

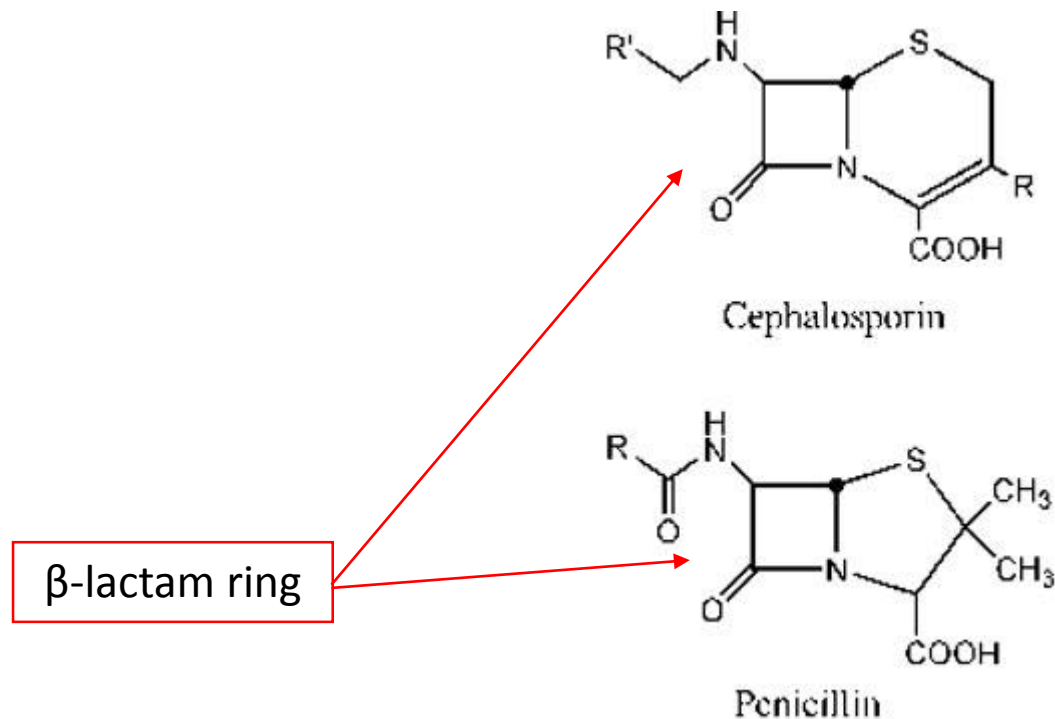
Cephalosporin

Introduction

- Cephalosporin are β -lactam antibiotics that are closely related both structurally and functionally to penicillin.
- Most Cephalosporin are produced semi-synthetically by the chemical attachment of side chain to 7-aminocephalosporinic acid. They were first obtained from fungus, cephalosporium.

Molecular Structure

- They have nucleus of 7-aminocephalosporinic acid instead of penicillin, 6-aminopenicillanic acid.



Cephalosporin Mode of Action

- Cephalosporins are a type of β -lactam antibiotic closely related to the penicillins. They are bactericidal, with the same MOA as other beta-lactams.
- Cephalosporins disrupt synthesis of the peptidoglycan layer of bacterial cell walls. Peptidoglycan is a strong structural molecule specific to the cells walls of bacteria. With the cell wall structure compromised, the bactericidal result is lysis and death of the cell.
- Our cells do not have cells walls or peptidoglycan, therefore, B-lactam antibiotics are able to target bacterial cells without harming human cells.

Classification of Cephalosporin

- They have been classified as 1st , 2nd , 3rd and 4th generation based largely on their bacterial susceptibility pattern and resistant to β lactamase.

First Generation

The first generation of cephalosporin act as penicillin G substitutes. They are resistant to staphylococcal penicillinase and also have activity against Proteus mirabilis, E.coli.

- ❖ Cefazolin
- ❖ Cefadroxil
- ❖ Cephalexin
- ❖ Cephalothin
- ❖ Cephapirin
- ❖ Cephradine

- **Cefazolin** has longer duration of action and similar spectrum of action compared to other first generation drugs.
- **Cephalexin is the prototype of 1st generation** oral cephalosporin . Oral administration twice daily is effective against pharyngitis.

Second Generation

- Second generation display greater activity against 3 additional gram –ive organisms, H.influenza, Enterobacter aerogenes and some Neissseria Species whereas activity against gram +ive bacteria is weaker.
- Antimicrobial coverage of cefotetan and cefoxitin also includes the anerobes, bacteroides fragilis..

- ❖ Cefuroxime sodium
- ❖ Cefuroxime axetil
- ❖ Cefmetazole
- ❖ Cefotetan
- ❖ Cefaclor
- ❖ Cefamandole
- ❖ Cefonicid
- ❖ Cefoxitin

- **Cefuroxime sodium is a prototype 2nd generation** parenteral cephalosporin has a longer half life than similar agents. It cross the BBB and it can be used for community acquired bronchitis or pneumonia or in elderly patient with immunocompromise.
- **Cefuroxime axetil** administered twice daily, this drug is well absorbed and is active β lactamase producing organism.

Third Generation

- These have assumed an important role in treatment of infectious diseases. 3rd generation have enhanced activity against gram –ive bacilli as well as other enteric organisms plus serratia marcescens (hosp. acquired infection from catheters)
- ❖ Cefdinir
- ❖ Cefixime
- ❖ Cefotaxime
- ❖ Ceftazidime
- ❖ Ceftributen
- ❖ Ceftriaxone
- ❖ cefoperazone

- **Ceftriaxone and cefotaxime** have become agent of choice in treatment of meningitis.
- **Cefidintr and Cefixime** are administered orally once daily.
- **Cefotaxime** penetrate well into CSF.
- **Ceftazidime** is active against *Pseudomonas aeruginosa*.
- **Ceftriaxone** has longest half life of any cephalosporin (6-8hr) which permits once a daily dosing. High level of this drug can be achieved in blood and CSF. it is effective against genital, anal and pharyngeal penicillin resistant *Neisseria gonorrhea*.
- **Ceftriaxone** is excreted in bile and maybe use in patient with renal insufficiency. It has good penetration in bone.

Fourth Generation

Cefepime is classified as 4th generation of 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 gram –ive micro organism such as E.coli , K. pneumoniae.

Fifth Generation

- Ceftriaxone,
- ceftazidime,
- ceftolozane

Resistance

- Mechanism of bacterial resistance to cephalosporin are essentially same as those described for penicillin.

Pharmacokinetic

- **Administration:**

All cephalosporin must be administered IV or IM because of their poor oral absorption except Cephlexin, cefadroxil, Cefadinir, Cefixime, Ceftibuten, Cefuroxime axetil

Distribution

- All cephalosporin distribute very well into body fluids. However, adequate therapeutic level in CSF, regardless of inflammation are achieved.
- Only with a select a few cephalosporin For example, ceftriaxone or cefotaxime is effective in treatment of neonatal and childhood meningitis caused by H.influenzae.

- Cefazolin finds application as a single prophylaxis dose prior to surgery because of its 1.8hr half life and its activity against penicillinase producing *S.aureus*.
- However, additional intra operative cefazolin doses maybe required if surgical procedure lasts longer than 3 hours.
- Cefazolin is effective for most surgical procedure including orthopedic surgery because of its ability to penetrate bone. They all can cross placenta.

Elimination

- Elimination occurs through tubular secretion or glomerular filtration.
- Therefore doses must be adjusted in case of severe renal failure to guard against accumulation and toxicity.
- An exception is ceftriaxone which is excreted through bile into feces and therefore is frequently employed in patients with renal insufficiency.

Adverse Drug Reactions

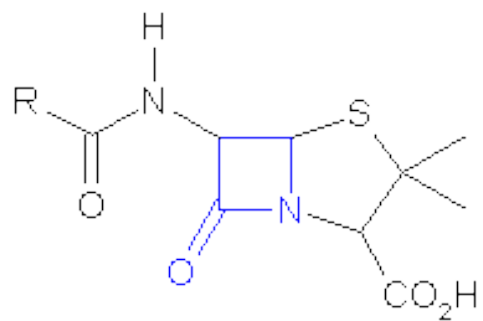
- Incidence of adverse effects with cephalosporin is relatively low.

Allergy: allergic reactions of penicillin type is cross allergy between penicillin and cephalosporin's in about 10% patient. If a patient had a severe or immediate allergy reaction to penicillin then cephalosporin should not be used.

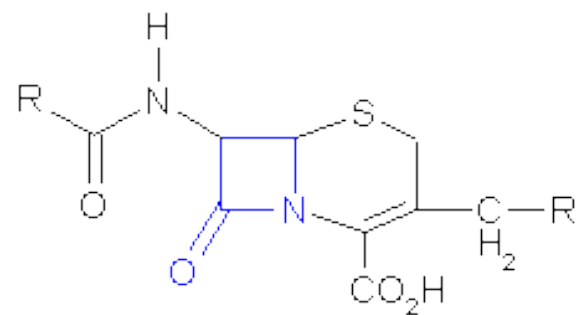
Other Common ADRs are:

- Diarrhea
- Nausea
- Rash
- Electrolyte Disturbances
- Super infection

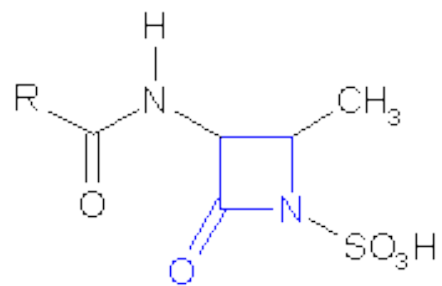
Other β - Lactam Antibiotics



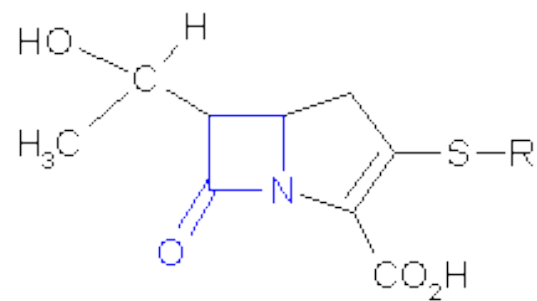
Penicillin nucleus



Cephalosporin nucleus



Monobactam nucleus



Carbapenem nucleus

Carbapenems

- Are synthetically β -lactam antibiotics that differ in structure from penicillin in sulfur atom of thiazolidine ring has been externalized and replaced by carbon atom.

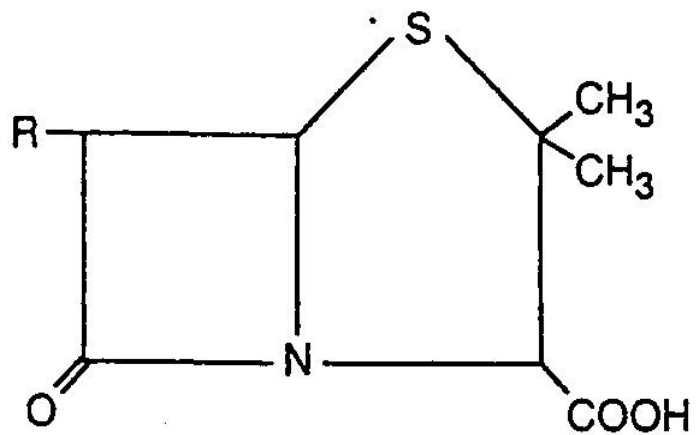
Members:

- Imipenem
- Meropenem
- Doripenem
- Eratapenem

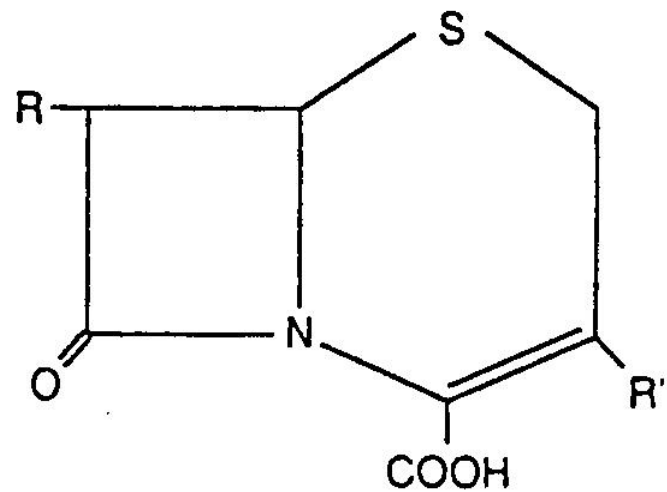
- They are broad spectrum antibiotic active against many aerobics and anaerobics. Gram +ive and gram –ive organisms.
- They are highly resistant to β - lactamase enzyme, making them very useful in treating bacterial infection. Where β -lactamase is produce that make other β -lactam antibiotics ineffective.

Monobactams

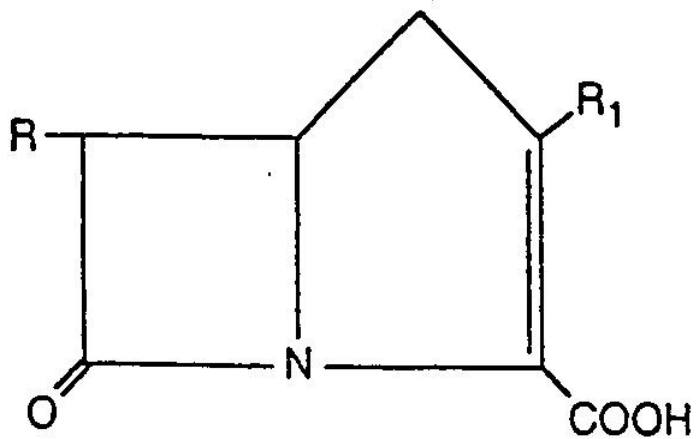
- Monobactam which also disrupt cell wall synthesis. They are unique because β -lactam is alone not fuse to any other.
- **Aztreonam** , is only commercially available monobactam, has antimicrobial activity directed primarily against enterobacteriaceae, including *P.aeruginosa*. It lacks activity against gram +ive organism and anaerobes.
- Aztreonam may offer a safe alternative for treating patients who are allergic and unable to tolerate penicillin or cephalosporin.



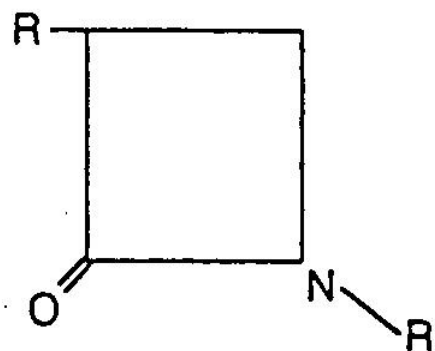
Penams (penicillins)



Cepham (cephalosporins)



Carbapenem



Monobactam

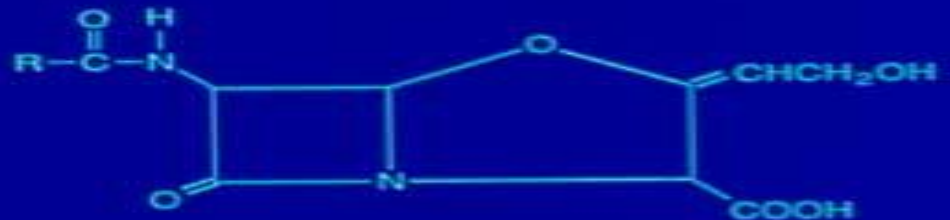
Penicillins
(5 membered
ring)



Cephalosporins
(6 membered
ring)



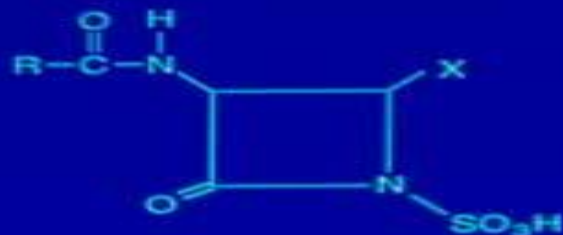
**β. lactamase
inhibitor**
(Clavulanate)



Carbapenem
(Imipenem)



Monobactam
Aztreonam



β - Lactamase Inhibitors

- Hydrolysis of β lactam ring either by enzymatic cleavage with β -lactamases or by acid, destroy the antimicrobial activity of β -lactam antibiotic.

β - lactamase inhibitors include:

- **Clavulanic acid**
- **Salbactam**
- **Tezobactam**

- β lactamase inhibitors contain a β - lactam ring but by themselves do not have significant antibacterial activity, Instead they bind to and inactivate β -lactamase thereby protecting β -lactam antibiotics that are normally substrate for this enzyme.
- The β -lactamase inhibitors are therefore formulated in combination with β –lactamase sensitive antibiotics.
- For example, Clavulanic acid + amoxicillin (Co-Amoxiclav)

Other Cell Wall Inhibitors

Vancomycin

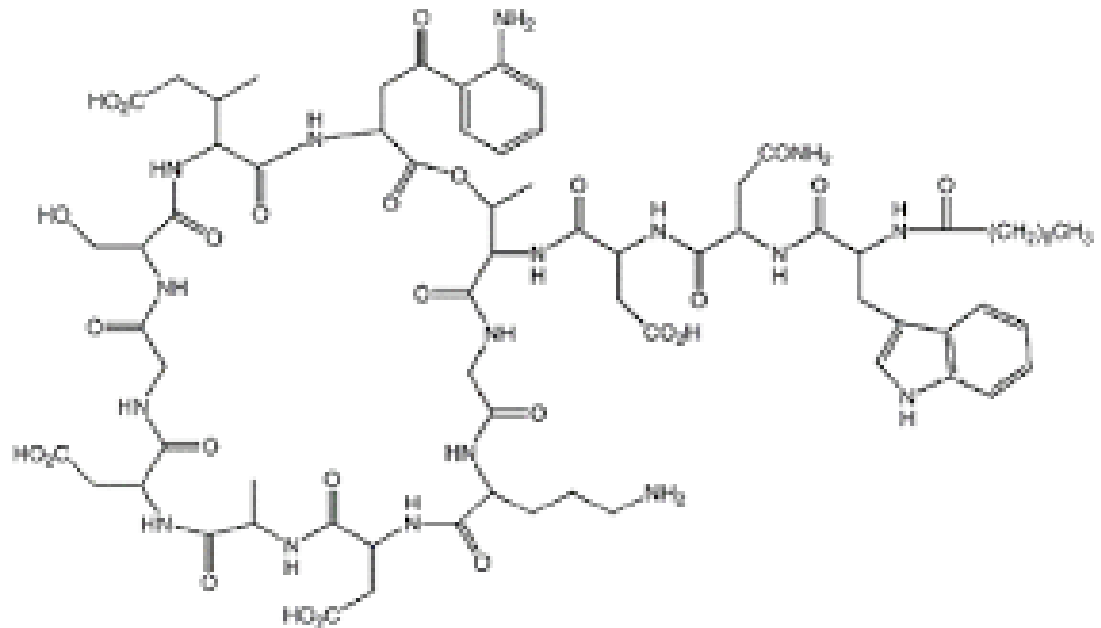
- Vancomycin is an antibiotic (tricyclic glycopeptide) that has become increasingly important because of its effectiveness against multiple drug resistant organisms, such as MRSA and enterococci.
- it is active against wide variety of gram +ive bacteria.
- It acts by inhibiting cell wall synthesis as well as peptidoglycan polymerization.

Adverse Effects

- Fever
- Chill
- Phlebitis at infusion site
- Ototoxicity and nephrotoxicity are more common when administered with another drug.

Daptomycin

- It is a cyclic lipopeptide antibiotic, use in treatment of systemic and life threatening infections cause by gram+ive organisms.



Mechanism

- Upon binding to bacterial cytoplasmic membrane, daptomycin induce rapid depolarization of membrane thus disrupting multiple aspects of membrane function and inhibiting intracellular synthesis of DNA, RNA and proteins.
- Daptomycin is bactericidal and bacteria killing is concentration depending

Telavancin

- Telavancin is a semi synthetic lipoglycopeptide antibiotic that is synthetic derivative of vancomycin.
- It is alternative to vancomycin, daptomycin in treating complicated skin and skin structure infections caused by resistant gram +ive organism including MRSA.
- Like vancomycin it also inhibit bacterial cell wall synthesis .
- Unlike vancomycin, it exhibit an additional mechanism of action similar to daptomycin that involved distrutpion of bacterial cell membrane due to presence of liphophilic side chain moiety.