 hourly,

Ceftizoxime (I.V., I.M.)

inhibits B. fragilis (anerobes) also .
Therefore preferred in Pelvic, abdominal, genitourinary tract or oral surgery

Ceftriaxone (I.V.,I.M.)

- **longer duration of action (t ½ 8 hr)**
- **Penetration into CSF (B.D. dose in Meningitis). Excreted in bile, safe in renal disease**

serious infections

- **bacterial meningitis (especially in children)**
- **Multi-resistant typhoid fever**
- **Typhoid (enteric) fever in children(I.V.)**

- complicated UTI
- abdominal sepsis
- septicaemias.
- Hypoprothrombinaemia and bleeding are specific adverse effects of Ceftriaxone.

Ceftazidime (I.V., I.M.)

- high activity against Pseudomonas
- used in febrile neutropenic patients with haematological malignancies, burn, etc
- less active on Staph. aureus, other gram positive cocci and anaerobes like Bact. fragilis.
- rise in plasma transaminases and blood urea have been reported.

Cefoperazone (I.V.,I.M.)

- stronger activity on Pseudomonas
- good for S. typhi and B. fragilis
- more susceptible to β-lactamases.
- Excreted in bile, no dose adjustment in renal disease
- A disulfiram-like reaction with alcohol
- Causes Hypoprothombinemia leading to bleeding→ requires Vit.-K inj Prophylactic

Cefixime (Oral):

- highly active against Enterobacteriaceae, H. influenzae, Salmonella Typhi.
- resistant to many β-lactamases.
- is not active on Staph. aureus, pneumococci and Pseudomonas
- Used in RTI,UTI & Biliary Tract Infections
- diarrhoea are the most prominent side effects.

Cefpodoxime proxetil

- highly active against Enterobacteriaceae and streptococci, it inhibits Staph. aureus

FOURTH GENERATION CEPHALOSPORINS

Cefepime ; Cefpirome (I.V.; I.M.)
Effective -> G+ve,-ve
highly resistant to β-lactamases,
Inhibits Ps. aeruginosa and Staph. aureus.
Kept as a Reserve drugs for refractory cases
Cefepime-> good CSF levels, Cefpirome-> good tissue penetrability.

Effective in many serious infections :-

-- **Hospital-acquired pneumonia**
-- **febrile neutropenia, immunocompromised pts**
-- **Septicaemia, SSTIs,RTI & UTIs**

ADVERSE EFFECTS of CEPHALOSPORINS

1. Pain after i.m. injection,
   Thrombophlebitis of injected vein
2. Diarrhoea → cefoperazone,cefixime
3. Hypersensitivity reactions

4. Nephrotoxicity → Cephalothin

5. Bleeding →cefoperazone, ceftriaxone, cefamandole -- due to methyltriotetrazole group and in malnourished patients

6. disulfiram-like interaction → cefoperazone

USES OF CEPHALOSPORINS

1. Respiratory, urinary and soft tissue infections due to gram –ve organism

   -- cefuroxime, cefotaxime, ceftriaxone

2. Penicillinase producing staphylococcal infection

3. Septicemias due to gram –ve organism (with aminoglycoside)

4. Surgical prophylaxis → cefazolin

5. Meningitis → for empirical therapy before bacterial diagnosis → cefotaxime/ceftriaxone combined with ampicillin

Ceftazidime + getnamicin → Pseudomonas meningitis

6. Gonorrhoea and chancroid → ceftriaxone single dose

7. Typhoid → ceftriaxone and cefoperazone (I.V.); Cefixime , Cefpodoxil proxetil & Cefdinir (Oral)

8. Mixed infections in cancer patients, colorectal surgery, Abdominal, Pelvic, Genitourinary Tract & Oral infections → cefuroxime

9. Hospital acquired infection → cefotaxime / cefepime

- 10. prophylaxis and treatment of infections in neutropenic patients

  3rd generation cephalosporins + aminoglycoside