β-lactam Antibiotics

β-lactam antibiotics are useful and frequently prescribed antimicrobial agents, that share a common structure and mechanism of Action. The group include Penicillins, cephalosporins and Carbapenems.

Penicillins consist of Penicillin G and V
↓
highly active against susceptible gram +ve cocci

Naficillin → Penicillinase resistant penicillin
Ampicillin → Broad spectrum
Piperacillin → Extended spectrum

Cephelosporins → classified by generation.

Carbapenems → Imipenem, Doripenem, Ertapenem & Meropenem
↓
Broadest antimicrobial spectrum

Monobactam & Aztreonam } has gram -ve pattern resembling to Aminoglycosides.

β-lactamase inhibitors → clavulanate
↓
used to extend spectrum of penicilline against β-lactamase prod. organisms.

[Mechanism of Action]

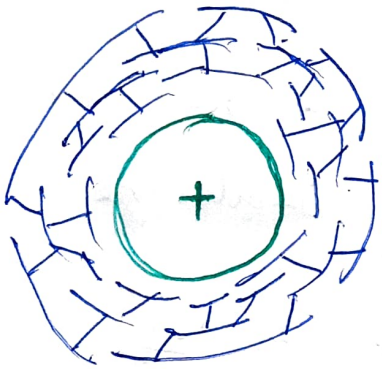
Cell wall of Gram +ve, -ve Microorganisms

Cell wall :-

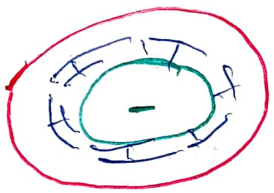
Sugar backbones made of → glycans.

* Cell wall is made up of Carbohydrates and Cross linked through peptide chains → Peptidoglycan layer

* Cell wall Thicker in gram +ve. (50–100 mol. thick)
  Thinner in gram -ve. (1–2 mol thick)



made up of 1 molecule of peptidoglycan



along with peptidoglycan membrane it also has additional membrane a lipid membrane. (ten porins)
↓
unique in nature.

* Penicillin Binding proteins are present in the outside of cytoplasmic membrane, where β-lactum ring binds / penicillin binds.

gram +ve → Highly porus ∴ PBP are easily available for binding.

gram -ve → lipid membrane ten porus → but presence of porins (channels)
↓
help in passing of drugs through into the cell.

33 PARACETAMOL T.DOLO 500MG

Cell wall synthesis :→

Each Peptidoglycan layer consists of multiple backbones of amino sugars with alternating N-acetylglucosamine (NAG) and N-acetyl muramic acid (NAM)

↓ involves 30 bacterial enzymes

↓ made of short peptide chains that are cross linked to form polymer lattice

STEP 1 :→ precursor formation takes place in cytoplasm.

Accumulation of UDPAMPP
[Uridine di Phosphate Acetyl Muramyl Pentapeptide]

↓

[PARK nucleotide]

last step in the synthesis of above nucleotide is addition of dipeptide D-alanyl D-alanine.

↓

involves the racemisation of L-alanine and condensation

↑

Catalysed by D-alanyl D-alanine synthase.

STEP 2 :- UDPAMPP and UDP AG are linked to form a long polymer with the release of Uridine nucleotides.

↓ cytoplasm

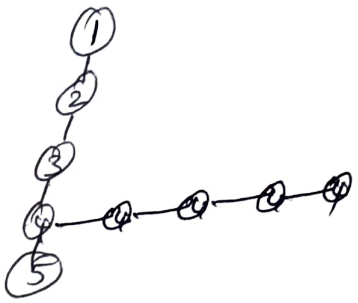
STEP 3 :- Formation of cross linkage.

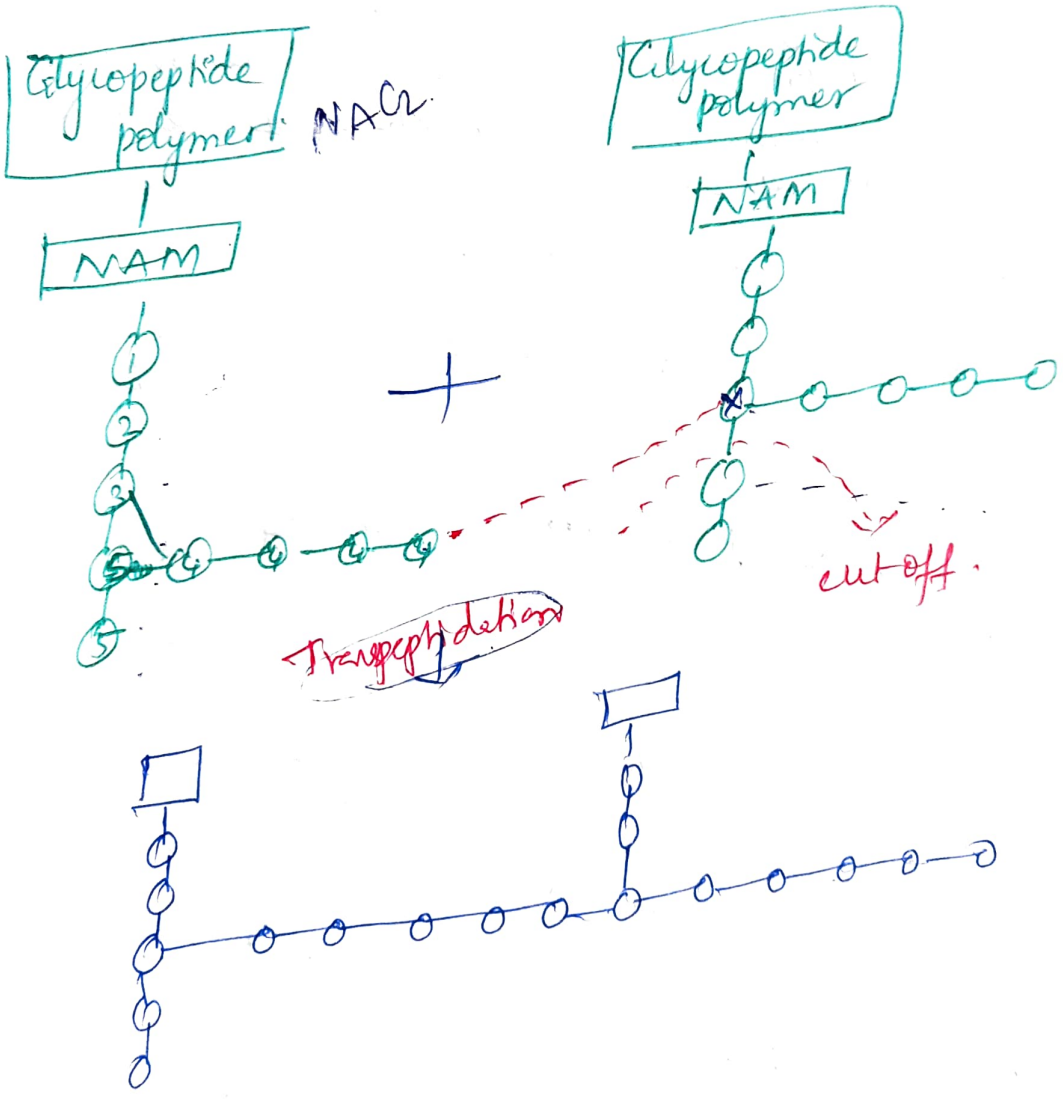
NAG, NAM sent out of cytoplasm to form cross linkages by transpeptidation reaction.

Transpeptidase enzyme is membrane bound and occurs at 5 amino acid residues of NAM.

1. L-Alanine
2. D-Glutamate
3. L-Lysine
4. D-Glycine
5. D-Alanine.

In case of bacteria Pentaglycine Bridge.





The terminal glycine attaching 4th & 5th a.a are cutoff.

Penicillins inhibit the enzyme Transpeptidase by Acylation

Additional targets include PBP's

PBP → Penicillin Binding Protein

↓

mostly all bacteroids will have PBP

Eg: Staphylococcus aureus → 4 PBP

E. coli → 7 PBP

↓

has high mol. wt PBP and have 2 subforms 1a and 1b

↓

are necessary for transpeptidation reaction & shape of the bacteria.

$PBP_{1a, 1b}$ → block

↓

no proper septum formation during division

PBP_2 → block → delayed lysis

PBP_3 → " → formation of long filamentous bacteria

The mechanism of penicillin can be of

Lytic or Non lytic mechanism

↓

Breaks balance b/w PBP mediated peptidoglycan assembly & murine hydrolase

↓

Autolysis of bacteria

↓

induces choline like protein in bacterial membrane

↓

disruption of membrane potential

↓

Cell is not killed but reproduction is stopped.

Classification of Penicillins :→

I. Natural Penicillins :→ P.G. (Benzyl penicillin)
Penicillin G & its Esters
Procaine P.G.
Benzathine P.G.

II. Semi Synthetic penicillins :→ P.V (Phenoxy methylpenicillin)

(a) Acid resistant penicillins → Pheneticillin (Phenoxy ethyl penicillin)

(b) Penicillinase resistant penicillins →
Acid labile } Methicillin, Nafcillin, Cloxacillin, Dicloxacillin
Acid resistant } Flucloxacillin

(c) Penicillins effective against both gram+ve & gram-ve organisms → Ampicillin, Amoxycillin, Talampicillin, Pivampicillin

(d) Extended spectrum Penicillins → Carbenicillin, Ticarcillin, Piperacillin, Mezlocillin, Azlocillin, Mecillinam, Pivmecillinam

(e) Penicillins with β-lactamase inhibitors →
Amoxycillin – clavulanic acid.
Ticarcillin – clavulanic acid.

Penicillins

- Narrow spectrum
  - Natural penicillins
    - Narrow spectrum
    - ↓
    - P.G. & P.V
    - moderately bulky molecules
    - ↓
    - Easily goes into gram +ve cocci, Bacilli, -ve cocci, Spirochetes
    - ↓
    - Bulky nature
    - Narrow spectrum
  - Very very narrow spectrum
    - ↓
    - Very Bulky molecules.
    - ↓
    - Anti staphylococcal penicillins
    - ↓
    - In order to protect the β-lactam ring, a side chain R- is introduced
    - ↓
    - made the mol. very Bulkey
    - ↓
    - narrowed the spectrum
    - ↓
    - Seen with staphylococci species.
    - ↓
    - Methicillin
      Nafcillin
      Cloxacillin
      Dicloxacillin
      Flucloxacillin
      oxacillin.
- wide spectrum
  - ↓
  - HELPS → cleared these org.
  - H → H. influenza (-ve)
    E → E-coli (-ve)
    L → Lysteria (+ve)
    P → Proteus (-ve)
    S → Salmonella (-ve)
  - ↓
  - Amoxicillin
    Ampicillin
- most potent
  - ↓
  - against Pseudomonas auroginosa
  - ↓
  - Piperacillin
    Ticarcillin
    Carbenicillin
    etc.

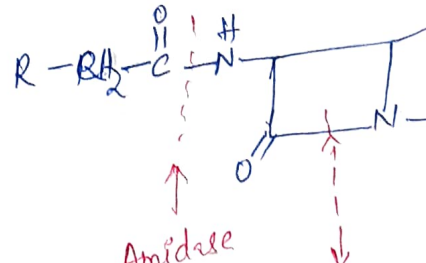
MRSA : Methicillin Resi

The gene encoding such high mol. wt PBP if present lead to

↓

MRSA.

Structure of Penicillin :-



↓

R – CH_2 – COOH +

6-aminopenicillinic acid

(therapeutic

Source — Penicillium

most potent

↓

against Pseudomonas auroginosa

↓

Piperacillin
Ticarcillin
Carbenicillin
etc.

MRSA : Methicillin Resistant Staphylococcus aureus.

↓

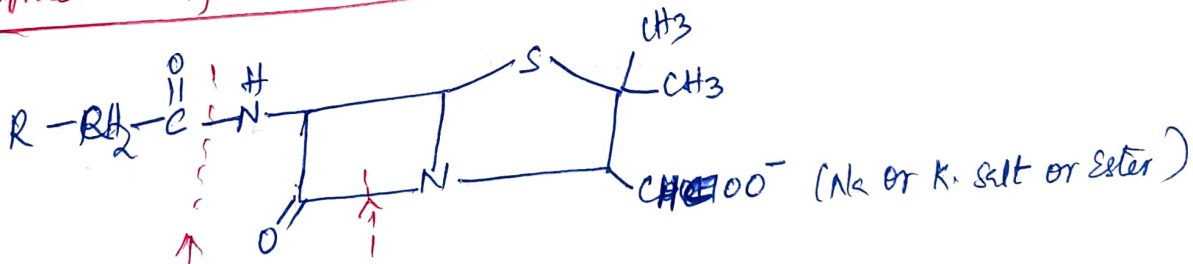
are resistant via acquisition of an additional high mol. wt. PBP with a very low affinity for all β-lactam antibiotics.

The gene encoding such high mol. wt PBP if present lead to

↓

MRSA.

Structure of Penicillin :→



Amidase

↓

Penicillinase ⟶ penicilloic acid.

R – CH_2 – COOH +

6-aminopenicillinic acid
(therapeutic action)

Source Penicillium notatum ; P. chrysogenum

Development of Resistance :→

Resistance may be due to

*) Influx is decreased
*) Enzymes degradation is increased
*) conformational changes in the binding site
*) Effective efflux of antibiotics
*) Increased cell division.

1 * → Resistance mainly through development of high mol.wt PBP (acquired) to resist the binding of penicillin

∴ ↓ influx of drug.

Eg:- MRSA.

2 * → Development of Penicillinase / β-lactamase enzyme which breaks the β-lactam ring. ↓ produced & transmitted through plasmids.

Eg:- Gonococci
- low level penicillin resistant → ↓ influx of penicillin
- High level penicillin resistant → By prod:n of β-lactamase.

Staphylococci
Pneumococci
Bacillus subtilus
H. influenza
E. coli

* production of β-lactamase differs in gram +ve & gram -ve bacteria

gram +ve → produced in large quantities.

-ve → " less "

gram +ve. → β-lactamases diffuses throughout to protect entire colony.

gram -ve → β-lactamase present in b/w lipoprotein & peptidoglycan layer.

→ by ↑ levels of penicillins they are made sensitive.

3* → Conformational changes in transpeptidase enzyme or porin channels.

Antibacterial Spectrum :→

Mostly effective against gram +ve bacteria

Cocci → Pneumococci
Streptococci
Staphylococcus aureus → originally sensitive but developed resistance.

gram -ve cocci → N. gonorrhoea, N. Meningitis } → development of resistance is quick.

Bacilli → B. anthracis
Corynebacterium diphtheriae
Clostridium tetani
C. botulinum.

Spirochetes → T. pallidum

Resistant strains :→ Bacteriods fragillus.
M. tuberculosis
Rickettsia
Chlamydia

(31) CLINID... AZOLAM ... INJ PCM ...

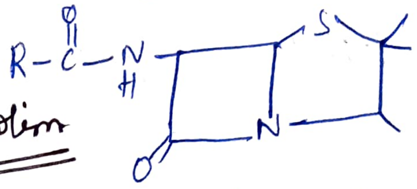
P. kinetics :→

Absorption :→

Penicillin G :→ about 1/3rd of an orally admn. PG. is absorbed from intestinal tract

Oral
Gastric juice pH → 2 rapidly destroys the antibiotic.
↓ in acid prodn with aging → better absorption of P.G from GIT.

Metabolism



—Alkaline pH→ Penicillic acid
↓
penicilloic acid.

↓ Acidic pH.

Penicillonic acid

↓

penamaldic acid

↓

Penicillamine + Penaldic acid

CO_2 ↓ H^+

penicilloaldehyde.

→ Orally in geriatrics → maximal concn 30-60 min.
ingestion of foods may enteric absorption
∴ admn. 30 min before the meal or
2 hrs later after the meal.

Oral P.V :→ more stable in acidic medium ∴ better absorption in GIT.
plasma concn 5 times greater than P.G.

Penicillins ADME

Parenteral administration of Penicillin G :→

IM injection → Peak Conc^n within 15-30 min.

$t_{1/2}$ – 30 min

Used as repository preparations

↓

long persistence of penicillin in blood after a suitable IM dose reduces cost, need for repeated injection & local trauma.

PG. Benzathine – absorbed very slowly from IM depots & produces the longest duration of detectable antibiotic

Distribution :→

* Widely distributed throughout the body but varies in conc^n in fluids & tissues.
* V_d ≈ 0.35 L/Kg
* 60% of P.G. reversibly bound to albumin
* distributed in liver, bile, kidney, semen, joint fluid, lymph and intestine.
* Meninges normal – No penetration in CSF
  Meningitidis – Penetration in CSF

  ↓

  Conc^n Vary & unpredictable

  5% of plasma

* Penicillin and other organic acids are secreted rapidly from CSF into bloodstream by an active transport process.

* Probenecid → ⊗ the active transport process & ↑ the conc? of Penicillin in CSF

Uremic condition → organic acids accumulate in CSF & compete with penicillin for secretion
↓
occasionally reaches toxic conc? in brain
↓
Convulsions

Excretion :-

P.G. → rapidly by kidney, small amounts in bile & other routes.

60-90% → eliminated in first one hr. of injection.

10% by GFR
90% by tubular secretion

Remaining is metabolised to penicilloic acid.

Probenecid → ↓ the tubular secretions
↓
↑ in plasma levels of P.G.

Doses must be adjusted during dialysis, Renal failure & Hepatic insufficiency.

Adverse effects

Hypersensitivity Reactions

→ The most common adverse effect reported.

0.7–4 % of all treatment courses → Allergic reaction complication

→ Maculopapular Rash
Urticarial Rash
Fever
Bronchospasm
Vasculitis
Serum sickness

exfoliative dermatitis
Stevens Johnson Syndrome
Anaphylaxis

→ Reactions occur with any dosage form of Penicillin & persist for 1-2 wks or longer after the therapy has been stopped.

→ Penicillins and their breakdown products act as haptens after covalent reaction with proteins.

Minor determinants
other products contribute to 25% of reactions
↓
these in vivo products formed

is

most abundant product penicilloyl moiety
Major determinant Moiety
↓
result in Major IgE mediated reactions.

Frequency of formation of these determinants refer to ~~the~~ which antibodies to haptens appear to be formed.

→ Antipenicillin antibiotics → are detectable in virtually all patients who have received the drug and in many who are unknowingly exposed.

Management of Hypersensitivity reactions

→ Evaluation of patient history to avoid use of Penicillin

→ Skin testing IgE-mediated immediate type responses

→ desensitization by increasing doses of penicillin to avoid severe reaction – performed only in intensive care.

1, 5, 10, 100, 1000 units – intradermally
with 60-minute intervals b/w doses.

↓

Well Tolerated Then 10,000 & 50,000 units S.C.

Desensitization is accomplished by the oral admn. of Penicillin

Other Adverse effects

- Bone marrow depression
- Agranulocytopenia
- Hepatitis
- pain at the site of injection.

P.G, Carbenicillin, Piperacillin, Ticarcillin } → Defects in Hemostasis impairment of platelet aggregation

- lethargy, confusion, twitching, localized seizures CSF > 10 µg/ml
- Rapid IV admn. of 20 million units of P.G. → Hyperkalemia in renal dysfunction patients.

- Procaine P.G. → immediate reaction

↓

dizziness, tinnitus, headache, hallucinations & sometimes seizures

↓

due to rapid liberation of toxic conc^n of procaine.

← Seen in 1 in 200 patients

Cell Wall of Gram +ve & Gram -ve bacteria

Therapeutic Uses of Penicillin

* Pneumococcal infections → Penicillin G
* Pneumococcal pneumonia → for penicillin resistant strains
  ↓ 3rd generation cephalosporin
  20-24 million units of P.G. daily by constant IV infusion
  500 mg P.V. every 6 hrs.
  therapy cont'd for 7-10 dys
* Pneumococcal meningitis → Resistant strains
  ↓ Vancomycin + 3rd generation cephalosporin.
  20-24 million units PG. By IV infusion Bolus for every 2-3 hrs.
  duration of therapy 14 dys.
* Streptococcal Infections, Pharyngitis, Scarlet fever
  ↓ S. pyogenes
  ↓
  orally P.V 500mg every 6 hrs for 10dys.
* Streptococcal Toxic shock and Necrotizing fasciitis →
  ↓
  Penicillin + Clindamycin.
* Streptococcal pneumonia, Arthritis, Meningitis, Endocarditis
  ↓
  P.G. daily doses 12-20 million units
  IV 2-4 weeks. 4 wks.

* Infections caused by other Streptococci.

PG. → MIC > 0.1 μg/ml

S. endocarditis → daily dose of 12-20 million units IV. for 2 wks.
for 4 weeks. → in combo with gentamicin 1mg/kg every 8 hrs.

(or) P.G or 12g Ampicillin daily I.V. with low dose of gentamicin. for 6 wks.

* Anaerobes :→ most of them are sensitive to P.G. except B. fragilis.

pulmonary & peridontal infections → P.G. → more effective than P.G. is clindamycin.

mild to moderate infection → PG / PV 4,00,000 units Q.i.d. (250 mg)

more severe → 12-20 million units PG. IV.

Brain abscess → PG. 20 million units/day + Metronidazole or chloramphenicol.

* Stephylococcal infections :→

Stphylo. Species

Vast majority of ~~infections~~ are penicillinase producing strains.

Hospital acquired MRSA → resistant to P.G., cephalosporins, etc.

∴ Vancomycin, linezolid, quinupristin, dalfopristin, daptomycin. Can be given.

community acquired MRSA → Trimethoprim-sulfamethoxazole, doxycycline, clindamycin.

* Meningococcal infections
↓
P.G. drug of choice.

* Gonococcal infections
↓
gradually have become resistant to P.G. & no longer used until the disease is penicillin sensitive.

uncomplicated gonococcal urethritis → Single I.M 250mg Ceftriaxone

Gonococcal arthritis, skin lesions etc → Ceftriaxone 1g daily IM/IV for 7-10 days.

* Syphilis → used in 1°, 2° & latent syphilis < 1yr duration

P.G. procaine → 2.4 million units per day I.M for 10 days
+ probenecid → 1.0 g/day orally

~~with 1-3 weekly~~

(or)
P.G. Benzathine → 2.4 million units IM for 1-3 wks.

Latent syphilis, neurosyphilis etc → 20 million units P.G daily for 10 days

Infants with Congenital syphilis → P.G. aqeous 50,000 units/kg daily in 2 divided doses
(or)
Procaine P.G. in a single daily dose 50,000 units/kg.

* Actinomycosis → P.G. drug of choice.
10-20 million units I.V per day for 6 weeks.
may continue for 2-3 months with oral P.V. 500 mg Q.i.d.

* Diphtheria :→ P.G. eliminates the Carrier state.
2-3 million units / day in divided doses for 10-12 days
(or)
Single daily injection of P.G. procaine

* Anthrax :→ gradually resistant.
But sensitive strains P.G. 12-20 million units per day

* clostridial infections :→
↓
choice of drug is P.G. especially gas gangrene
↓
12-20 million units per day I.V. as an adjunct to antitoxin

* Fusospirochetal infections :→
Gingivostomatitis → 500 mg P.V. given for every 6 hrs. for several day till clear of disease.

* Rat-Bite fever :→
↓
Caused by Spirillum minor & Streptobacillus moniliformis
↓
12-15 million units parenterally for 3-4 wks.

* Listeria → P.G. + Ampicillin / gentamycin (in immune sensitive).
↓ 1-2g IV/ 4 hrs.
duration is 4 wks. (15-20 million units / day / 2 wks.

* Lyme disease :→ Tetracycline drug of choice for early disease.

Amoxicillin – 500mg | t.i.d. — 21 dys.

Severe → 3rd Gener. Cephalo. or

20 million units P.G. daily for 10-14 days.