β-lactams

A β-lactams is an internal amide with the amine in the β-position in relation to the carboxylic acid.

All β-lactams will have similar mechanisms of action and many general properties.
The largest group of antibiotics forms about 60% of total known antibiotics.

The nitrogen atom is neutral (very weak base, amide nitrogen) because it’s lone pair electrons are delocalized by resonance and presence of carbonyl group.

The β-lactam ring is responsible for the following characters:

- Activity of antibiotics.
- Allergenicity
- Stability
  - Stable for 7-14 days at 4°C
  - Stable for 1-2 days at room temp
  - Dry form stable for up to 5 years
Penicillins

They are the first group of antibiotics discovered

Natural penicillin e.g. Penicillin G.

Semi-synthetic Penicillins divided into the following:

- Penicillin-V.
- **Penicillinase resistant penicillins** e.g. Methicillin, Nafcillin, Oxacillin, Cloxacillin, Dicloxacillin and Fluocloxacillin
- **Broad spectrum penicillins** e.g. Ampicillin, Amoxicillin, Bacampicillin, Carbencillin and Ticarcillin.
- **Mega-spectrum penicillins** e.g. Ureidopenicillins as Azalocillin, Mezlocillin and Piperacillin.
Stability

The β-lactam ring is unstable (highly strained 4-membered ring) in the following:

- Presence of β-lactamase enzymes produced by resistant micro-organisms e.g. *Staphylococcus aureus*, *Haemophilus influenzae* and *Neisseria gonorrhoea*.
- Presence of acid
- Presence of base
Common Characteristics

- All Penicillins are acids, with a pKa around 2.5 to 3.
- They are crystalline and should be protected from moisture
  - If it is stored under dry conditions, it will be stable for years.
- They have an unpleasant taste.
- They are not suitable to formulate as a free acid, so used as sodium or potassium salts.
Generally safe in pregnancy and during lactation
- It will pass into the milk, so only precaution is to watch out for anaphylactic shock and diarrhea.

Differ in their protein binding capability, between 20 and 90% protein bound
- This leads to a change in the free drug available in the bloodstream.
Common Characteristics

- Immunological reaction; an anaphylactic shock can occur in less than 0.1% of the population, or a rash in 5 - 7%

- This results from the reaction of the β-lactam ring with a terminal amine on a lysine in a polypeptide, leading to the formation of an allergen.
Antibodies are formed the first time the patient is exposed to the antibiotic, and the reaction will be severe in consequent times.

If the preparation is not well purified, then residual proteins will cause the reaction to be more severe.

First line of treatment is the use of Adrenaline to stabilize the blood pressure and relieve the bronco-constriction.
Several drug interactions have been reported, such as oral contraceptives and the antigout, probenecid.

- Probenecid compound will compete with Penicillins for active tubular sites of active excretion, resulting in higher blood levels and may lead it to reach toxic levels.
Penicillin G

Crystapen

- Source: *Penicillium chrysogenum*

- Mixture of compounds, including Penicillin G, K, V, O, and S are produced in the medium.

- We can obtain exclusively Penicillin G by the addition of phenyl acetic acid.

- It is used in units. In the USP one unit is equal to the antibiotic activity present in 0.6 µg.
Essential Structural components of Penicillin G
Pharmaceutical Forms

- **Water soluble salts:**
  - They are used IV, IV infusion or IM.
  - Rapid onset and short duration ( \( t_{1/2} = 1/2 \) hour).
  - Potassium preferred in hypertension.
  - Sodium preferred in renal insufficiency (hyperkalemia & Cardiac arrest).

- **Procaine Penicillin G (Wycillin®):**
  - Procaine (local anesthetic) : Pen.G = 1:1
  - Water Solubility (1:250 ml) used as IM suspension.
  - Duration of action (up to 1 week)
Benzathine Penicillin G (Bicillin®)

(Pencitard, Durapen, Penadur, Retaepen, Aqua Pen, Depo Pen)

- Benzathine:Pen.G = 1:2
- Water Solubility (1:5000 ml) used as IM suspension.
- Duration of action (up to 3-4 week)
- Metabolism by amine oxidase yields pen.G + Oxalic acid (toxic metabolite).
- Must be used with urine alkaliniser to prevent crystallization of calcium oxalate formed.
Pharmacokinetics

- Route of administration IM, IV, **but not orally**.
- Distribution to almost all body tissues and fluid.
- It penetrate to CSF in case of meningitis.
- Concurrent administration of probencid, kidney will excrete probenecid before Pen G leads to increase blood level concentration of Pen G five times.
Mechanism of Action

- Inhibition of transpeptidation leading to loss of murine layers during cell division.
- Inhibits stage III and thus prevents cross-linking of peptidoglycan.
- Less effective against Gram negative bacteria due to the presence of outer mucopolysaccharide membrane.
Antimicrobial Spectrum

- **Narrow spectrum** (effective against limited number of micro-organisms, mostly **Gram positive**):
  - *Staph. aureus*
    - Soft tissues infections.
    - Osteomyelitis (infection of bone marrow and hard tissues) Pen G is effective but not drug of choice.
    - Toxic Shock Syndrome (TSS), during menstruation or wound infection with *Staph. aureus*
Streptococci

- Sterpt. viridans:
  non-pathogenic, one of the normal flora it can pass to the blood stream causing sub-acute bacterial endocarditis. Treatment by benzathine Pen.

- Sterpt. Pneumonia:
  Besides causing pneumonia, can cause meningitis in adult. Treatment, with pen G

- Strept. pyogenes
  Tonsillitis, boils, sore throat, scarlet fever, endocarditis and rheumatic fever. Treatment with Pen G
Enterococci

- *Sterpt. faecalis*, normal large intestine flora, can cause UTI and endocarditic. Treatment by Pen G and streptomycin

Coryn bacterium diphtheria (*Diphtheria*). Treatment by Pen G

Clostridium tetani (*Tetanus*). Treatment by Pen G
Gram negative bacteria:

- **Neisseria meningitides** (Meningitis): Pen G is the drug of choice as it can cross the Blood Brain Barrier BBB.

- **N. gonorrhoeae** (Gonorrhea)

- **Treponema pallidum** (Syphilis)

- In case of allergy or penicillin-resistant strain, ceftriaxone or cefuroxime are used.
Properties of penicillin G

- Active versus Gram-positive bacilli (e.g. staphylococci, meningitis, and gonorrhoea) and many (but not all) Gram-negative cocci.
- Non-toxic
- Narrow spectrum.
- Ineffective when taken orally since it breaks down in the acid conditions of the stomach.
- Sensitive to all known β-lactamases. These are enzymes produced by penicillin resistant bacteria which catalyze the degradation of penicillins.
- Allergic reactions are suffered by some individuals.
Penicillin V
(Ospen, Pen os)

Production: from *P. chrysogenum* by the addition of phenoxyacetic acid instead of phenyl-acetic acid.
Properties Penicillin V

- Relatively acid stable, given orally due to:
  - Electron withdrawing group makes the side chain carbonyl less electronegative and can not attack the lactam carbonyl.

- Blood level concentration (BLC) of Pen V is moderate so it is not the good choice for treating *N. gonorrheae* and *Strept. pneumonia* infections.
In Acidic Solution

Penicilloic Acid (Inactive)
Clinical Uses

- Prophylactic against sub-acute endocarditis and in rheumatic.

- Prophylaxis in sickle cell babies against pneumococcal infections.

- Mouth infections.

- Treatment of tonsillitis and sore throat.
Semisynthetic Penicillins
Aim

- Increase the Spectrum
  - Improve cell wall permeability by adding polar groups.

- Decrease Penicillinase susceptibility
  - Steric hinderness by bulky group close to the $\beta$-lactam ring.

- Increase Acid liability
  - Electron withdrawing groups at the side chain.
How they are produced?

In 1959 6-aminopenicillanic acid (6-APA) was obtained by:

- Action of acylase enzyme on Pen G
- Chemical hydrolysis
Structure-Activity Relationship (SAR)

1-position, if the sulfur is oxidized to the sulfone/sulfoxide, gives it better acid stability, but becomes less active.

2-position, any change will lower activity.

3-position, the carboxylic acid is a must. If changed to an alcohol/ester, it will be inactive.
4-position, must have a nitrogen.

5-position, no substitutions allowed.

7-position, must have the carbonyl
6-position, specifically the R group:

- If an electron withdrawing group (NO2, Cl, Fl..) is added, then the amide oxygen will be less nucleophillic and will thus give the compound better acid stability.
- If a bulky group (ph, diph,…) is added close to the ring, then it makes the drug better resistant to β-lactamases.
- If a polar group (NH2, COOH, OH) is added, its spectrum becomes broader, since it can pass through the porin in the Gram negative bacterial cell walls.
Classes of Semisynthetic Penicillins

- Penicillinase – Resistant Penicilins (PRP).
- Broad Spectrum Penicillins (BSP).
- Mega – Spectrum Penicillins (MSP).
Penicillinase-Resistant Penicillins

1- Methicillin

- Dimethoxy groups increase resistance of the drug to penicillinase, but also increase the acid – sensitivity as the OCH$_3$ group as electron releasing group.
Uses

- It is used for treatment of infection caused by penicillinase producing *Staph. aureus*.
- Treatment of respiratory, urinary tracts infections, skin, bone and joint infections due to *Staph. aureus* penicillinase producing strains.

Toxicity

- Hypersensitivity reactions.
- Nephropathy in a large i.v. dose.
2- Nafcillin

- Penicillinase stable.
- Acid stable.
- More lipophilic.
- DOC for meningitis as it penetrates CSF.
Side effects:

- Reversible neutropenia (abnormally low number of neutrophil granulocytes), platelets dysfunction leading to abnormal bleeding time.

- Very irritant at injection site (causes phlebitis).
3- Isoxazolyl Penicillins

Oxacillin
Cloxacillin = Prostaphlin
Dicloxacillin
Flucloxacillin = Fluxapen

\[ \begin{align*}
\text{Oxacillin} & : R_1 = H, R_2 = H \\
\text{Cloxacillin} = \text{Prostaphlin} & : R_1 = H, R_2 = \text{Cl} \\
\text{Dicloxacillin} & : R_1 = \text{Cl}, R_2 = \text{Cl} \\
\text{Flucloxacillin} = \text{Fluxapen} & : R_1 = \text{F}, R_2 = \text{Cl}
\end{align*} \]
Characters:

- Resistant to β-lactamas enzymes.
- Resistant to gastric acidity.
- Active against Staphylococcal infections.
Toxicity:

- Hypersensitivity
- GIT side effects
- Hepatotoxicity
- Neurotoxicity
- Neutropenia
Cloxacillin (Prostaphlin):
- Oral and parenteral
  Cloxacillin + Ampicillin = Hi Flucil, Ampiclox, Rivaclox

Dicloxacillin
- Oral only. Most potent due to higher lipid solubility.
  Dicloxacillin + Ampicillin = Cloxapen, Dipebacid

Flucloxacillin (Fluapen)
- Oral only
  Flucloxacillin + Ampicillin = Ampiflux
Broad Spectrum Penicillins

1- Ampicillin = Amino-pencillin G
   (Epicocillin)

- Penicillinase sensitive penicillin.
- Acid Stable
- Forms an Zwitter ion at PH = 7 leading to increases the penetration of the Gram negative bacterial cell walls (Broad Spectrum).
Spectrum:

- **Gram (+ve) micro-organisms that are susceptible to penicillin G.**

- **Gram (-ve) micro-organisms:**
  - *E. coli* which causes UTI
  - *Proteus mirabilis* cause UTI
  - *Brucella spp.*
  - *Haemophilus influenzae* causes infections of upper respiratory tract (URT).
  - *Gardnerella vaginalis* (bacterial infection) causing vaginitis
Pharmacokinetics:

- Less bound to plasma proteins.
- Rapidly excreted through kidney.
- 35-50% only absorbed.
- Actively transported in the intestine as phenylalanine.
- Should be taken 1 hr before meals or 2 hr after meal.
Adverse effects:

- **Mild Diarrhea**
  - Loosely stool (5-6 times/day of diarrhea)
  - Watery stool (15-20 times/day). Treatment must be stopped and replaced with amoxycillin.

- **Sever Diarrhea (Bloody stool).**

- **Decrease level of hormones in contraceptive pills.**

- **Ampicillin rash due to hypersensitvity.**

- **Pseudomembranous colitis (PMC)**
Pseudomembraneous colitis (PMC):  

- On treatment with Ampicillin suppression of the normal intestinal flora occurs leading to super infection with *Clostridium difficile* (ampicillin resistant bacteria). This bacteria produces two toxins A and B and causing diarrhea.

- **Treatment:**
  - Cholestyramine to absorbs the toxin.
  - *Lactobacillus* organism to Re-establish normal flora
  - Vancomycin, metronidazole or bacitracin
Ampicillin Combinations:

- **Unasyn** (ampicillin: sulbactam sodium salt = 2:1):
  (Ampictam, Sabect, Unictam, Ampictam, Ultracillin, Synerpen)

  - Sulbactam is an inactive penicillin analogue that binds irreversibly to penicillinase active site leading to deactivation of the enzyme.
  - Unasyn is used usually as i.v. or i.m.
  - Unasyn prepared as sodium salt, caution of hypertension
  - Unasyn is effective against *E. coli* and *H. influenza*
Bacampicillin:

- It is more absorbed than ampicillin and undergo hydrolysis with esterase enzymes in plasma to release ampicillin in high yield.

\[
\text{Esterase in plasma} \quad \text{AMPICILLIN} + \text{CH}_3\text{CHO} + \text{CO}_2 + \text{CH}_3\text{CH}_2\text{OH}
\]
Amoxycillin

Amoxil- E mox- Hymox- Ospamox- Glomox- Remox- Julphamox

Advantages:

- Acid stable but pencillinase sensitive.
- More absorbed than ampicillin by tyrosine active transport (75% absorbed).
- High absorption from GIT decrease incidence of diarrhea and PMC
- Food will not interfere with absorption.
- Longer $t_{1/2}$ due retain in polar body fluids (long acting).
Spectrum:

- Amoxycillin is more active against *Salmonella typhi* (Typhoid) but not DOC.
- Amoxycillin is active against *Helicobacter pylori* (gastric and duodenal ulcer) in combination (Amoxycillin + Clarithromycin + Omeprazole).
- Amoxycillin is less active against *Shigella* spp. (Shigellosis bacillary dysentery).

Excretion:

Amoxicillin is excreted by urine.
Amoxycillin Combination:

- **Augmentin- Julmentin- Megamox- Klavox- Curam:**
  - Amoxycillin + K-clavulanate (250mg/125mg, 500/125, and 850/125)
  - Sodium free so no risk for hypertensive patients.
  - Clavulanic acid is a β-lactam penicillin analog inactivate β-lactamases by blocking the active sites of these enzymes.

- **Spectrum:**
  - Lower respiratory tract infections (such as pneumonia)
  - Ear Infections
  - Sinus Infections
  - Skin Infections
  - UTI such as bladder infections or kidney infections.
α- Carboxy penicillins
Characteristics

- Acid and penicillinase sensitive.

- Active against ampicillin resistant *Pseudomonas aeruginosa*, *Proteus* and *Providenica* spp.

- More effective against gram (-ve) *Bacilli* due to the COOH that provide better penetration to their cell walls.

- Combination with Gentamycin for serious *Pseudomonal* and *Coliform* infections.

- However, the two drugs are incompatible chemically and should never be combined in the same i.v. solution.
Carbenicillin
Carindacillin
Geocillin

It is indenyl ester (pro-drug) of carbenicillin sodium salt absorbed orally and hydrolyzed by esterase enzyme to yielded carbenicillin.

One of few antibiotics that active against *Pseudomonas aeruginosa* orally.
Ticarcillin
Advantages:

- Not used orally, but i.v. or i.m.
- Give higher serum levels more than carbenicillin.
- Longer duration of action, replacing carbenicillin in clinical uses.
- Greater potency against gram (-ve) Bacilli *Ps. aeruginosa* and *Bacteroid fragilis*.
- Timentin consists of Ticarcillin sodium salt and clavulanate potassium (3 g+100 mg)
Mega Spectrum Penicillins
(Ureidopenicillins)

- They contain ureido group (NH-CO-NH)
- These antibiotics are highly polar, high penetration power and high potency.
- They are too polar to be absorbed orally so they administered parenterally.
- They are penicillinase sensitive, therefore they are reserved for use with hospital acquired infections.
- They bind more to proteins so have high potency and mega-spectrum activity
- Low MIC, so low therapeutic doses
- Low toxic effect on platelets
- DOC for meningitis caused by *Pseudomonas aeruginosa* as a combination with Gentamycin.
They have expanded spectrum against the following gram (-ve) bacteria:

- *E. coli.*
- *Pr. mirabilis.*
- *H. influenzae.*
- *Ps. aeruginosa.*
- *Klebsiella pneumoniae.*
- *Bacteroides fragilis.*
- *Enterobacter spp.*
Piperacillin
NH-CO- group in the side chain make it mega spectrum for a many types of bacteria.

The most potent ureidopenicillin antipseudomonal antibiotic

MIC = 4µg/ml.

Synergistic with amino-glycosides against *Enterobacteriacea* which are resistant to the amino-glycoside and β-lactam antibiotics.

Zosyn- Tazocin (Piperacillin + Tazobactam), (2 g + 0.25 g). Tazobactam is a strongest suicidal substrate (penicillinase inhibitor).
Toxicity

- Hypersensitivity reactions.
- Neuro-toxicity in massive doses.
- Bleeding disorder through platelets function disturbance.
- Reversible neutropenia.
- Electrolyte and acid-base balance disturbance.
**β-Lactam Monobactam**

- β-lactam ring is alone and not fused to another ring.
- They work only against aerobic Gram negative bacteria (e.g., *Neisseria, Pseudomonas*).
- No cross-hypersensitivity reactions with penicillin.
- Resistant to some beta-lactamases.
1- Aztreonam (Azactam- Cayston)

- Administration: I.M., I.V., Inhalation.
- Active against Gram-negative bacteria, including *Pseudomonas aeruginosa*.
- It has no useful activity against Gram-positive bacteria or anaerobes.

**Side Effects:**

- Injection site reactions.
- Gastrointestinal side effects generally include diarrhea, nausea and vomiting.