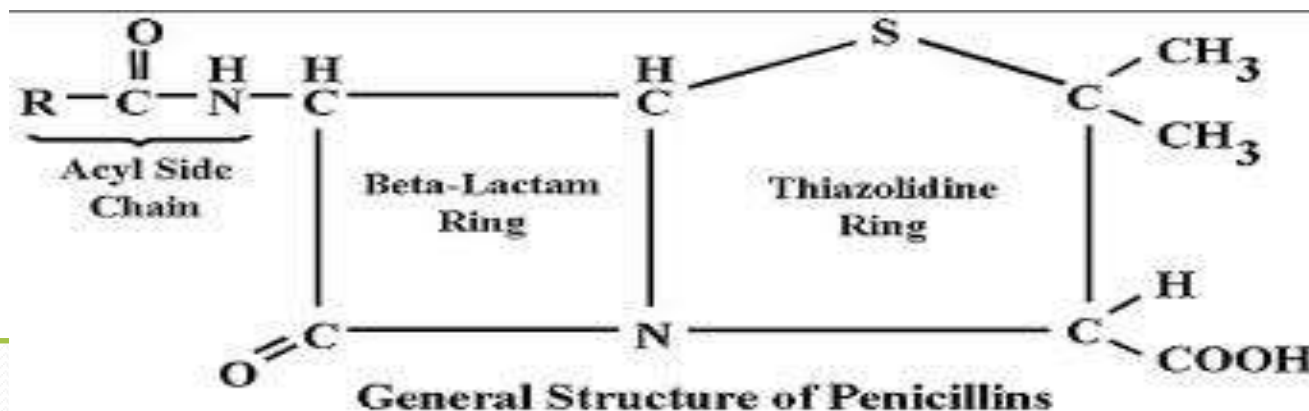


Penicillin

- Obtained from fungus *Penicillium chrysogenum*.
- Sulfur containing thiazolidine ring fused with beta-lactam ring to which a side chain is attached at position -6 (-NHCOR).
- Activity is due to the 6-amino penicillanic acid (6-APA), hence named β -lactam antibiotics.



Mechanism of action

- Interfere with synthesis of bacterial cell wall.
- Cell wall composed of peptidoglycan, glycon consist of two amino sugars;
- 1)N-acetylmuramic acid (NAcM).
- 2)N-acetylglucosamine(NAcG).
- Peptidoglycan residues are linked together forming long strands &UDP is split off.
- Final step is cleavage of terminal D-alanine of the peptide by transpeptidase, process known as transpeptidation.
- This cross bridging provide neccessry strength to bacterial cell wall.
- β -lactam ABs inhibit the transpeptidase so that cross-linking does not take place.
- This will cause cell wall deficient forms of bacteria are produced

Cont.....

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- β -lactam ABs inhibit the transpeptidase so that cross-linking does not take place.
- This will cause cell wall deficient forms of bacteria are produced
- Thus shows bactericidal action.

Penicillin G

- Narrow spectrum antibiotic.
- Primarily to gram positive bacteria and few others, active against....
- Cocci-Streptococci (except group D), *Staph.aureus* ; gram negative *N.gonorrhoeae* and *N.meningitis*.
- Bacilli-majority of *B.anthraxis*, *Corynebacterium diptheriae* etc

Uses

- Strptococcal infections-Pharyngitis, otitis media,scarlet fever
- Syphillis- *T.pallidum* does not show any resistance, drug of choice.
- Diptheria-Antitoxin therapy.

Adverse Effects

- Local irritancy and direct toxicity; pain at i.m injection site nausea on oral ingestion and thrombophlebitis of injected vein.
- Hypersensitivity-rashes,itching,urticaria
- Contact dermatitis and Jarisch-Herxheimer reaction

Drawbacks of Penicillin G

- Poor oral efficacy.
- Susceptibility to penicillinase
- Narrow spectrum of activity.
- Hypersensitivity.
- Destroyed by acid
- “To overcome these problems, developed new penicillins and classified according to the anti microbial spectrum”.

β -lactamase Sensitive

Natural penicillin

| Acid stable | Acid labile |
|--|--------------|
| Penicillin -V (Phenoxymethylpenicillin) | Penicillin G |
| | |

β -Lactamase resistant Anti-staphylococcal Penicillin)

| Acid stable | Acid labile |
|-----------------------------|-------------------------|
| Cloxacillin (oral, I.M) | Methicillin (I.M, I.V) |
| Dicioxacillin (oral, I.M) | Nafcillin (I.M, I.V) |
| Flucioxacillin (oral, I.M) | |
| | |

Reference; K.K Sharma, page no.720 , 2nd edition 2011

All are sensitive to β -lactamase degradation

| Acid stable (amino penicillin) | Acid labile(anti-pseudomonal penicillin) |
|---------------------------------|--|
| Ampicillin (oral/ parenteral) | Carbenicillin (parenteral) |
| Bacampicillin (oral/parenteral) | Ticarcillin (parenteral) |
| Talampicillin (oral/parenteral) | Piperacillin(parenteral) |
| Amoxicillin(oral/parenteral) | Mezlocillin(parenteral) |
| | Azocillin(parenteral) |

Reference; K.K Sharma, page no.720 , 2nd edition 2011

β -lactamase inhibitors

- Clavulanic acid.
- Sulbactam.

Narrow spectrum, β -lactamase resistant group

- Similar to penicillin-G, additionally effective against β -lactamase producing staphylococcal hence named anti-staphylococcal penicillins.
- Methicillin no use –due to –nephrotoxicity.
- Nafcillin is preferred for parenteral use, while cloxacillin and dicloxacillin-orally.
- Used to treat osteomyelittis, septicaemia, endocarditis.

Extended spectrum penicillins

- All penicillins are β -lactamase sensitive, but Ampicillin and amoxicillin –acid stable .
- Carbenicillin, ticarcillin and piperacillin are acid labile can be given by I.V or I.M.
- Food decreases the bioavailability of ampicillin but does not happen in case of Amoxycillin.
- Ampicillin & amoxycillin are effective against Streptococcus viridans, and enterococci(SABE)

Penicillin Units

- Activity of natural penicillins (e.g penicillin) is defined in terms of units.
- Crystalline sodium penicillin G contains 1600 units per mg.
- Semi-synthetic penicillins are prescribed by weight basis rather than units, e.g amoxicillin 500 mg 8 hourly orally.

Resistance to penicillins

- Inactivation of β -lactam ring by Beta-lactamase
- *S.aureus*, *haemophilus influenza* and *E.coli*
- These bacteria produce beta- lactamase which can hydrolyze penicillins .
- *Pseudomonas*, *Enterobacter*, *Neisseria gonorrhoeae* and *Moraxella catarrhalis* have a broader degradative activity

Cont...

- **Resistance due to modification of penicillin binding proteins**-resistance bacteria like Methicillin resistant *Staphylococcal aureus (MRSA)*, *Streptococcus pneumoniae* and *Enterococcus* produce mutant PBPs which have low affinity to penicillins.
- **Reduction of penicillin permeability to reach PBPs**-bacteria reduce the antibiotic access to PBPs through porin channels.e.g *Pseudomonas aeruginosa*, the porin mutant block the *penicillin* transfer across the outer membrane.

β - lactamase inhibitors

- Resemble to beta-lactam antibiotics only structurally but do not possess any significant antimicrobial action.
- Drug include –Clavulanic acid and sulbactam.
- Bind irreversibly to catalytic site of susceptible β -lactamases (produced by bacteria) to prevent hydrolysis of penicillins.
- Can inhibit plasmid mediated β -lactamases which are responsible for transferred drug resistance like MSRH.
- G.I intolerance, stomatitis and rashes are recorded

Drug interactions

- **Antagonistic combination;**
- **Oral penicillins;**
- antagonised by bacteriostatic antibiotics such tetracyclines, chlramphenicol, erythromycin.
- Penicillin and aminoglycosides should not mixed in the same syringe ,inactivate each other.
- Hydrocortisone inactivates ampicillin if mixed in the I.V fluid.

Cont....

- Synergistic combinations;
- Probenecid prolongs the action of penicillin by decreasing its tubular secretion.
- Beta –lactamase inhibitors extend the spectrum of penicillins against beta lactamase producing bacteria.
- A fixed dose combination of ampicillin or amoxycillin 250 mg with cloxacillin 250 mg has been promoted as synergistic combination useful in postoperative and respiratory infection.