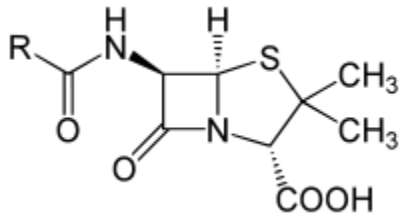
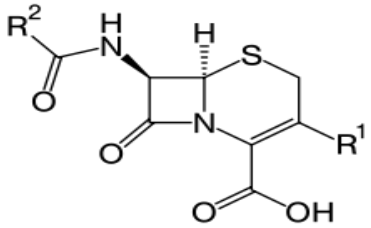
Beta-lactams

The beta (ß) -lactam antibiotics constitute one of the oldest and most popular classes of antibacterial agents, all containing the beta lactam ring (consist of 3-carbon atoms and one nitrogen atom) . The different groups within the family are distinguished by the structure of the ring attached to the beta lactam ring-in pencillins this is a five –membered ring, in cephalosporins a six-membered ring ,and by the side chains attached to these rings.



Structure of penicillin



Structure of cephalosporin

- **Penicillins**

Penicillin was discovered by Sir Alexander Fleming in 1928, but it was not mass-produced until the 1940s. The antibiotic is naturally produced by fungi of the genus *Penicillium* **,** (eg, *Penicillium notatum*).

Penicillins can be classified according to their spectrum of action into the following :

1. Natural penicillins

• **Penicillin G:** Active against Gram-positive organisms that do not produce beta-lactamases, *Neisseria* and some anaerobes

2. Penicillinase-resistant penicillins

• **Penicillin M:** Active against penicillinase-producing *Staphylococci* eg, Oxacillin; Methicillin.

3. Extended-spectrum penicillins

• **Aminopenicillins:** less active than Penicillin G against *Pneumococci, Streptococci and Meningococci*, but active against many strains of *Salmonella, Shigella,* and *P.mirabilis, H.influenzae*).eg, Ampicillin; Amoxicillin.

• **Carboxypenicillins :** More stable than aminopenicillins to hydrolysis by the ß-lactamases of most *Enterobacteriaceae* and *Pseudomonas aeruginosa* eg, Ticarcillin.

• **Ureidopenicillins:** Greater activity than carboxypenicillins against Gram-positives, enterics and *P.aeruginosa* eg, Piperacillin.

4. Co-Drugs (Beta-lactam + beta-lactamase inhibitor)

• **ß-lactamase inhibitors (BLI) combinations:** Additional activity against beta-lactamase producing organisms . eg,Amoxicillin + clavulanic acid.

5. Amidinopenicillins

• **Mecillinam:** Restricted use to urinary infection with *Escherichia coli*. Active against penicillinase and low-level cephalosporinase.

Beta-lactamase inhibitors (BLI) have a beta -lactam ring, weak or poor antibacterial activity alone, but a strong affinity for beta lactamases . They act as a trap, and are hydrolyzed in preference to the ß-lactam drug, then the drug is left intact to act on the bacteria (cell wall).

eg. Clavulanic Acid

Sulbactam

Tazobactam

Combination β-lactams - β-lactamase inhibitor:

Amoxicillin / clavulanic acid

Ampicillin / sulbactam (sultamicillin)

Piperacillin / tazobactam

Cephalosporins

The first isolation of cephalosporin compounds were from cultures of *Cephalosporium acremonium* in 1948. The cephalosporins contain an aminocephalosporanic acid nucleus consisting of a β-lactam ring fused to a dihydrothiazine ring. They are similar to the penicillins in structure, mechanism of action, toxicity, and act by binding to PBPs of susceptible organisms. Cephalosporins are sometimes grouped into "generations" by their antimicrobial properties. The first cephalosporins were designated first-generation cephalosporins, whereas, later, more extended-spectrum cephalosporins were classified as second-generation cephalosporins. Each newer generation has significantly greater gram-negative antimicrobial properties than the preceding generation, in most cases with decreased activity against gram-positive organisms.

• **1st generation cephalosporins :**Narrow spectrum; good Gram-positive activity and relatively modest Gram-negative activity. Inactivated by Gram-negative beta-lactamases (Derived from *Cephalosporium acremonium*). eg, Cephalothin, Cefazolin.

• **2nd generation cephalosporins :**Better Gram-negative coverage (more beta-lactamase stability), but less *Staphylococcal* activity. eg, Cefuroxime, Cefamandole.

• **3rd generation cephalosporins :** Wider spectrum of action when compared to C1G and C2G. Less active than narrow spectrum agents against Gram-positive cocci, but much more active against the *Enterobacteriaceae* and *Pseudomonas aeruginosa* (better beta lactamase stability). eg,Cefotaxime; Ceftazidime; Ceftriaxone.

• **4th generation cephalosporins :**Broadest spectrum of action. Active against high level cephalosporinases of *Enterobacteriaceae* and *Pseudomonas aeruginosa* .eg, Cefepime.

•**5th generation cephalosporin:** Broad spectrum; active against the common Gram-negative bacteria. Some Gram-positive activity. Notable for activity against methicillin resistant *Staphylococcus aureus*, Bactericidal. eg, Ceftobiprole.