



PHARMACOLOGY — II

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TOPIC OUTCOMES

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

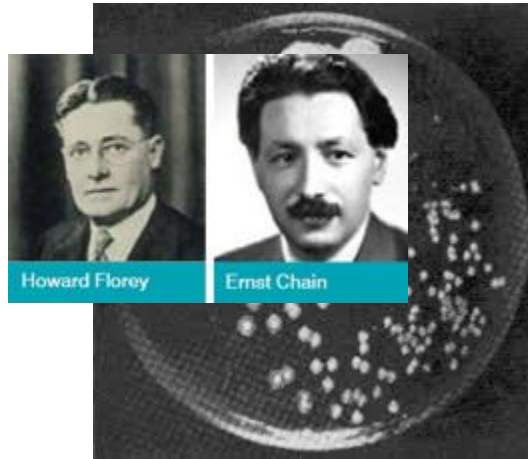
1. Know the history of Penicillin discovery
2. MOA, ADME, Clinical usage of Penicillin's
3. Resistance encountered



PENICILLINS; HISTORY



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





PENICILLINS; HISTORY



Howard Florey



Ernst Chain

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



PENICILLINS; HISTORY



laboratory assistant, Mary Hunt, arrived with a cantaloupe with a "pretty, golden mold."

Mold turned out to be the fungus *Penicillium chrysogenum*, 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*



PENICILLINS; HISTORY



In 1945, Fleming, Florey, and Chain were awarded the Nobel Prize in Physiology or Medicine

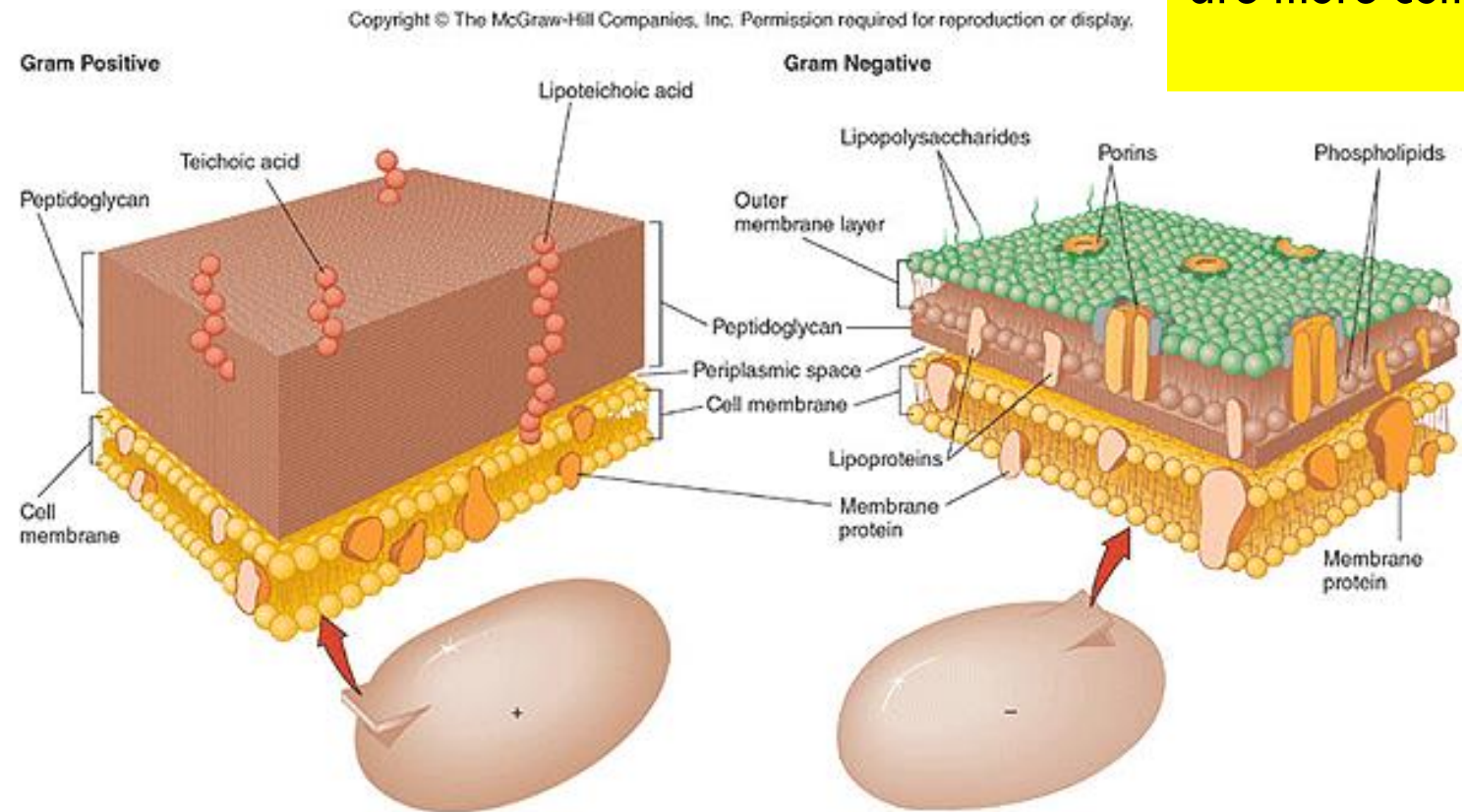


BACTERIAL CELL WALL

Peptidoglycan:

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

Gram -ve cell wall are more complex





BACTERIAL CELL WALL

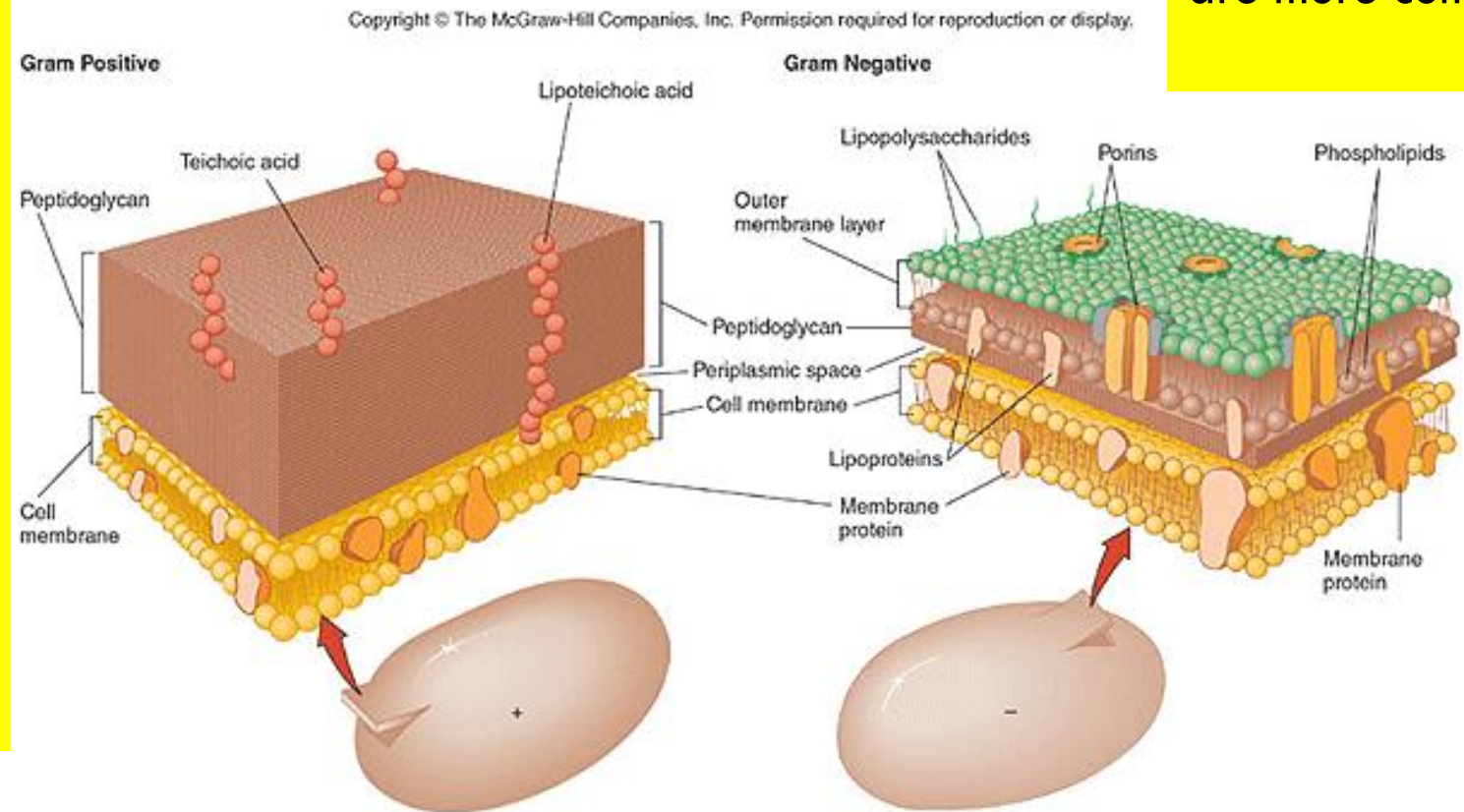
Peptidoglycan:

Gram-positive bacteria (20 to 80 nanometers)

Gram-negative bacteria (7 to 8 nanometers)

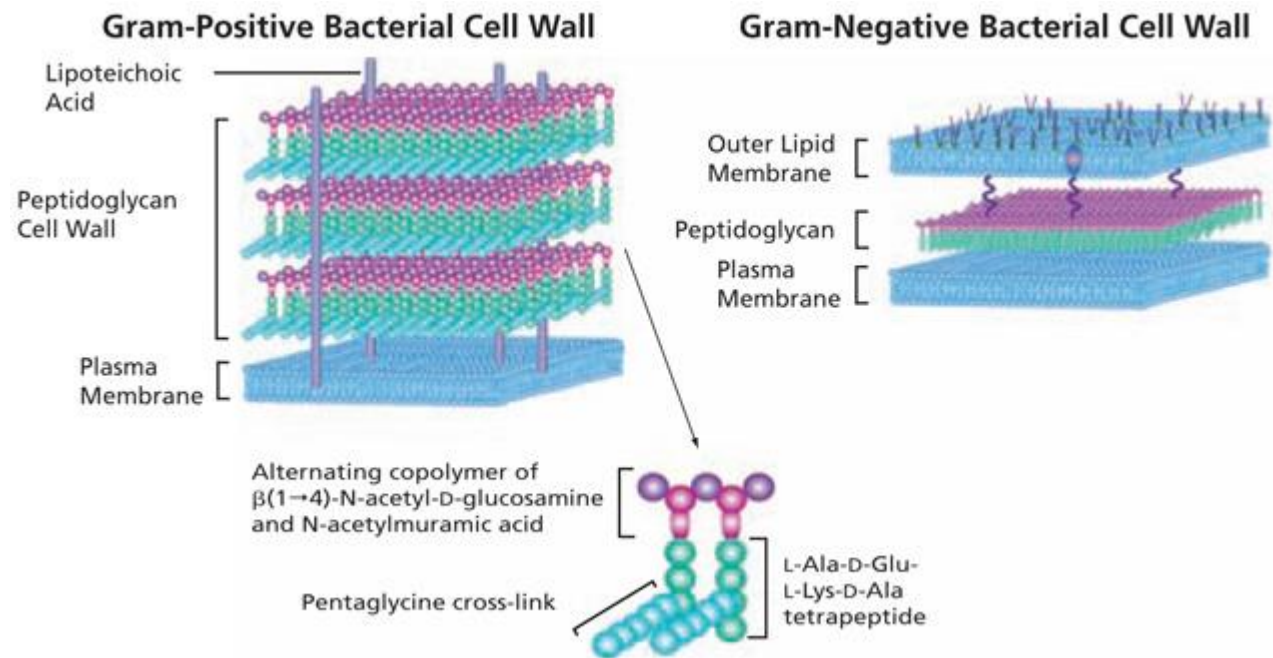
Peptidoglycan forms around 90% of the dry weight of Gram-positive bacteria but only 10% of Gram-negative strains.

Gram -ve cell wall are more complex





BACTERIAL CELL WALL

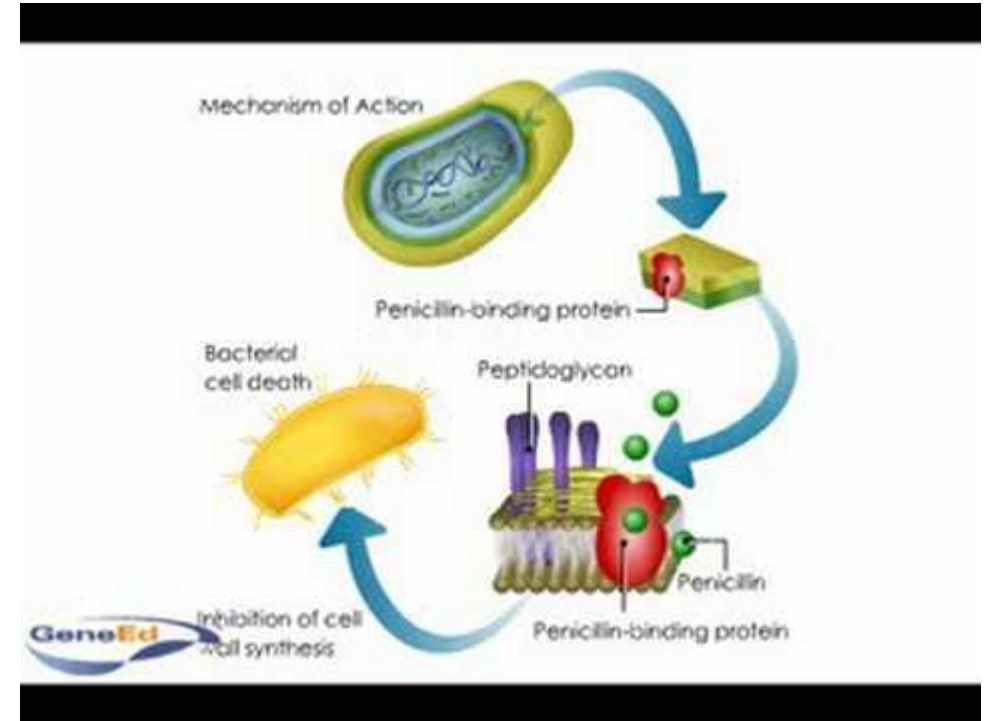


Gram -ve cell wall are more complex



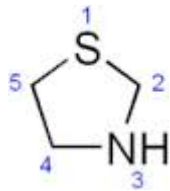
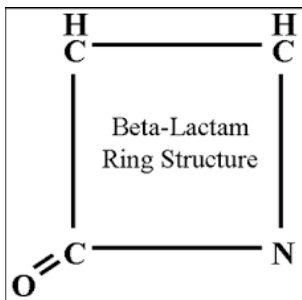
MECHANISM OF ACTION

- ❖ 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)

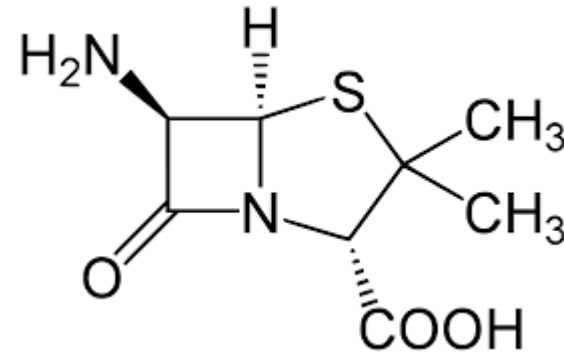




PENICILLIN STRUCTURE



Thiazolidine Ring



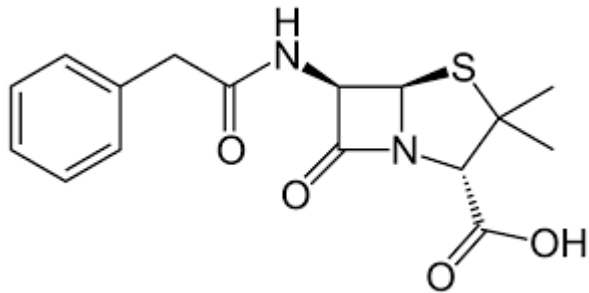
6-Aminopenicillanic acid

Essential Nucleus

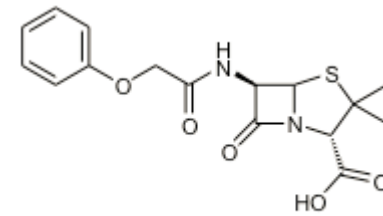
Necessary for Activity



PENICILLIN STRUCTURE



Penicillin G
(Benzyl Penicillin)



Phenoxymethylpenicillin

Penicillin V



STRUCTURE ACTIVITY RELATIONSHIP

- ❖ 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)
- ❖



ADME

- ❖ 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



ADME

- ❖ Sustained release formulations developed due to Short half life or quick elimination
- ❖ Sustained release not effective in serious conditions due to low conc



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



PENICILLIN ALLERGY DETECTION

- ❖ **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 Gonorrhoea & 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



PENICILLIN REGIMENS

Regimen 1 (Oral)	Regimen 2 (IM)	Regimen 3 (IM, Large dose)	Regimen 4 (IV, large dose)
Penicillin V (250-500 mg) Pen-G every 6 hrs	Fortified Pen G Once a day (600,000 units)	Pen G (1-2 mega units) Every 4 – 6 hrs	Pen G (2 mega units) Every 2 hrs



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 results in 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



INSPIRATION OF THE DAY !

The only way
to do great
work
is **to** love what
you do.

- Steve Jobs

