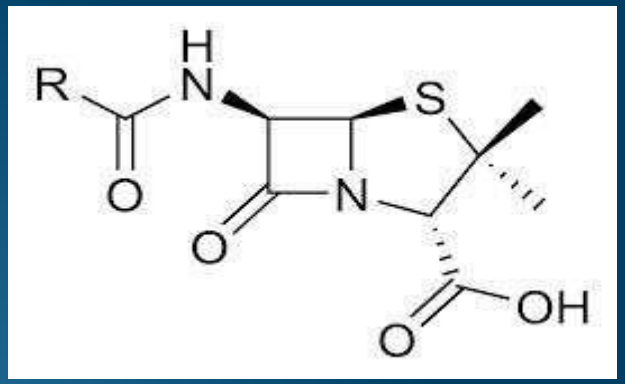
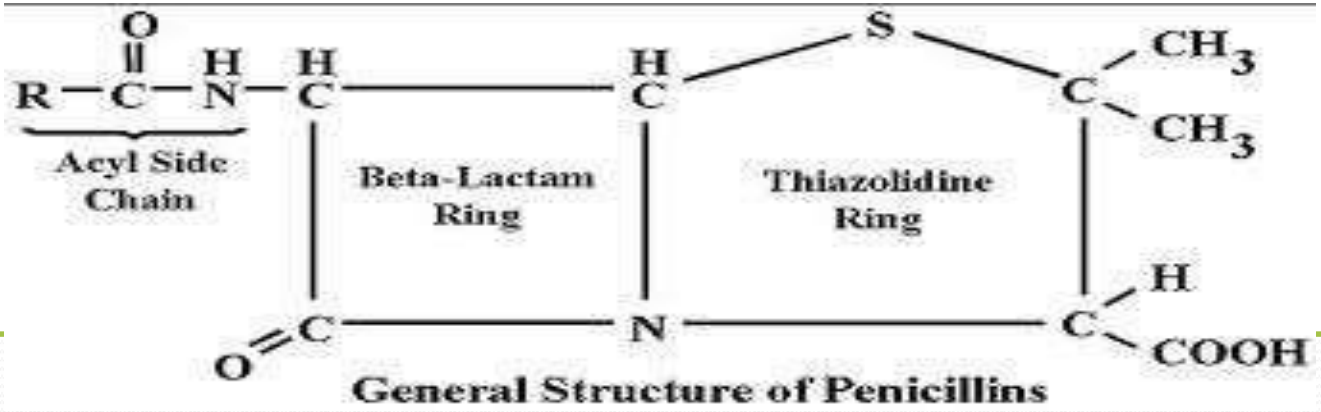
PENICILLIN



-By Rupam Swain

Penicillin

- Obtained from fungus *Penicllium chrysogenum*.
- Sulfur containing thiazolidine ring fused with b-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.



General Structure of Penicillins

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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- 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.gonorrheoe* and *N.meningitis*.
- Bacilli-majority of *B.anthracis, 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".

Refernce; K.D.Tripathi.pg.no 658,6th edition

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.
- Salbactam.

Narrow spectrum, β-lactamase resistant group

- Similar to penicillin-G, additionally effective against B-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 amoxycillin 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 .
- *Psedomonas, Enterbacter, Neisseria gonorrhoeae*

and *Moraxella catarrhalis* have a broader degradative activity

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- **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.