

# PHARMACOLOGY-III

## UNIT-II

### *TOPIC: cephalosporins*



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**CEPHALOSPORINS** These are a group of semisynthetic antibiotics derived from 'cephalosporin-C' obtained from a fungus *Cephalosporium*. They are chemically related to penicillins; the nucleus consists of a  $\beta$ -lactam ring fused to a dihydrothiazine ring, (7-aminocephalosporanic acid). By addition of different side chains at position 7 of  $\beta$ -lactam ring (altering spectrum of activity) and at position 3 of dihydrothiazine ring (affecting pharmacokinetics), a large number of semisynthetic compounds have been produced.

**First generation:** The first-generation cephalosporins act as penicillin G substitutes. They are resistant to the staphylococcal penicillinase and also have activity against *Proteus mirabilis*, *E. coli*, and *Klebsiella pneumoniae*.

**Second generation:** The second-generation cephalosporins display greater activity against three additional gram-negative organisms: *H. influenzae*, *Enterobacter aerogenes*, and some *Neisseria*

species, whereas activity against gram-positive organisms is weaker [Note: The exception to this

generalization is the structurally related cephamycin, cefoxitin which has little activity against *H.*

*influenzae* yet is effective against the anaerobe *Bacteroides fragilis*

**Third generation:** These cephalosporins have assumed an important role in the treatment of infectious disease. Although inferior to first-generation cephalosporins in regard to their activity

against gram-positive cocci, the third-generation cephalosporins have enhanced activity against gram-negative bacilli, including those mentioned above, as well as most other enteric organisms

plus *Serratia marcescens*. Ceftriaxone [sef-trye-AKS-own] or cefotaxime [sef-oh-TAKS-eem] have become agents of choice in the treatment of meningitis. Ceftazidime [sef-TA-zi-deem] has

activity against *P. aeruginosa*.

**Fourth generation:** Cefepime is classified as a fourth-generation cephalosporin and must be administered parenterally. Cefepime has a wide antibacterial spectrum, being active against streptococci and staphylococci (but only those that are methicillin-susceptible). Cefepime is also

effective against aerobic gram-negative organisms, such as *enterobacter*, *E. coli*, *K. pneumoniae*,

*P. mirabilis*, and *P. aeruginosa*.

### C. Pharmacokinetics

**Administration:** Many of the cephalosporins must be administered IV or IM. because of their

poor oral absorption.

1. Distribution: All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved only with the third-generation cephalosporins. For example, ceftriaxone or cefotaxime are effective in the treatment of neonatal and childhood meningitis caused by *H. influenzae*. Cefazolin [se-FAzo-lin] finds application as a single prophylaxis dose prior to surgery because of its 1.8-hour half-life and its activity against penicillinase-producing *S. aureus*. However, additional intraoperative cefazolin doses may be required if the surgical procedure lasts longer than 3 hours. Cefazolin is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone. All cephalosporins cross the placenta.

2. Fate: Biotransformation of cephalosporins by the host is not clinically important. Elimination occurs through tubular secretion and/or glomerular filtration). Therefore doses must be adjusted in cases of severe renal failure to guard against accumulation and toxicity. Ceftriaxone is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency

Adverse effects

Cephalosporins are generally well tolerated, but are more toxic than penicillin.

1. Pain after i.m. injection occurs with many. This is so severe with cephalothin as to interdict i.m. route, but many others can be injected i.m. (see individual compounds). Thrombophlebitis of injected vein can occur.

2. Diarrhoea due to alteration of gut ecology or irritative effect is more common with oral cephadrine and parenteral cefoperazone (it is significantly excreted in bile).

3. Hypersensitivity reactions caused by cephalosporins are similar to penicillin, but incidence is lower. Rashes are the most frequent manifestation, but anaphylaxis, angioedema, asthma and urticaria have also occurred. About 10% patients allergic to penicillin show cross reactivity with cephalosporins. Those with a history of immediate type of reactions to penicillin should better not be given a cephalosporin. Skin tests for sensitivity to cephalosporins are unreliable. A positive Coombs' test occurs in many, but haemolysis is rare.

4. Nephrotoxicity is highest with cephaloridine, which consequently has been withdrawn.
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5. Bleeding common inpatients with cancer, intra-abdominal infection or renal failure.
6. Neutropenia and thrombocytopenia are rare adverse effects reported with ceftazidime and some others.
7. A disulfiram-like interaction with alcohol has been reported with cefoperazone.