



CEPHALOSPORINS



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Notes and MCQs for all Medical fields

Introduction



- **Cephalosporins** - a class of β -lactam antibiotics originally derived from *Cephalosporium acremonium*
- **Cephameycins**: methoxy group at position 7 of beta-lactam ring (7-aminocephalosporanic acid nucleus)
- Together with cephameycins they constitute a subgroup of β -lactam antibiotics called **cephems**



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History and Source

- First source of the cephalosporins: *Cephalosporium acremonium*
- *Streptomyces lactamdurans*
- Isolated in 1948 by Italian scientist **Giuseppe Brotzu** from the sea near a sewer outlet off the Sardinian coast



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History and Source



- **First agent cephalothin (cefalotin) was launched by Eli Lilly in 1964**
- **With isolation of the active nucleus of cephalosporin C : 7-aminocephalosporanic acid
And with the addition of side chains :
semisynthetic compounds**



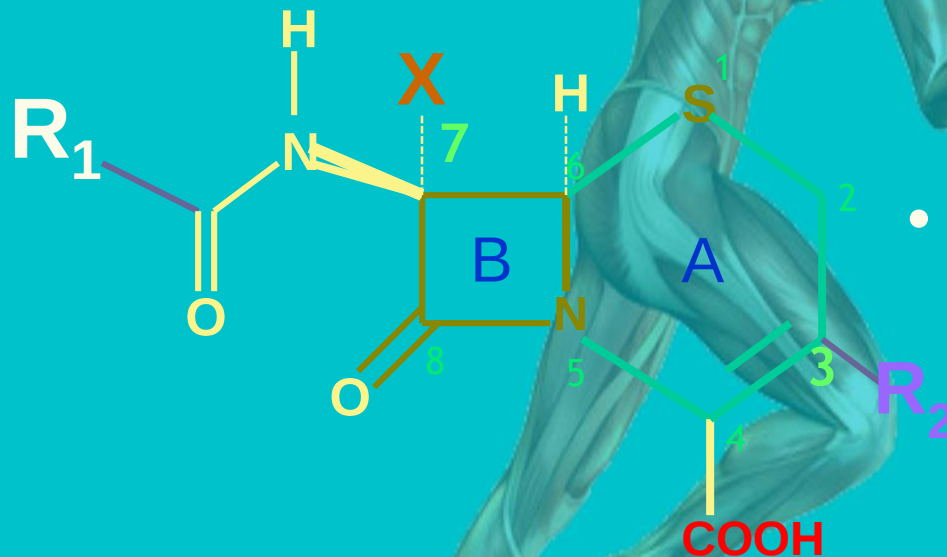
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CHEMICAL STRUCTURE

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- **A-Presence of dihydrothiazine ring**
- **B-Presence of β lactam ring**



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Chemistry

- Compounds containing 7-aminocephalosporanic acid are relatively stable in dilute acid and highly resistant to penicillinase
- Modifications at position 7 of the β -lactam ring - associated with alteration in antibacterial activity
- Substitutions at position 3 of the dihydrothiazine ring - associated with changes in the metabolism & pharmacokinetic properties of the drugs



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Classification

- **Based on:**
 - Their chemical structure
 - Clinical pharmacology
 - Resistance to b-lactamase or
 - Antimicrobial spectrum
- Well-accepted system of classification by "generations" is very useful



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Classification

- 1st generation:

- Cefazolin (IM, IV)
- Cephalexin(O)
- Cephadroxil(O)
- Cephalothin)IM)
- Cephradine(O, IM, IV)

- 2nd generation:

- Cefuroxime (O)
- Cefaclor (O)
- Cefprozil (O)
- Cephameycins:
 - Cefoxitin (IM, IV)
 - Cefotetan (IM)
 - Cefmetazole



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Classification

- 3rd generation:

- Cefotaxime (IM, IV)
- Ceftriaxone (IM, IV)
- Ceftazidime (IM, IV)
- Cefoperazone (IM, IV)
- Cefixime (O)
- Cefpodoxime (O)

- 4th generation:

- Cefepime (IV)
- Cefpirome (IM, IV)

- 5th generation:

- Ceftobiprole
- Ceftaroline



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1st Generation:

- They have good activity against gram-positive bacteria & relatively modest activity against gram-negative microorganisms
- Most gram-positive cocci (with the exception of enterococci, methicillin-resistant *S. aureus*, and *S. epidermidis*) are susceptible
- Most oral cavity anaerobes are sensitive, but the *B. fragilis* group is resistant
- Activity against *Moraxella catarrhalis*, *E. coli*, *K. pneumoniae*, and *P. mirabilis* is good (PEK)



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2nd generation cephalosporins:

- increased activity against *gram-negative* microorganisms
- HENPEK (H. influenzae, Enterobacter, N. gonorrhea, Proteus, E. coli, K. pneumoniae)
- Less active than the third-generation agents
- A subset of second-generation agents (*cefoxitin*, *cefotetan*, and *cefmetazole*) also active against the *B. fragilis* group



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3rd generation cephalosporins:



- Generally are less active than first-generation agents against gram-positive cocci
- More active against the Enterobacteriaceae, including beta-lactamase-producing strains
- A subset of third-generation agents (*ceftazidime* and *cefoperazone*) also active against *Pseudomonas aeruginosa*
- Less active than other third-generation agents against gram-positive cocci



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4th generation cephalosporins:



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- An extended spectrum of activity against Gram (+) Bacilli compared with the third generation
- Increased *stability* from hydrolysis by plasmid and chromosomally mediated β -lactamases
- Fourth-generation agents are particularly useful
 - Empirical treatment of serious infections in hospitalized patients
 - Gram-positive microorganisms
 - Enterobacteriaceae and
 - *Pseudomonas*



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5th generation cephalosporins:



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- Broad spectrum , advanced generation
- Active against MRSA and streptococcus pneumoniae & enterococcus
- Gram-ve activity similar to 3rd generation
- P. aeruginosa, extended spectrum β - lactamase (ESBL)-producing Enterobacteriaceae, and Acinetobacter baumannii.
- Limited activity against anaerobes



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MoA of cephalosporins

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- Inhibit synthesis of bacterial cell wall and produce bactericidal effect.



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Mechanism of action

- Cell wall synthesis inhibition by binding to **cephalosporins** binding proteins (PBPs) which include transpeptidase enzyme
- Inhibition of 'transpeptidase' by beta lactam ring

Prevent cross linking of NAM and NAG

Lysis of cell (bactericidal)



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Mechanisms of Bacterial Resistance



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- Inability to reach site of action
 - Impermeability
 - Efflux
- Alteration in PBPs- decrease affinity of drug
- Elaboration of beta lactamases (cephalosporinase)



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Pharmacokinetics



- Route of Administration:
 - oral, IM, IV
- Distribution:
 - CSF, placenta, synovial and pericardial fluids, aqueous humor of eye, bile
- Excretion:
 - kidney (dosage thus should be altered in patients with renal insufficiency)



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Uses:

- Upper respiratory tract infections
- Cutaneous and soft tissue infections
- ENT infections
- Urinary tract infections
- Septicaemias caused by Gr negative org
- Surgical prophylaxis
- Meningitis



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Uses

- Gonorrhea
- Chancroid
- Typhoid
- Mixed aerobic anaerobic infections
- Hospital acquired infections
- Community acquired pneumonia
- Prophylaxis & treatment of infections in neutropenic patients



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Adverse effects:



- Hypersensitivity reactions:
 - Anaphylaxis , bronchospasm, urticaria, rashes
 - Cross reactivity to penicillin is seen in some patients.
 - Skin test
- Pain after injection, thrombophlebitis
- Diarrhoea, vomiting and anorexia
- Nephrotoxicity(cephaloridine)



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Adverse effects:



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- Bleeding (cefoperazone) can occur either due to hypoprothrombinaemia or thrombocytopaenia and or platelet dysfunction.
- Neutropenia, thrombocytopenia
- Disulfiram like interaction(cefoperazone)
- Positive coomb's test



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