CH- PENICILLINS & CEPHALOSPORINS

B-LACTAM ANTIBIOTICS

- The B-lactam antibiotics have a B-lactam ring in their structure.

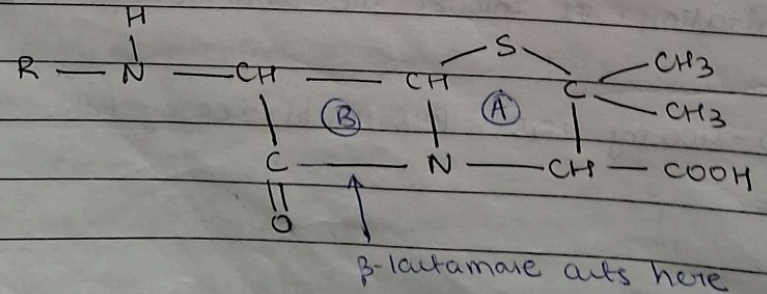
β-lactam antibiotics
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

* PENICILLINS

- Sir Alexander Fleming discovered penicillin in 1928 from Penicillium notatum. In 1941, penicillin became available for therapeutic use.
- Though several antibiotics have been introduced since then, penicillins are one of the most important groups of antibiotics. Penicillin is now obtained from the fungus penicillium chrysogenum for therapeutic use.

→ Chemistry

The structure of penicillin consist of a thiazolidine ring (A) attached to a β-lactam ring (B) to which a side chain (R) is attached. A & B together is called 6-aminopenicillanic acid nucleus or penicillin nucleus which is essential for the antibacterial activity. The side chains determine some of the pharmacokinetic & antibacterial properties. Modification of the side chains resulted in semisynthetic penicillins with some variations in pharmacological properties.



→ Mechanism of Action

β-lactam antibiotics

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Bind PBP (Penicillin Binding Proteins)

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Inhibit cross-linking of peptidoglycan

↓

Cell wall defecient bacteria

↓

Undergo lysis

↓

Bactericidal effect.

- Gram positive Bacteria are more susceptible to penicillins because they have a thick cell wall which is vital for their living and is easily accesible to penicillins while gram negative bacteria have a thin cell wall. Penicillins are highly safe because the peptidoglycon layer is unique to bacteria and is absent in higher animals.

→ Resistance to β-lactams:

- Bacteria develop resistance to penicillins by one of the following mechanisms: Many organisms like staphylococci produce a penicillinase which is a β-lactamase - it opens the β-lactam ring & inactivates penicillins - most common mechanism of resistance to penicillins.
- There are several types of β-lactamases. Some of them selectively hydrolyse penicillins while others can inactivate both penicillins & cephalosporins.
- Carbapenems are resistant to most β-lactamases but are inactivated by carbapenemases.
- Alter target proteins (PBPs) on the bacterial cell which reduce affinity for penicillins. Poor penetration of the drug into the bacteria as in gram negative bacteria.
- Efflux of penicillin from the gram -ve bacteria by an efflux pump.

Classification of Penicillins

A. Natural
- Regular — Penicillin G
- Repository penicillins — Procaine penicillin, Benzathine Penicillin

B. Semisynthetic
- Acid Resistant — Penicillin V
- Penicillinase Resistant — Methicillin, Oxacillin, Cloxacillin, nafcillin
- Aminopenicillins — Ampicillin, Bacampicillin, Talampicillin, pivampicillin, Amoxicillin
- Antipseudomonal penicillins
  - Carboxypenicillins — Carbenicillin, Carbenicillin-indanyl, Ticarcillin
  - Ureidopenicillins — Azlocillin, Mezlocillin, piperacillin

(A) Natural Penicillins:

* Penicillin G (Benzyl Penicillin)

→ Antibacterial Spectrum
- Penicillin G (PnG) has a narrow antibacterial spectrum & is effective against gram positive cocci & Bacilli & afew gram negative cocci.
- Penicillins are also effective against some anaerobes.

→ Pharmacokinetics
- Benzyl penicillin is destroyed by gastric juice (acid labile), has a very low bioavailability, hence given parenterally.
- food interferes with its absorption - hence should be given 2hr before or after food.

- Penicillins are widely distributed into most tissues & Body fluids but remain mostly extracellularly as they are polar compounds and generally doesn't cross BBB.
- Benzyl penicillin ~~attacks~~ attains peak levels in 15-30 min, has $t_{1/2}$ of 30-60 min & about 60% is bound to plasma albumin. Penicillin G is rapidly excreted by kidneys.
- In renal failure and in neonates in whom renal function is not fully developed, the duration of action of penicillins gets prolonged & the $t_{1/2}$ may be increased to 10hr.

* Repository Penicillins

- Oral penicillin can be used only in minor infections & benzyl penicillin is short acting. Hence, repository forms like procaine penicillin & benzathine penicillin are formulated so that they are slowly absorbed with prolonged Blood levels and are longer acting.
- Given deep IM they release penicillin slowly from the site. Procaine Penicillin is given 12-24 hourly while a single injection of Benzathine penicillin is effective for 3-4 weeks.

→ Adverse effects

- Penicillins are highly safe drugs with a high therapeutic index; most adverse effects are not serious in therapeutic doses except hypersensitivity reactions.
- Hypersensitivity: Allergic reactions range from skin rashes, urticaria pruritis, fever, bronchospasm, serum sickness & rarely exfoliative dermatitis & anaphylaxis.

→ Other Adverse effects

- Local: Pain at the site of IM injection (due to irritation) thrombophlebitis on IV injection particularly large doses due to irritation.

CNS: Large doses of PnG >20 mega units injected IV may produce confusion, muscle twitchings, convulsions & coma particularly in the presence of renal dysfunction.

Suprainfections: are rare because of narrow spectrum of activity of penicillins.

Jarisch-Herxheimer reaction: When penicillin is injected to a patient with syphilis, there is sudden destruction of spirochetes & release of their lytic products. This triggers a reaction with fever, myalgia, shivering, exacerbation of syphilitic lesions & vascular collapse.

→ Uses

- Penicillin G is the antibiotic of choice for several infections unless the patient is allergic to it. Pneumococcal infections, streptococcal infections, Meningococcal infections, staphylococcal infections, Syphilis, Diphtheria, Anaerobic infections, Tetanus, etc.
- Prophylactic use: Rheumatic fever, Gonorrhea & syphilis, Valvular heart diseases.

→ Disadvantages of Natural Penicillins:

- Natural Penicillins have narrow spectrum of activity.
- Not effective orally – acid labile
- Susceptible to penicillinase
- Risk of hypersensitivity
- Hence, semisynthetic penicillins were obtained in an effort to overcome these disadvantages.

(B) Semi-synthetic penicillins

(1) **Acid resistant penicillins:** Penicillin V (phenoxymethyl Penicillin) is acid stable & can be given orally. It is used only in mild infections as it has a low bio-availability, short action (6 hrly dosing) & a narrow spectrum of activity. It may be given in streptococcal pharyngitis, sinusitis & trench mouth.

Dose: 250-500 mg 6 hourly

(2) **Penicillinase resistant penicillins:**

- Methicillin is destroyed by gastric juice - hence given parentrally. Methicillin resistant ~~spt~~ staph. aureus (MRSA) are fairly common & such staphylococci are also resistant to other penicillins
- Oxacillin, cloxacillin, dicloxacillin are relatively acid stable but food interferes with their absorption - to be given 1 hr before or after food.
- Nafcillin is highly resistant to penicillinase & also has useful activity against nonpenicillinase producing organisms. It requires parental administration because of its unreliable absorption from the gut. Nafcillin is extensively bound to plasma proteins & primarily excreted in the bile.

* Uses

- Penicillinase resistant penicillins are the drugs of choice for infections with susceptible penicillinase producing staphylococci. For more severe staphylococcal infection, nafcillin / oxacillin may be given by intermittent IV infusion. Methicillin-resistant strains have now emerged & are treated with vancomycin.

(3) **Aminopenicillins**

- Aminopenicillins are extended spectrum penicillins - cover a wider antibacterial spectrum including many gram negative bacilli. They are orally effective but are sensitive to β-lactamases.

* Ampicillin:

- Both gram positive & gram negative organisms including streptococci, meningococci, pneumococci & H. influenzae are sensitive.
- Ampicillin is acid stable & well absorbed orally; food interferes with its absorption. On IM injection peak levels are attained in about 60 min. It is excreted mainly through kidneys and $t_{1/2}$ gets prolonged in renal failure.
- Dose: 0.5 - 2g 6hrly - oral or IM/IV inj. AMPICIN

→ Adverse effects

- Diarrhoea due to irritation of gut by the unabsorbed drug is the most common adverse effect with ampicillin. skin rashes are also fairly frequent particularly in patients with infectious mononucleosus & AIDS & in those receiving allopurinol. The rashes usually subside by themselves.

→ Uses

- Respiratory tract infections, UTIs, meningitis, typhoid, etc.

* Amoxicillin: is similar to ampicillin but differs from ampicillin in the following:

1) Amoxicillin is better absorbed orally
2) food does not interfere with its absorption.
3) Attains high blood levels after oral administration. It is also less protein bound.
4) Diarrhoea is rare (because it is well absorbed). Given thrice daily - as it is longer acting than ampicillin.

Amoxicillin is used in similar infections as ampicillin like respiratory infections, salmonella gastroenteritis & urinary tract infections. Amoxicillin is a component of the various regimens to eradicate H. pylori. Amoxicillin is preferred over ampicillin

by many except for shigellosis for which amoxicillin is not very effective.

- Dose: 250-500 mg TDS

(4) Antipseudomonal Penicillins

(a) Carboxypenicillins

* Carbenicillin: In addition to activity against gram positive & gram negative organisms, carbenicillin is also effective against pseudomonas aeruginosa & Proteus infections & may be combined with an aminoglycoside. Carbenicillin is given parentrally.

- Dose: 2-5g 6hrly IM or IV

* Carbenicillin indanyl: is effective orally as it is acid stable but is not available in India. Ticarcillin, an analog of carbenicillin, has better activity than carbenicillin against P. aeruginosa. It is often combined with an aminoglycoside for synergistic activity against Pseudomonas. It reaches the CSF, pleural fluid & sputum. Ticarcillin may be given Both IM & IV.

→ Adverse effects: Carbenicillin is used as a sodium salt & in higher doses the excess sodium may cause oedema and CCF; may also cause Bleeding due to abnormal platelet aggregation.

→ Uses: Ureidopenicillins are preferred to carboxypenicillins in all relevant indications. Carbenicillin indanyl & ticarcilin are not marketed in India. Carbenicillin may be used in serious infections by Pseudomonas & Proteus like in Burns.

(b) Ureidopenicillins:

- Piperacillin, azlocillin & mezlocillin are ureidopenicillins. They have a wider antibacterial spectrum & are effective against a variety

of gram negative organisms including Pseudomonas, Klebsiella, Proteus & H. influenzae.

- Piperacillin is administered intravenously though it can also be given IM. When combined with a β-lactamase inhibitor, piperacillin can be considered to have the broadest antibacterial spectrum among the penicillins. It crosses the BBB & is, therefore, useful in meningitis.
- Dose: 100-150 mg/kg in 3 divided doses IV

→ Uses: Piperacillin is indicated in severe infections particularly due to Pseudomonas & Klebsiella. It can be used with a β-lactamase inhibitor tazobactam in severe infections. piperacillin can be considered to have the broadest antibacterial spectrum among the penicillins. In serious gram negative infections in immuno suppressed patients, an aminoglycoside may be added.

- ~~Az~~locillin & mezlocillin have similar actions & uses.

(5) Amidinopenicillins

* Mecillinam: is an amidinopenicillin with high efficacy against some gram negative organisms (but not gram positive bacteria) including Salmonella, Shigella, E. coli, Proteus, Klebsiella & Aerobacter (but not pseudomonas). It acts by inhibiting cell wall synthesis by a mechanism that is different from that of penicillins. It is given IM as oral absorption is poor. Pivmecillinam is a prodrug of mecillinam that is effective orally. The two drugs are tried in UTI, typhoid & dysentry. Amidopenicillins are not available in India