TOPIC OUTCOMES

- At the end of this section, You will be able to

1. Know the history of Penicillin discovery
2. MOA, ADME, Clinical usage of Penicillin's
3. Resistance encountered
Dr. Alexander Fleming, the bacteriologist on duty at St. Mary’s Hospital (1928)

Dr. Fleming noted that a mold called Penicillium notatum had contaminated his Petri dishes.

Mold prevented the normal growth of the staphylococci
Dr. Florey & Chain further took the research

Confirmed findings in Mice injected with Lethal deadly streptococcus

Half the mice died miserable deaths from overwhelming sepsis. The others, which received penicillin injections, survived

Challenge “P. Notatum” yield of penicillin was poor

2,000 liters of mold culture fluid to obtain enough pure penicillin to treat a single case of sepsis in a person
laboratory assistant, Mary Hunt, arrived with a cantaloupe with a "pretty, golden mold."

Mold turned out to be the fungus *Penicillium chrysogeum*, and it yielded 200 times the amount of penicillin.

Further increase in yields by mutation-causing X-rays.

Ultimately increasing production by 1000 times compared to *P. Notatum*. 
In 1945, Fleming, Florey, and Chain were awarded the Nobel Prize in Physiology or Medicine.
BACTERIAL CELL WALL

Gram−ve cell wall are more complex

Peptidoglycan:
Polymer consisting of sugars and amino acids that forms a mesh-like layer outside the plasma membrane of most bacteria
**Peptidoglycan:**

Gram-positive bacteria (20 to 80 nanometers)  
Gram-negative bacteria (7 to 8 nanometers)

Peptidoglycan forms around 90% of the dry weight of Gram-positive bacteria but only 10% of Gram-negative strains.
BACTERIAL CELL WALL

Gram–ve cell wall are more complex
MECHANISM OF ACTION

- Bacterial enzymes (Penicillin Binding Protein) involved in biosynthesis of cell wall (Peptidoglycan)
- Penicillin inhibits the action of these enzymes
- Weakens Bacterial cell wall, vulnerable to rupture by solutes
- Most activity on cells that are dividing (actively multiplying)
- In addition, Penicillins activate bacterial autolytic system (initiate cell lysis, death)
PENICILLIN STRUCTURE

Beta-Lactam Ring Structure

Thiazolidine Ring

6-Aminopenicillanic acid

Essential Nucleus
Necessary for Activity
Penicillin G
(Benzyl Penicillin)

Penicillin V
Thiazolidine ring fused with beta-lactam ring

Combined form results in basic structure of all penicillins: 6-Amino-penicillanic acid (6-APA)

Side chain to 6-APA

Both nucleus & 6-APA is needed for activity, side chain determines acid stability, enzyme stability (penicillinase)
ANTIBACTERIAL SPECTRUM

- Effective mainly against G+ cocci and some G- cocci
- Majority of Staphylococci, Streptococci, Gonococci, Pneumococci, Meningococci
- B. Anthracis, Corynebacterium.Diptheria and other anaerobic (Clostridium Species)
On Oral administration, destruction by GI Acid, microbial flora
Results in variable absorption, 4-5 large dose compared to IM
Rapid absorption after IM or SC, peak levels in 15-30 minutes
Wide distribution in body, high levels in Kidney
60 % Protein bound
Kidney is major clearing organ, minor role for liver
Major pathway in kidney is Tubular Secretion
Elimination half life short (30 minutes), frequent dosing required
Sustained release formulations developed due to short half life or quick elimination.

Sustained release not effective in serious conditions due to low concentration.
**ADVERSE REACTION**

- Well tolerated, minor GI issues
- **Allergic Reactions:**
  - Risk of Allergic reactions is 5-10%
  - Anaphylaxis (Cardiovascular collapse, bronchospasm) rare (0.01%)
  - Topical > Aerosol > Oral form (Chance of Allergic reaction)
  - Metabolites are highly Immunogenic, Penicilloic Acid
  - Penicilloic Acid forms Covalent bonding with tissue proteins
  - Cross Allergy can be developed
  - Skin Rash
NO single reliable method

Patient history

Skin Test:

Skin surface scratched, Benzyl penicillin added, if skin reacts then patient might be allergic

Administer 0.005 ml of penicilloyl-polylysine intradermally, if inflammatory response then positive

Both test combined will predict all Allergy reactions
**THERAPEUTIC USE OF PENICILLIN'S**

- **Pneumococcal Infections:**
  1. Most strains of Pneumococci (*Pneumococcal Pneumonia*) are sensitive to Penc
  2. Therapeutic effect within 48-72 hrs
  3. S.Pneumonia have started to show resistance

- **Streptococcal Infections:**
  1. Pen effective in Streptococcal infections leading to endocarditis
  2. High IM/IV doses initially to counter infection
  3. Proper selection of antibiotics is key to proper treatment
**THERAPEUTIC USE OF PENICILLIN'S**

- **Meningococcal meningitis:**
  1. Drug of choice
  2. However not recommended for prophylactic treatment

- **STD:**
  1. Pen effective in Gonorrhea & Syphilis
PROPHYLACTIC USE OF PENICILLIN

- **Rheumatic fever:**
  1. Inflammation fever post infection by Streptococci
  2. Customary to give Pen to prevent spread of infections

- **Bacterial Endocarditis:**
  1. Prophylactic treatment for patients with Rheumatic or congenital heart disease that undergo minor surgeries
<table>
<thead>
<tr>
<th>Regimen 1 (Oral)</th>
<th>Regimen 2 (IM)</th>
<th>Regimen 3 (IM, Large dose)</th>
<th>Regimen 4 (IV, large dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin V (250-500 mg)</td>
<td>Fortified Pen G</td>
<td>Pen G (1-2 mega units)</td>
<td>Pen G (2 mega units)</td>
</tr>
<tr>
<td>Pen-G every 6 hrs</td>
<td>Once a day (600,000 units)</td>
<td>Every 4 – 6 hrs</td>
<td>Every 2 hrs</td>
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BACTERIAL RESISTANCE

- Natural Resistance:
  - Org with NO cell wall or impermeable to drug
- Acquired Resistance:
  - Occurs by Plasmid transfer
BACTERIAL RESISTANCE

- Acquiring resistant plasmid would result in the following:
  - Bacteria produce enzyme, Beta-lactamase that hydrolyses beta-lactam ring
  - Hydrolysis of ring inactivates Penicillin
  - Staphylococci, E.Coli, M.Tuberculosis, B.Antracis produce beta-lactamase
  - Decreased permeability of drugs
  - Altered PBP
The only way to do great work is to love what you do.

- Steve Jobs